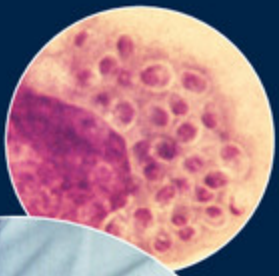
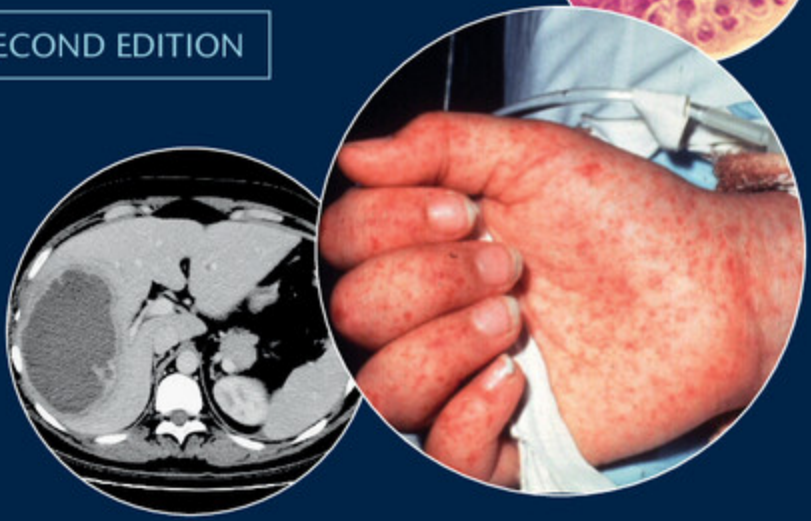
Clinical Infectious Disease

Edited by

DAVID SCHLOSSBERG

SECOND EDITION





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Edited by

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Every effort has been made in preparing this book to provide accurate and up-to-date information which is in accord with accepted standards and practice at the time of publication. Although case histories are drawn from actual cases, every effort has been made to disguise the identities of the individuals involved. Nevertheless, the authors, editors, and publishers can make no warranties that the information contained herein is totally free from error, not least because clinical standards are constantly changing through research and regulation. The authors, editors, and publishers therefore disclaim all liability for direct or consequential damages resulting from the use of material contained in this book. Readers are strongly advised to pay careful attention to information provided by the manufacturer of any drugs or equipment that they plan to use.

This book is dedicated to Dr. Jonas A. Shulman, respected mentor and valued friend.
In the Sayings of the Fathers, we are advised:

עשה לך רב, וקנה לך חבר
Provide yourself a teacher; take for yourself a friend.

I was very lucky to find both in the same person.

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Preface

The gratifying response to *Clinical Infectious Disease* has prompted this second edition. As with the first edition, our goal remains a complete and user-friendly guide to the diagnosis and treatment of infectious diseases.

The book is divided into 10 sections. First, Clinical syndromes, both general and by organ system, provides a traditional anatomic orientation, although within this section additional chapters are devoted to particularly challenging entities that are often difficult to research, such as infectious thyroiditis, deep neck infection, periocular infection, lymphadenopathy, mediastinitis, pacemaker infection, sexually transmitted enteric infection, bursitis, polyarthritis, psoas abscess, splenic abscess, spinal epidural abscess, cerebrospinal shunt infection, myelitis and peripheral neuropathy, and prion disease.

The second section, The susceptible host, includes individual chapters on infection in various immunocompromised states, including diabetes, transplantation, neutropenia, dialysis, pregnancy, and asplenia. Subsequent entire sections are devoted to HIV, nosocomial infection, surgery and trauma, prophylaxis, travel and recreation, and bioterrorism.

Organism-specific chapters follow, with individual chapters for specific bacteria, viruses, fungi, parasites, and other pathogens. Finally, a major section on antimicrobial therapy includes chapters on principles of antibiotic therapy, antifungal therapy, antiviral therapy, and hypersensitivity to antibiotics. A final chapter lists antimicrobial agents in tabular form, providing a convenient reference for dosage, side effects, cost, pregnancy class, effect of food, and dose adjustment for renal dysfunction. All chapters include suggested readings.

For this new edition every chapter has been updated, and four new chapters have been added: Tungiasis and bedbugs (in Skin and lymph nodes), Biologics (in Compromised host), Antibacterial agents (in Antimicrobial therapy), and Probiotics (in Antimicrobial therapy).

We hope this text continues to provide a practical, clinically oriented, and convenient resource for the diagnosis and treatment of infectious disease.

I am enormously grateful for the vision, talent, and dedication of the staff at Cambridge University Press, particularly Richard Marley, Jane Seakins, Rob Sykes, Ross Higman, Sarah Payne, Anne Kenton, and Ed Robinson.

PART I

Clinical syndromes: general

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1. Fever of unknown origin (FUO)

Cheston B. Cunha and Burke A. Cunha

OVERVIEW

Fever of unknown origin (FUO) describes prolonged fevers >101°F lasting for 3 or more weeks that remain undiagnosed after a focused FUO outpatient/inpatient workup. The causes of FUO include infectious and noninfectious disorders. A variety of infectious, malignant, rheumatic/inflammatory disorders may be associated with prolonged fevers, but relatively few persist undiagnosed for sufficient duration to be classified as FUOs.

CAUSES OF FUO

The distribution of disorders causing FUOs is dependent on age, demographics, family history, zoonotic exposures, and previous/current conditions, e.g., malignancies, rheumatic/inflammatory disorders, cirrhosis. Each category of FUO may also be approached by subgroups, e.g., elderly, immunosuppressed, transplants, febrile neutropenia, zoonoses, HIV, nosocomial, returning travelers. The differential diagnosis in each subgroup reflects the relative distribution of disorders within the subgroup, and the geographic distribution of endemic diseases. The relative distribution of causes of FUO has changed over time but, with few exceptions, the disorders responsible for FUOs have remained relatively constant over time (Table 1.1).

DIAGNOSTIC APPROACH TO FUOs

In patients presenting with prolonged fevers, the clinician should first determine if the patient indeed has an FUO. Because there are many causes of FUO, there is no "cookbook or algorithmic approach" for diagnosing FUOs. In medicine, the history provides important initial diagnostic clues and a general sense of the likely FUO category, e.g., weight loss with early anorexia suggests malignancy, arthralgias/myalgias suggest a rheumatic/inflammatory disorder, and fever with chills suggests an infectious etiology.

After an FUO category is suggested by historical clues, the physical examination should focus on history relevant findings in the differential diagnosis. The physical examination should not be comprehensive but more importantly should be carefully focused on demonstrating the presence or absence of key findings in the differential diagnosis, e.g., a complete neurologic exam is unhelpful in an FUO patient with probable adult Still's disease. On physical examination particular attention should be given to eye findings, liver, spleen, lymph nodes, joint findings, and skin lesions (Table 1.2). At this point, based upon the presence or absence of history and physical examination clues, the initial FUO diagnostic workup, e.g., nonspecific laboratory tests, should also be focused on ruling in or ruling out the most likely diagnostic possibilities. Since the patient has already been seen by one or more physicians prior to presentation, routine laboratory tests have already been done, e.g., CBC, liver function test (LFTs), urinalysis (UA), but these tests should be carefully re-reviewed for diagnostic clues, e.g., relative lymphopenia.

The "shot gun" approach to laboratory testing for FUOs should be avoided. Since the number of FUO causes are legion, it is not clinically or cost-effective to test for every cause of FUO. When asked why he robbed banks, Willy Sutton replied, "Because that's where the money is!" Similarly, a focused FUO workup should be directed at the most likely, not all, diagnostic possibilities, as suggested by the history, physical, and nonspecific laboratory tests. Nondirected testing often provides misleading information. It makes no sense to obtain thyroid function tests (TFTs) in FUOs with joint symptoms; neither should TFTs be obtained in FUOs likely due to adult Still's disease, giant cell arteritis/temporal arteritis (GCA/TA), or periarteritis nodosa (PAN).

Blood cultures should not be obtained in all cases of FUO. If the FUO differential diagnosis

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Table 1.1 Classic causes of fever of unknown origin (FUO)

Type of disorder	Common	Uncommon	Rare
Malignancy/neoplastic disorders	Lymphoma[a] Hypernephromas/renal cell carcinoma (RCC)	Pre-leukemias (AML)[a] Myeloproliferative disorders (MPDs)	Atrial myxomas Multiple myeloma Colon carcinoma Pancreatic carcinoma CNS metastases Hepatomas Liver metastases
Infectious diseases	Miliary TB SBE Brucellosis[a] Q fever[a]	Intra-abdominal/pelvic abscess Intra/perinephric abscess Typhoid fever/enteric fevers[a] Toxoplasmosis Cat scratch disease (CSD)[a] EBV CMV HIV Extrapulmonary TB (renal TB, CNS TB)	Periapical dental abscess Chronic sinusitis/mastoiditis Subacute vertebral osteomyelitis Aortoenteric fistula Relapsing fever[a] Rat-bite fever[a] Leptospirosis[a] Histoplasmosis Coccidiomycosis Visceral leishmaniasis (kala-azar) LGV Whipple's disease[a] Castleman's disease[a] (MCD) Malaria Babesiosis Ehrlichiosis
Rheumatologic/inflammatory disorders	Adult Still's disease[a] Giant cell arteritis (GCA)/temporal arteritis (TA)[a]	PAN/MPA[a] Late-onset rheumatoid arthritis (LORA)[a] SLE[a]	Takayasu's arteritis[a] Kikuchi's disease[a] Sarcoidosis (CNS) Felty's syndrome Gaucher's disease Polyarticular gout[a] Pseudogout[a] Schnitzler's syndrome[a] Behçet's disease[a] FAPA syndrome[a] (Marshall's syndrome)
Miscellaneous disorders	Drug fever[a] Alcoholic cirrhosis[a]	Subacute thyroiditis[a] Regional enteritis (Crohn's disease)[a]	Pulmonary emboli (small/multiple) Pseudolymphomas Kikuchi's disease[a] Rosai–Dorman disease[a] Erdheim–Chester disease (ECD)[a] Cyclic neutropenia[a] Familial periodic fever syndromes[a] • FMF • Hyper IgD syndrome[a] • TNF receptor-1-associated periodic syndrome (TRAPS) • Muckle–Wells syndrome Systemic mastocytosis Hypothalamic dysfunction Hypertriglyceridemia Factitious fever[a]

[a] Also cause of recurrent FUOs.

Disorders with FUO potential include any not easily diagnosed disorder with prolonged fevers, travel-related infections with prolonged fevers presenting in nonendemic areas, any relapsing/recurrent disorder with prolonged fevers, or any disorder with prolonged fevers with unusual clinical findings.

Abbreviations: CNS = central nervous system; TB = tuberculosis; SBE = subacute bacterial endocarditis; CMV = cytomegalovirus; HIV = human immunodeficiency virus; EBV = Epstein–Barr virus; LGV = lymphogranuloma venereum; PAN = periarteritis nodosa; MPA = microscopic polyangiitis; SLE = systemic lupus erythematosus; FMF = familial Mediterranean fever; MCD = multicentric Castleman's disease; FAPA = fever, aphthous ulcers, pharyngitis, adenitis; TNF = tumor necrosis factor; AML = acute myelogenous leukemia.

Adapted from: Cunha BA. Fever of unknown origin (FUO). In: Gorbach SL, Bartlett JB, Blacklow NR (Eds.) *Infectious Diseases in Medicine and Surgery*. (3rd edn.) Philadelphia: WB Saunders, 2004; pp. 1568–1577 and Cunha BA. Overview. In: Cunha BA (Ed.) *Fever of Unknown Origin*. New York: Informa Healthcare; 2007; pp. 1–16.

Table 1.2 History and physical examination clues to fever of unknown origin (FUO) categories

	Historical features		Clues from the history	Physical examination findings		Clues from the physical examination
Malignant/ neoplastic disorders	• PMH/FMH malignancy	→	Possibility of same disease likely	• Fever pattern:		
	• HA/mental confusion	→	CNS metastases, lymphomas, multiple myeloma, atrial myxoma (CNS emboli)	Relative bradycardia	→	CNS, malignancies, lymphomas
				Hectic/septic fevers (Pel-Ebstein)	→	Lymphomas
	• Weight loss (with early decreased appetite)	→	Any malignant/neoplastic disorder	• Cranial nerve palsies	→	CNS lymphomas, CNS neoplasms
	• Early satiety	→	Lymphomas, any malignant/neoplastic disorder causing splenomegaly	• Fundi: Roth spots	→	Lymphomas, atrial myxoma
				• Fundi: cytoid bodies (cotton wool spots)	→	Atrial myxoma
	• Pruritus (post hot shower/bath)	→	Lymphoma, MPDs	• Fundi: retinal hemorrhages	→	Pre-leukemia (AML)
	• Night sweats	→	Any malignant/neoplastic disorder	• Adenopathy	→	Lymphoma, Kikuchi's disease, Rosai–Dorfman disease
	• Abdominal discomfort/pain	→	Hypernephroma, hepatoma, liver metastases, colon carcinoma, pancreatic carcinoma	• Sternal tenderness	→	Pre-leukemia (AML), MPDs
				• Heart murmur	→	Marantic endocarditis, atrial myxoma
	• Testicular pain	→	Lymphoma	• Hepatomegaly	→	Hepatoma, hypernephroma, liver metastases
	• Bone pain	→	Multiple myeloma, any malignant/ neoplastic disorder with bone involvement	• Splenomegaly	→	Lymphomas, MPDs
				• Splinter hemorrhages	→	Atrial myxoma
				• Epididymitis	→	Lymphomas
Infectious diseases	• PMH/FMH of infections	→	Possibility of same disease high	• Fever pattern:		
	• HA/mental confusion	→	Brucellosis, CSD, ehrlichiosis, Q fever, malaria, leptospirosis, Whipple's disease, typhoid fever/enteric fevers, rat-bite fever, relapsing fever, CNS TB, HIV, LGV	Relative bradycardia	→	Typhoid fever/enteric fevers, leptospirosis, Q fever, malaria, babesiosis, ehrlichiosis
				Double quotidian fever	→	Visceral leishmaniasis (kala-azar)
				Camelback fever curve	→	Ehrlichiosis, leptospirosis, brucellosis, rat-bite fever (*S. minus*)
	• Recent/similar illness exposure	→	Possibility of same disease high		→	Miliary TB, typhoid fever/enteric fevers
	• Surgical/invasive procedures	→	Abscess, SBE	Morning temperature spikes		
	• Aortic aneurysm/ repair	→	Q fever, enteric fever	Relapsing fevers	→	Brucellosis, malaria, rat-bite fever (*S. moniliformis*)
	• STD history	→	LGV	• Abducens (CN VI) palsy	→	CNS TB
	• Recent travel	→	Typhoid/enteric fevers, leptospirosis, malaria, visceral leishmaniasis (kala-azar), brucellosis, Q fever	• Conjunctival suffusion	→	Trichinosis, relapsing fever, leptospirosis
				• Conjunctival hemorrhages	→	SBE
	• Insect exposure	→	Malaria, ehrlichiosis, babesiosis, visceral leishmaniasis (kala-azar), relapsing fever	• Chorioretinitis	→	Toxoplasmosis, TB, histoplasmosis
				• Choroid tubercles	→	Miliary TB
	• Pet/animal contact	→	Q fever, CSD, toxoplasmosis, rat-bite fever, relapsing fever, leptospirosis, brucellosis	• Roth spots	→	SBE
				• Palatal petechiae	→	EBV, CMV, toxoplasmosis
	• Unpasteurized milk/ cheese consumption	→	Q fever, brucellosis	• Tongue ulcer	→	Histoplasmosis
				• Adenopathy	→	CSD, EBV, CMV

	Historical features		Clues from the history	Physical examination findings		Clues from the physical examination
	• Undercooked meat consumption	→	Toxoplasmosis, trichinosis	• Heart murmur	→	SBE
				• Spinal tenderness	→	Subacute vertebral osteomyelitis, typhoid fever/enteric fever, skeletal TB, brucellosis
	• Blood transfusions	→	Malaria, babesiosis, ehrlichiosis, CMV, HIV	• Hepatomegaly	→	Q fever, typhoid fever/enteric fevers, brucellosis, visceral leishmaniasis (kala-azar), rat-bite fever, relapsing fever
	• Poor dentition	→	SBE, apical root abscess			
	• Sleep disturbances	→	Brucellosis, relapsing fever, leptospirosis	• Splenomegaly	→	Miliary TB, EBV, CMV, typhoid fever/enteric fevers, brucellosis, histoplasmosis, ehrlichiosis, malaria, Q fever, SBE, CSD Rat-bite fever, relapsing fever
	• Early satiety	→	EBV, CMV, Q fever, brucellosis, SBE, miliary TB			
	• Arthralgias	→	Rat-bite fever, LGV, Whipple's disease, brucellosis	• Splinter hemorrhages	→	SBE
				• Ostler's nodes/ Janeway lesions	→	SBE
	• Myalgias	→	Q fever, leptospirosis, relapsing fever, trichinosis	• Skin hyperpigmentation	→	Visceral leishmaniasis (kala-azar), Whipple's disease
	• Sinusitis	→	Chronic sinusitis			
	• Night sweats	→	Miliary TB, histoplasmosis	• Epididymitis	→	EBV, renal TB, brucellosis
	• Weight loss	→	Miliary TB, histoplasmosis			
	• Tongue pain	→	Histoplasmosis, relapsing fever			
	• Neck pain	→	Subacute vertebral osteomyelitis, chronic mastoiditis			
	• Tender finger tips	→	SBE			
	• Abdominal pain	→	Relapsing fever, leptospirosisv, typhoid fever/enteric fevers, trichinosis			
	• Back pain	→	Subacute vertebral osteomyelitis, brucellosis, SBE			
	• Testicular pain	→	EBV			
Rheumatic/ inflammatory disorders	• PMH/FMH of rheumatic disorders	→	Possibility of the same disease likely	• Fever pattern:		
	• HA/mental confusion	→	GCA/TA, CNS sarcoidosis, adult Still's disease	Double quotidian fever	→	Adult Still's disease
				Morning temperature spikes	→	PAN
	• Transient facial edema	→	Takayasu's arteritis			
	• Hearing loss	→	PAN	• Lacrimal gland enlargement	→	LORA, sarcoidosis, SLE
	• Nasal stuffiness	→	Sarcoidosis	• Parotid gland enlargement	→	Sarcoidosis
	• Joint pain/swelling	→	SLE, LORA, sarcoidosis, adult Still's disease	• Rash	→	Sarcoidosis, SLE, adult Still's disease
				• Unequal pulses	→	Takayasu's arteritis
	• Eye symptoms	→	PAN, sarcoidosis	• Conjunctival nodules	→	Sarcoidosis
	• Transient blindness	→	PAN, SLE, GCA/TA, Takayasu's arteritis	• Dry eyes	→	Sarcoidosis
	• Neck/jaw pain	→	GCA/TA, Takayasu's arteritis	• Watery eyes	→	PAN
	• Sore throat	→	SLE, adult Still's disease	• Argyll-Robertson or Adies' pupils	→	Sarcoidosis
	• Tongue tenderness	→	GCA/TA	• Band keratopathy	→	Adult Still's disease, sarcoidosis
	• Mouth ulcers	→	SLE	• Episcleritis	→	GCA/TA, LORA, PAN
	• Night sweats	→	Takayasu's arteritis	• Scleritis	→	SLE
	• Rash	→	Adult Still's disease, SLE, sarcoidosis	• Iritis	→	Adult Still's disease, SLE, sarcoidosis

Table 1.2 *(continued)*

	Historical features		Clues from the history	Physical examination findings		Clues from the physical examination
	• Dry cough	→	Sarcoidosis, GCA/TA	• Uveitis	→	Adult Still's disease, SLE, LORA, sarcoidosis
	• Acalculous cholecystitis	→	SLE	• Fundi: optic neuritis with "macular star"	→	PAN
	• Intermittent abdominal pain	→	SLE, PAN, adult Still's disease			
	• Tender finger tips	→	SLE, PAN			
	• Testicular pain	→	PAN, SLE			
				• Fundi: cytoid bodies (cotton wool spots)	→	SLE, GCA/TA, PAN, adult Still's disease
				• Fundi: "candlewax drippings"	→	Sarcoidosis
				• Fundi: Roth spots	→	SLE, PAN
				• Fundi: central/ branch retinal artery occlusion	→	SLE, GCA/TA, Takayasu's arteritis
				• Fundi: central retinal vein occlusion	→	SLE, sarcoidosis
				• Oral ulcers	→	SLE, Behçet's disease, FAPA syndrome
				• Tongue ulcers	→	GCA/TA
				• Adenopathy	→	SLE, LORA, sarcoidosis
				• Splenomegaly	→	Felty's syndrome, SLE, adult Still's disease, sarcoidosis
				• Heart murmur	→	SLE (Libman–Sacks)
				• Arthritis/joint effusion	→	Any rheumatic/inflammatory disorder
				• Epididymitis	→	PAN, SLE, sarcoidosis
Miscellaneous disorders	• Negative HPI/PMH for infectious, rheumatic/ inflammatory, malignant/neoplastic disorders	→	Non-miscellaneous disorders unlikely	• Fever pattern: Relative bradycardia	→	Drug fever, factitious fever
	• PMH of periodic fevers (FMF, hyper IgD syndrome, TRAPS, Muckle–Wells syndrome)	→	Possibility of same disease likely	• Periorbital edema	→	TRAPS
				• Parotid enlargement	→	Alcoholic cirrhosis
				• Episcleritis	→	Regional enteritis (Crohn's disease)
	• Drugs/medications	→	Drug fever, pseudolymphoma	• Fundi: lipemia retinalis	→	Hypertriglyceridemia
	• Fume exposure	→	Fume fever	• Oral ulcers	→	Hyper IgD syndrome
	• Alcoholism	→	Alcoholic cirrhosis	• Adenopathy	→	Pseudolymphoma, hyper IgD syndrome (cervical), Schnitzler's syndrome (axillary/inguinal)
	• Regional enteritis (Crohn's disease)	→	Abscess	• Signs of alcoholic cirrhosis	→	Alcoholic cirrhosis
	• Thyroid disease	→	Subacute thyroiditis	• Hepatomegaly	→	Schnitzler's syndrome, hyper IgD syndrome
	• Hyperlipidemia	→	Hypertriglyceridemia			
	• Medical personnel	→	Factitious fever	• Splenomegaly	→	Regional enteritis (Crohn's disease), alcoholic cirrhosis, FMF, hyper IgD syndrome, Muckle–Wells syndrome, Schnitzler's syndrome
	• Sore throat	→	Subacute thyroiditis, hyper IgD syndrome			
	• Neck/jaw pain	→	Subacute thyroiditis	• Epididymitis	→	FMF, TRAPS
	• Intermittent abdominal pain	→	Regional enteritis (Crohn's disease), FMF, Muckle–Wells syndrome	• Perirectal fistula	→	Regional enteritis (Crohn's disease)

Historical features		Clues from the history	Physical examination findings	Clues from the physical examination
• Arthralgias/joint pains	→	FMF, hyper IgD syndrome, TRAPS, Muckle–Wells syndrome, cyclic neutropenia, Schnitzler's syndrome		
• Testicular pain	→	FMF, TRAPS		
• Bone pain	→	Schnitzler's syndrome		
• Intermittent urticaria	→	Schnitzler's syndrome Hyper IgD syndrome		

Abbreviations: PMH = past medical history; FMH = family medical history; HA = headache; CMV = cytomegalovirus; EBV = Epstein–Barr virus; ESR = erythrocyte sedimentation rate; PAN = periarteritis nodosa;
MPA = microscopic polyangiitis; SBE = subacute bacterial endocarditis; SLE = systemic lupus erythematosus; TB = tuberculosis;
MPDs = myeloproliferative disorders; LORA = late-onset rheumatoid arthritis; RCC = renal cell carcinoma; GCA = giant cell arteritis;
TA = temporal arteritis; AML = acute monocytic leukemia; HIV = human immunodeficiency virus; CNS = central nervous system;
CSD = cat scratch disease; FMF = familial Mediterranean fever; TRAPS = tartrate-resistant acid phosphatase; LGV = lymphogranuloma venereum; STD = sexually transmitted disease; CN VI = cranial nerve VI; FAPA = fever, aphthous ulcers, pharyngitis, adenitis.
Adapted from Cunha CB. Infectious disease differential diagnosis. In: Cunha BA, ed. *Antibiotic Essentials* 12th edn.; Jones & Bartlett, Sudbury, MA, 2013; pp. 475–506 and Cunha BA. Nonspecific tests in the diagnosis of fever of unknown origin. In: Cunha BA, ed. *Fever of Unknown Origin*. New York: Informa Healthcare; 2007; pp. 151–158.

includes adult Still's disease, subacute thyroiditis, or GCA/TA, blood cultures make little sense. Even if an infectious etiology is likely, blood cultures should not always be obtained, e.g., Epstein–Barr virus (EBV), cytomegalovirus (CMV), HIV. Blood cultures are ordered to rule out subacute bacterial endocarditis (SBE). The diagnosis of SBE is based on an otherwise unexplained high-grade/continuous bacteremia (with a known endocarditis pathogen) *plus* a cardiac vegetation. The diagnosis of culture-negative endocarditis (CNE) is not based on the presence of negative blood cultures and a vegetation. Rather, the diagnosis of CNE is based on three essential key findings, i.e., a cardiac vegetation, negative blood cultures *plus* peripheral signs of SBE. The differential diagnosis of CNE includes marantic endocarditis (usually due to a malignancy). The diagnosis of marantic endocarditis is based on the size/shape of vegetation (different from SBE vegetations). Alternately, if an infectious etiology of CNE is suspected, then serologic tests for brucella and Q fever should be obtained. While brucella SBE vegetations are easily seen, Q fever SBE vegetations may be small or undetectable.

Because the appropriateness of therapy is based on a correct diagnosis, the main focus of the clinical approach to FUOs is diagnostic rather than therapeutic. The diagnostic workup should be focused based on signs, symptoms, and non specific laboratory abnormalities, which may either enhance or diminish particular diagnostic possibilities. Nonspecific laboratory tests often provide important albeit often subtle clues in the FUO workup. By definition nonspecific laboratory tests are nonspecific, but when considered in concert often are helpful in narrowing diagnostic possibilities and in prompting specific diagnostic testing to rule in or rule out the most likely diagnoses being considered. Importantly, the diagnostic workup should not be excessive and should not include every conceivable cause of FUO. Focused diagnostic testing should be based on the pertinent aspects of the history, the presence or absence of characteristic physical findings, and a presumptive syndromic diagnosis based on combining key nonspecific laboratory findings.

NONSPECIFIC LABORATORY TEST CLUES

Nonspecific laboratory clues are important in focusing the FUO diagnostic workup. In addition to the initial history and physical examination, selected nonspecific laboratory tests are helpful. If malignancy is a likely cause of an FUO, highly elevated ferritin, LDH, or B_{12} levels often point to an occult malignancy. Serum protein electrophoresis (SPEP) is helpful in demonstrating monoclonal or polyclonal gammopathy which may be a clue to specific disorders. As with all laboratory tests, nonspecific findings should be interpreted in the appropriate clinical context, e.g., an FUO

Table 1.3 FUO nonspecific: laboratory tests

Nonspecific tests for FUOs
• CBC
• ESR
• LFTs
• Ferritin
• SPEP
• UA
CBC
• Leukocytosis [a] → malignant/neoplastic and infectious focused workup
• Leukopenia [a] → malignant/neoplastic, infectious, and rheumatic inflammatory focused workup
• Anemia [a] → malignant /neoplastic, infectious, and rheumatic/inflammatory focused workup
• Myelocytes/metamyelocytes [a] → malignant/neoplastic focused workup
• Lymphocytosis [a] → malignant/neoplastic and infectious focused workup
• Lymphopenia [a] → malignant/neoplastic, infectious, and rheumatic/inflammatory focused workup
• Atypical lymphocytes [a] → infectious and malignant/neoplastic focused workup
• Eosinophilia[a] → malignant/neoplastic, rheumatic/inflammatory, and infectious focused workup
• Basophilia[a] → malignant/neoplastic focused workup
• Thrombocytosis [a] → malignant/neoplastic, infectious, and rheumatic inflammatory focused workup
• Thrombocytopenia [a] → malignant/neoplastic, infectious, and rheumatic/inflammatory focused workup
ESR
• Highly elevated [a] → malignant/neoplastic, infectious, and rheumatic/inflammatory focused workup
LFTs
• Elevated SGOT/SGPT [a] → infectious and rheumatic/inflammatory focused workup
• Elevated alkaline phosphatase [a] → malignant/neoplastic and rheumatic/inflammatory focused workup
Ferritin
• Highly elevated [a] → malignant/neoplastic, rheumatic/inflammatory, and miscellaneous disorders focused workup
SPEP
• Monoclonal gammopathy → malignant/neoplastic and miscellaneous disorders workup
• Polyclonal gammopathy → infectious rheumatic/inflammatory and miscellaneous disorders focused workup
UA
• Microscopic hematuria → malignant/neoplastic, infectious, and rheumatic/inflammatory focused workup[a]

[a]See Table 1.4.

Abbreviations: CBC = complete blood count; ESR = erythrocyte sedimentation rate; LFTs = liver function tests; UA = urine analysis; RD = rheumatic disease; SGOT/SGPT = serum glutamic-oxaloacetic transaminase/serum glutamic pyruvate transaminase; SPEP = serum protein electrophoresis.

Adapted from Cunha BA. A focused diagnostic approach. In: Cunha BA (Ed.) *Fever of Unknown Origin*. New York. Informa Healthcare; 2007; pp. 9–16 and Cunha, BA. Fever of unknown origin: focused diagnostic approach based on clinical clues from the history, physical examination, and laboratory tests. *Infect Dis Clin North Am* 2007;21:1137–1187.

with polyclonal gammopathy, heart murmur, negative blood cultures, and peripheral signs of endocarditis, and should suggest an atrial myxoma. In an adult with FUO, otherwise unexplained highly elevated serum ferritin levels should suggest either a neoplasm/malignancy, myeloproliferative disorder (MPD), or a rheumatic/inflammatory disorder. Elevated serum ferritin levels are also present in systemic lupus erythematosus (SLE) flares, adult Still's disease, and GCA/TA. Elevated ferritin levels also have exclusionary diagnostic importance in FUOs, e.g., malignancy is less likely with unelevated/minimally elevated serum ferritin levels (Tables 1.3, 1.4, and 1.5).

THERAPEUTIC CONSIDERATIONS

The clinical approach to FUO is based on making a correct diagnosis. Empiric therapy is rarely justifiable unless a potentially treatable life-threatening disease is a definite/highly probable diagnosis. Antipyretics should be used only under unusual circumstances. Fever, per se, should not be treated, as treatment eliminates a potentially important diagnostic sign, i.e., the fever curve. Temperature/pulse relationships may also have important diagnostic implications, i.e., relative bradycardia. With an FUO if the differential diagnosis is between malignancy and infection, the Naprosyn test (naproxen

Table 1.4 FUO: nonspecific laboratory clues

Leukopenia
- Miliary TB
- Lymphomas
- Pre-leukemia (AML)
- Typhoid fever/enteric fevers
- Felty's syndrome
- Gaucher's disease

Monocytosis
- Miliary TB
- Histoplasmosis
- PAN/MPA
- GCA/TA
- LORA
- SLE
- Sarcoidosis
- CMV
- Brucellosis
- SBE
- Lymphomas
- Carcinomas
- MPDs
- Regional enteritis (Crohn's disease)
- Gaucher's disease

Eosinophilia
- Trichinosis
- Lymphomas
- Hypernephroma (RCC)
- PAN/MPA
- Kikuchi's disease
- Drug fever

Basophilia
- Carcinomas
- Lymphomas
- Pre-leukemia (AML)
- MPDs

Lymphocytosis
- Miliary TB
- Histoplasmosis
- Typhoid fever/enteric fevers
- Brucellosis
- EBV
- CMV
- Toxoplasmosis
- Visceral leishmaniasis (kala-azar)
- Lymphomas

Relative lymphopenia
- Q fever
- Brucellosis
- Whipple's disease
- Miliary TB
- Histoplasmosis
- Malaria
- Babesiosis
- Ehrlichiosis
- EBV
- CMV
- SLE
- Lymphomas

Atypical lymphocytes
- Malaria
- Babesiosis
- Ehrlichiosis
- EBV
- CMV
- Toxoplasmosis
- Brucellosis
- Kikuchi's disease
- Drug fever

Thrombocytosis
- SBE
- Q fever
- Miliary TB
- Histoplasmosis
- Subacute vertebral osteomyelitis
- Carcinomas
- Lymphomas
- Hypernephroma (RCC)
- MPDs
- PAN/MPA
- GCA/TA

Thrombocytopenia
- Leukemias
- Lymphomas
- MPDs
- Multiple myeloma
- EBV
- CMV
- Alcoholic cirrhosis
- Drug fever
- PAN/MPA
- SLE
- Malaria
- Babesiosis
- Ehrlichiosis
- Brucellosis
- Relapsing fever
- Miliary TB
- Histoplasmosis
- Visceral leishmaniasis (kala-azar)
- Ehrlichiosis

Rheumatoid factors
- SBE
- Visceral leishmaniasis (kala-azar)
- LORA
- Sarcoidosis
- SLE
- Alcoholic cirrhosis

Elevated alkaline phosphatase
- Hepatoma
- Miliary TB
- Lymphomas
- GCA/TA
- Gaucher's disease
- Systemic mastocytosis
- Schnitzler's syndrome

ESR (>100 mm/hr)
- SBE
- Abscesses
- Subacute vertebral osteomyelitis
- Hypernephroma (RCC)
- Carcinomas
- Lymphomas
- MPDs
- Atrial myxoma
- PAN/MPA
- Takayasu's arteritis
- Hyper IgD syndrome
- Erdheim–Chester disease (ECD)
- Rosai–Dorman disease
- Kikuchi's disease
- Schnitzler's syndrome
- Castleman's disease (MCD)
- Adult Still's disease
- GCA/TA
- LORA
- Drug fever

SPEP

Polyclonal gammopathy
- HIV
- CMV
- Alcoholic cirrhosis
- Castleman's disease (MCD)

Monoclonal gammopathy
- Multiple myeloma
- Hyper IgD syndrome
- Schnitzler's syndrome (IgM > IgG)
- Castleman's disease (MCD)

Elevated α_1/α_2 globulins
- Lymphoma
- SLE

Elevated serum transaminases
- EBV
- CMV
- Typhoid fever/enteric fevers
- Brucellosis
- Q fever
- Malaria
- Babesiosis
- Ehrlichiosis
- Adult Still's disease
- Kikuchi's disease
- Drug fever

Microscopic hematuria
- SBE
- Renal TB
- Brucellosis
- PAN/MPA
- Lymphomas
- Hypernephroma (RCC)

Multiple myeloma	Erdheim–Chester disease (ECD)
Alcoholic cirrhosis	Adult Still's disease
LORA	GCA/TA
Whipple's disease	PAN/MPA
Typhoid fever/enteric fevers	Hypernephroma (RCC)
	Liver metastases
	Subacute thyroiditis
	Elevated serum ferritin
	Malignancies
	Pre-leukemia (AML)
	MPDs
	Rosai–Dorfman disease
	Erdheim–Chester disease (ECD)
	SLE (flare)
	GCA/TA
	LORA
	Adult Still's disease
	Subacute thyroiditis

Abbreviations: CMV = cytomegalovirus; EBV = Epstein–Barr virus; ESR = erythrocyte sedimentation rate; PAN = periarteritis nodosa; MPA = microscopic polyangiitis; SBE = subacute bacterial endocarditis; SLE = systemic lupus erythematosus; TB = tuberculosis; MPDs = myeloproliferative disorders; LORA = late-onset rheumatoid arthritis; RCC = renal cell carcinoma; GCA = giant cell arteritis; TA = temporal arteritis; AML = acute monocytic leukemia; HIV = human immunodeficiency virus; MCD = multicentric Castleman's disease.

Adapted from Cunha CB. Infectious disease differential diagnosis. In: Cunha BA (Ed.) *Antibiotic Essentials* (12th edn.). Jones & Bartlett, Sudbury, MA; 2013; pp. 475–506 and Cunha BA. Nonspecific tests in the diagnosis of fever of unknown origin. In: Cunha BA (Ed.) *Fever of Unknown Origin*. New York: Informa Healthcare; 2007; pp. 151–158.

Table 1.5 FUO: sign and symptom focused testing

FUO infectious disease tests	FUO neoplastic disease tests	FUO rheumatic/inflammatory tests	Miscellaneous other tests
Blood tests (if suspected by history and physical examination)			
• Q fever IgM/IgG titers • Brucella IgM/IgG titers • Bartonella IgM/IgG titers • Salmonella IgM/IgG titers • EBV IgM/IgG titers • CMV IgM/IgG titers • HHV-8 IgM/IgG titers • **Blood cultures** If PVE suspected or if peripheral signs of SBE present *and* TTE/TEE shows a vegetation **Culture-negative endocarditis (CNE)** TTE shows a vegetation *plus* negative blood cultures *plus* peripheral signs of SBE present **Infectious CNE** If vegetation on TTE/TEE *and* blood cultures are negative, *and* peripheral signs of SBE present → proceed with *infectious CNE workup* (Q fever, etc.) **Noninfectious CNE (marantic endocarditis)** If *infectious CNE workup negative* → proceed with marantic endocarditis workup (malignancy, lymphoma, etc.)	• Ferritin • LDH • B_{12} levels • β-2 microglobulin levels • ACE† • SPEP	• RF • ANA • DsDNA • Ferritin • CPK • ACE • Anti-CCP • Antiphospholipid antibodies • SPEP	• **TFTs** (thyroid function tests) and **ATAs** (anti-thyroid antibody tests) If subacute thyroiditis suspected • **GGTP** • **B_{12} levels** If alcoholic cirrhosis suspected • **MEFV gene studies** If FMF suspected

FUO infectious disease tests	FUO neoplastic disease tests	FUO rheumatic/inflammatory tests	Miscellaneous other tests
Radiologic tests (if suspected by history, physical examination or nonspecific tests)			
• **TTE** If **SBE suspected with a** murmur *plus* peripheral signs of SBE If **marantic endocarditis** suspected, *negative* BCs *plus* peripheral signs of SBE ± signs of extracardiac malignancy • **TEE** If **PVE suspected or** if **TTE equivocal** (can't exclude vegetation) • **CT/MRI abdomen/pelvis**[a] If intra-abdominal/pelvic infection suspected • **Gallium/indium scan** If occult infection suspected • **Panorex film of jaws** If apical root abscess suspected • **Abdominal PET/CT scan** If infected graft/focal vascular infection suspected • **BM biopsy/culture** If miliary TB, SBE, brucellosis, Q fever, typhoid/enteric fevers suspected	• **CT/MRI abdomen/pelvis** If intra-abdominal/pelvic neoplasm suspected • **Gallium/indium scan** If neoplasm suspected • **PET/CT scan** If occult neoplasm likely	• **CT/MRI abdomen** If hepatomegaly/splenomegaly or peritoneal adenopathy suspected	• **Abdominal CT scan** • **Gallium/indium scan** If regional enteritis (Crohn's disease) suspected • **Chest CT (pulmonary embolus protocol)** If pulmonary emboli suspected • **Abdominal CT/PET scan** If Erdheim–Chester disease suspected (periaortic fibrosis or "coated aorta")
Other tests (if suspected by history, physical examination, or nonspecific tests)			
• **Naprosyn test** If infection or malignancy suspected • **Anergy panel/PPD and T-spot** If TB suspected	• **Naprosyn test** If infection or malignancy suspected • **BM biopsy** If myelophthisic anemia/abnormal RBCs/WBCs • **TTE** If atrial myoma or marantic endocarditis suspected • **β-2 microglobulins** If lymphoma suspected	• **Temporal artery biopsy** If GCA/TA suspected • **Low-dose steroids** If PMR suspected, prednisone 10 mg/day diagnostic/therapeutic for PMR	

[a]Chest/head CT/MRI (if head/chest infectious etiology suspected).

Abbreviations: EBV = Epstein–Barr virus; CMV = cytomegalovirus; HHV-8 = human herpesvirus-8; CPK = creatinine phosphokinase; SPEP = serum protein electrophoresis; ACE = angiotensin converting enzyme; CCP= cyclic citrullinated peptide antibody; TFTs = thyroid function tests; ATAs = anti-thyroid antibody tests; PVE = prosthetic valve endocarditis; TTE = transthoracic echocardiogram; TEE = transesophageal echocardiogram; GGTP = gamma-glutamyl transpeptidase; PMR = polymyalgia rheumatica; GCA = giant cell arteritis; TA = temporal arteritis; RF = rheumatoid factor; ANA = antinuclear antibody; LDH = lactic acid dehydrogenase; CPK = creatinine phosphokinase; SBE = subacute bacterial endocarditis; FMF = familial Mediterranean fever; CBs = blood cultures; BM = bone marrow.

Adapted from Cunha CB. Infectious disease differential diagnosis. In: Cunha BA (ed.) *Antibiotic Essentials* (12th edn.). Jones & Bartlett, Sudbury, MA, 2013; pp. 475–506 and Cunha BA. A focused diagnostic approach and non-specific tests in the diagnosis of FUO. In: Cunha BA (ed.) *Fever of Unknown Origin*. New York: Informa Healthcare; 2007; pp. 9–16, 151–158.

375 mg orally every 12 hours × 3 days) is useful for *diagnostic* purposes. During the 3 days of Naprosyn little/no decrease in temperature points to an infectious disorder (a *negative* Naprosyn test), whereas a sustained decrease in the febrile response points to a malignancy (*positive* Naprosyn test). The Naprosyn test should not be used and is not interpretable if a

rheumatic/inflammatory or miscellaneous cause of FUO is suspected.

If an FUO is likely due to miliary TB, empiric anti-TB therapy may be lifesaving. Among rheumatic/inflammatory disorders, empiric therapy of polymyalgia rheumatica (PMR) with low-dose prednisone (5–10 mg orally per day) is both diagnostic and therapeutic. Patients with FUO due to GCA/TA may develop acute unilateral visual impairment and blindness may be prevented with high-dose steroid therapy (prednisone 60–80 mg/day).

Once the cause of the FUO has been determined, specific therapy, if available, may be given. Therapy may also involve removal of the underlying cause of the FUO, e.g., discontinuing the drug causing drug fever, abscess drainage, specific therapy of treatable infections and rheumatic/inflammatory disorders.

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2. Sepsis, severe sepsis, and septic shock

Joseph Adrian L. Buensalido and Rodger D. MacArthur

DEFINITIONS

Sepsis is a complex syndrome that results from a host's response to infection. Simply put, it is the systemic inflammatory response syndrome (SIRS) arising because of documented or suspected infection. Clinically, SIRS is identified by the presence of at least two of the following: fever or hypothermia, tachycardia, tachypnea, and leukocytosis or leukopenia. Severe sepsis is sepsis with organ dysfunction or tissue hypoperfusion from the infection. Septic shock is severe sepsis plus hypotension that is not corrected by fluid resuscitation. Since 1991, the definitions and diagnostic criteria have expanded with inflammatory, hemodynamic, organ dysfunction, and tissue perfusion variables, but general definitions are the same. Sepsis-related terminology and definitions are in Table 2.1. Diagnostic criteria for sepsis are in Table 2.2. The document by a consensus committee of international experts called "Surviving Sepsis Campaign" has become one of the most comprehensive guidelines for clinicians as to best practice (though not yet standard of care) in the care of patients with severe sepsis and septic shock.

EPIDEMIOLOGY

The incidence of sepsis, severe sepsis, and septic shock are probably underestimated since most estimates are based on hospital databases that rely on the International Classification of Diseases, and so are biased toward a more severely ill population. The global incidence of sepsis is reported as from 22 to 240 cases/100 000 persons; severe sepsis from 13 to 300 cases/100 000 persons; and for septic shock, 11 cases/100 000 persons (based on a 2012 study). Case-fatality rates are as high as 30% for sepsis, 50% for severe sepsis, and 80% for septic shock. In the United States, the incidence of severe sepsis had been rising but in-hospital mortality was decreasing and not significantly different from Europe.

The elderly, neutropenic patients, and infants have higher attack and mortality rates. The incidence appears to be higher in nonwhites and men for unknown reasons. However, women admitted to ICUs for severe sepsis had higher risk of death, possibly due to gender-associated bias for men as to the level of care given. Age-adjusted case-fatality rates are similar for hospitalized septic whites and blacks, but blacks have higher rates of hospitalization and population-based mortality for sepsis. No differences in quality of care between groups exist, but there may be disparities in preventive medicine and care of preexisting conditions in blacks.

PATHOGENESIS

The clinical manifestations of the sepsis syndrome are caused by the body's immune, inflammatory, and coagulation responses to toxins and other components of microorganisms. Endotoxin, the lipoidal acylated glucosamine disaccharide core of the cell wall of many aerobic gram-negative bacteria, starts the cascade of inflammatory mediators. Known as lipid A, it is highly conserved in Enterobacteriaceae and in Pseudomonaceae. Anaerobic gram-negative bacteria, such as *Bacteroides fragilis*, lack lipid A, perhaps explaining why sepsis is not as common when infection is caused by anaerobes.

Once a pathogenic organism invades a host barrier, its cell wall molecules (lipid A in gram-negative bacteria; and peptidoglycan, teichoic acid, or toxic shock toxin-1 [TSST-1] in gram positives) are sensed by local defense cells expressing specific host proteins on their surface, such as CD14 and toll-like receptors (TLRs). The peptidoglycan of gram-positive bacteria is recognized by TLR2, and the lipopolysaccharide (LPS) of gram negatives by TLR4. Activation of TLRs initiates intracellular signaling pathways. Subsequently, macrophages are activated, leading to the rapid production (minutes to hours) of cytokines and

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Table 2.1. Sepsis-related terminology and definitions

Infection	A pathologic process caused by invasion of normally sterile host tissue by pathogenic or potentially pathogenic microorganisms
Bacteremia	The presence of viable bacteria in the blood
SIRS	The systemic inflammatory response to a wide range of infectious and noninfectious conditions. Currently used criteria include two or more of the following: temperature $>38^{\circ}C$ or $\leq 36^{\circ}C$; heart rate >90 beats/min; respiratory rate >20 breaths/min, or $PaCO_2 \leq 32$ mm Hg; WBC >12 000 cells/mm^3 or ≤ 4000 cells/mm^3, or $\geq 10\%$ immature (band) forms
Sepsis	The clinical syndrome defined by the presence of both infection and a systemic inflammatory response
Severe sepsis	Sepsis complicated by organ dysfunction, hypotension, or signs of hypoperfusion (e.g., lactic acidosis, renal failure, altered mental status, and acute respiratory failure)
Septic shock	Sepsis accompanied by acute circulatory failure, characterized by persistent arterial hypotension that, despite adequate fluid resuscitation, requires pressor therapy
MODS	Multiple organ dysfunction syndrome; the presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention; primary multiple organ dysfunction syndrome is the direct result of a well-defined insult in which organ dysfunction occurs early and can be directly attributable to the insult itself; secondary multiple organ dysfunction syndrome develops as a consequence of a host response and is identified in the context of SIRS

Abbreviations: SIRS = systemic inflammatory response syndrome; MODS = multiple organ dysfunction syndrome; WBC = white blood cells.

Table 2.2. Diagnostic criteria for sepsis

Infection (documented or suspected) and some of the following parameters must be present:	
General parameters	(1) Fever ($>38^{\circ}C$), (2) hypothermia (core temperature $<36^{\circ}C$), (3) heart rate>90 beats/min or > than 2 SDs above the normal value, (4) tachypnea, (5) altered mental status, (6) significant edema or positive fluid balance (>20 mL/kg over 24 hours), (7) hyperglycemia (plasma glucose>140 mg/dL or 7.7 mmol/L) in the absence of diabetes
Inflammatory parameters	(1) Leukocytosis (white blood cell count >12 000/μL), (2) leukopenia (white blood cell count <4000/μL), (3) normal white blood cell count with >10% immature forms, (4) plasma C-reactive protein (CRP) > than 2 SDs above the normal limit, (5) plasma procalcitonin > 2 SDs above the normal limit
Hemodynamic parameter	(1) Arterial hypotension (SBP <90 mm Hg, MAP <70 mm Hg, or an SBP decrease of >40 mm Hg in adults or >2 SDs below normal for age
Organ dysfunction parameters	(1) Arterial hypoxemia (PaO_2/FiO_2 <300), (2) acute oliguria (urine output <0.5 mL/kg/h for at least 2 hours despite adequate fluid resuscitation), (3) creatinine increase >0.5 mg/dL or 44.2 μmol/L, (4) coagulation abnormalities (INR >1.5 or aPTT >60 s), (5) ileus (absent bowel sounds), (6) thrombocytopenia (platelet count <100 000/μL), (7) hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 μmol/L)
Tissue perfusion parameters	(1) Hyperlactatemia (>1 mmol/L), (2) decreased capillary refill or mottling

Abbreviations: SBP = systolic blood pressure; MAP = mean arterial pressure; SD = standard deviation; INR = international normalized ratio; aPTT = activated partial thromboplastin time.

In the pediatric population, the diagnostic criteria for sepsis are: (1) signs and symptoms of inflammation plus (2) infection with (3) hyper- or hypothermia (rectal temperature $>38.5^{\circ}C$ or $<35^{\circ}C$), (4) tachycardia (may be absent in hypothermic patients), and at least one of the following indications of altered organ dysfunction – (a) altered mental status, (b) hypoxemia, (c) increased serum lactate level, or (d) bounding pulses.

immunomodulatory molecules that have potent biologic effects and mediate an inflammatory response.

Tumor necrosis factor-α (TNF-α) is the most important cytokine in sepsis. Interleukin (IL)-1β has similar effects. The two stimulate the release of stress hormones, other cytokines (e.g., IL-2, IL-6, IL-8, IL-10), and other inflammatory mediators of sepsis (e.g., nitric oxide, lipoxygenase and cyclooxygenase metabolites, platelet activation factor, interferon-γ, and adhesion molecules). All of these interact in a complex fashion to effect the various changes to multiple organ systems.

The resulting sepsis, multiorgan system failure, and death were previously believed to be solely from an exaggerated, uncontrolled inflammatory response, known as "cytokine storm." But it is now thought that they also arise from subsequent immunosuppression – the result of an "injured" adaptive immune response. This state includes the alteration of neutrophil migration at multiple stages, as these cells become more rigid and sequestered in organs (limiting blood flow, causing tissue ischemia and multiorgan failure), as well as suppressed because of reduced TLR expression and signaling. Nitric oxide blocks

neutrophil migration and the interaction between leukocytes and endothelial cells. Likewise, peroxisome proliferator-activated receptor (PPAR)-γ contributes to neutrophil chemotaxis suppression. There is also evidence that gene expression of TNF-α and interferon-β stops with continued insult, necrosis, and infection. The initial release of, and exposure to, high levels of chemoattractants "desensitizes" G-protein-coupled receptor (GPCR) responsiveness, resulting in downregulation of GPCR cell surface expression. All of these effects show that the innate immune system seems unable to respond to continuous inflammatory stimuli, progressing to a dysfunctional stage and ending in an irreversible phase of sepsis and end-organ injury (Figure 2.1).

ETIOLOGY

Historically, antibiotic recommendations for therapy of sepsis and septic shock were based on coverage of gram-negative organisms. However, sepsis caused by gram-positive organisms is clinically identical to sepsis caused by gram negatives. After 1987, gram-positive bacteria became the predominant pathogens in most areas. In recent studies, 47% to 55% of sepsis cases were due to gram positives (e.g., *Staphylococcus aureus*, coagulase-negative staphylococci, *Streptococcus pneumoniae,* and enterococci), while gram negatives made up 38–51%. *Escherichia coli* has remained the most common gram-negative pathogen in community and nosocomial infections. *Staphylococcus epidermidis* has become the most common cause of nosocomial bacteremias, followed by *S. aureus*, enterococci, and *Candida* species. Infections caused by vancomycin-resistant enterococci (VRE), particularly *Enterococcus faecium* (resistant to ampicillin and aminoglycosides) and non-*albicans Candida* species have become more common. Gram-negative bacteria, including multidrug-resistant (MDR) *Pseudomonas aeruginosa,* extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, *Enterobacter* species and other plasmid-mediated AmpC β-lactamase producing bacteria, and *Acinetobacter* species, are increasing and becoming resistant to multiple antibiotics.

DIAGNOSIS

Sepsis should be considered when a patient displays symptoms and signs of systemic inflammation in response to infection. The diagnostic criteria are in Table 2.2. Prompt administration of empiric antibiotics is appropriate, but every attempt should be made to determine the source, microbiology, and pathophysiology of the infection so as to guide optimal management. Often, various underlying risk factors predispose individuals to infection with specific organisms. Some of these conditions and associated pathogens are in Table 2.3.

A thorough history and physical examination are crucial. Multiple cultures from suspected infected sites need to be obtained. All culture specimens should be delivered promptly to the microbiology laboratory. Gram staining should be done and read as soon as possible on specimens submitted for culture. Ideally, cultures should be obtained before starting antibiotics. Any significant delay (>45 minutes) in antimicrobial administration should be avoided. For clinically or hemodynamically unstable patients, antibiotics should be given immediately.

At least two sets of blood cultures from different sites should be obtained from all sepsis suspects. Each blood culture set consists of one aerobic and one anaerobic bottle. Typically, at least 10 mL of blood needs to be injected into each bottle to increase the likelihood of culturing pathogens. If an indwelling venous or arterial catheter is present, it is important to obtain additional cultures through each port, unless the device was just recently placed (<48 hours). If the culture set taken from the line becomes positive much earlier (>2 hours faster) than the one from the peripheral vein, then the vascular access site is more likely to be the source of infection. Quantitative cultures of the catheter and the peripheral blood may be used when seeking more evidence for or against catheter-associated infection. The catheter is the likely source if it has significantly more bacterial colonies versus the peripheral blood.

Sputum for culture can be spontaneously expectorated, induced with 3% saline, or obtained by nasotracheal, endotracheal, or transtracheal techniques. Specimens should have ≥25 polymorphonuclear cells and ≤10 squamous epithelial cells per low-power microscopic field to decrease the chance that the specimen is contaminated with upper airway flora. Semi-quantitative or quantitative cultures may be used for ventilator-associated pneumonia (VAP) diagnosis.

Urine should be obtained for culture when the suspected source of infection is the urinary tract. Clean-catch or straight-catheterization specimens are preferred. Urine that has been present in a closed collection system for more than 1 hour

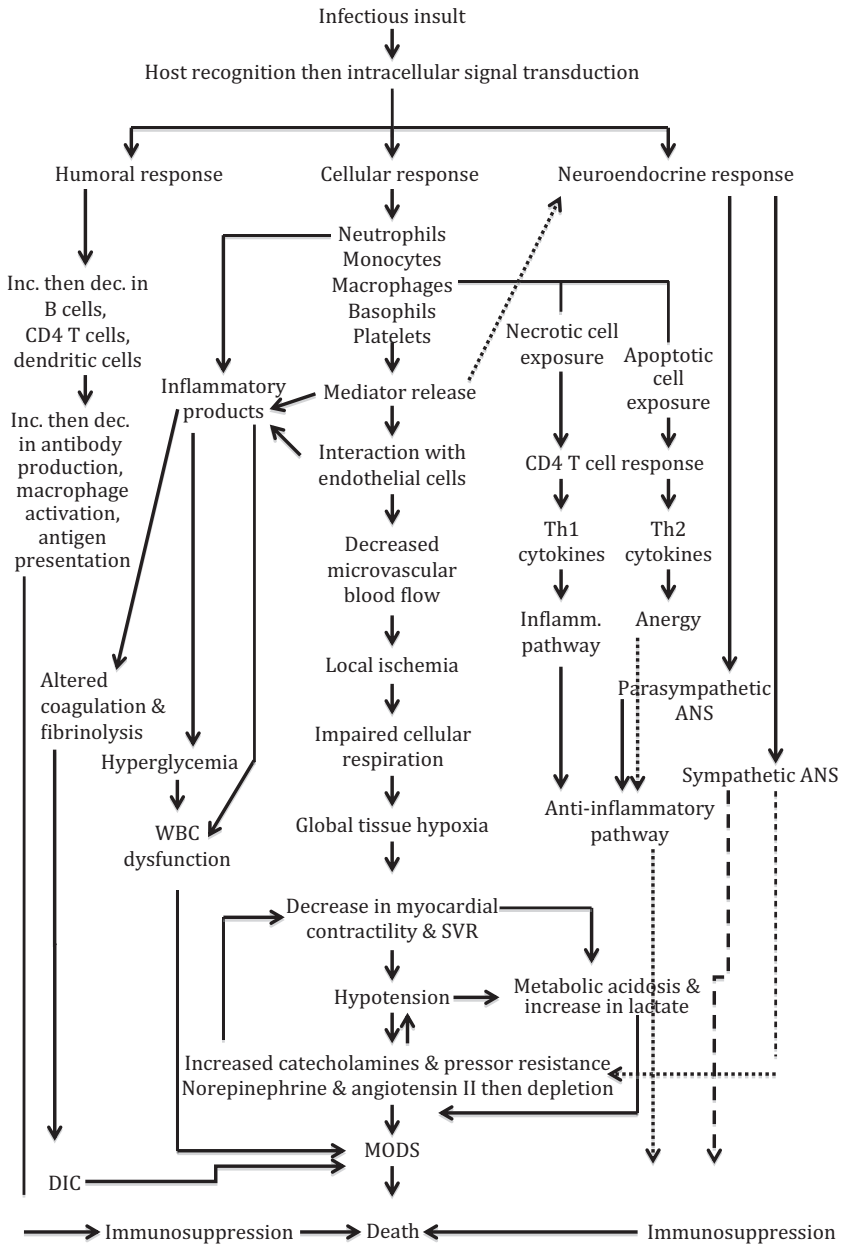

Figure 2.1
Comprehensive flow chart on the pathophysiology of severe sepsis/septic shock. Abbreviations: ANS = autonomic nervous system; dec. = decrease; DIC = disseminated intravascular coagulation; inc. = increase; inflamm. = inflammatory; MODS = multiorgan dysfunction syndrome; SVR = systemic vascular resistance; Th = T helper cell.

should not be sent for culture. If necessary, urine can be obtained directly from the catheter tubing or bladder (suprapubic aspiration) using a syringe and a small-gauge needle. Remember that many bacteriuric patients, especially those with indwelling urinary catheters, may be septic from another source. The presence of $\geq$100 000 bacteria/mL in urine culture suggests infection; however, this criterion has been validated only for ambulatory young women with gram-negative bacteria. Cultures from other sites should be obtained if clinically indicated.

Order an initial lactate at the Emergency Department (ED) and repeat it in 6 hours to compute the 6-hour lactate clearance (shown to be a predictor of mortality), since 36% clearance may be an appropriate resuscitation end point.

A novel method called endotoxin activity assay (EAA) measures the chemiluminescence

Table 2.3. Special circumstances in septic patients

Circumstance	Possible pathogens
Splenectomy (traumatic or functional)	Encapsulated organisms: *Streptococcus pneumoniae, Haemophilus influenzae*, and *Neisseria meningitidis*
Neutropenia (≤500 neutrophils/μL)	Gram-negatives, including *Pseudomonas aeruginosa*; gram-positives, including *Staphylococcus aureus*; fungi, especially *Candida* species
Hypogammaglobulinemia (e.g., CLL)	*Streptococcus pneumoniae, Escherichia coli*
Burns	MRSA, *Pseudomonas aeruginosa*, resistant gram-negatives, *Candida* species
AIDS	*Pseudomonas aeruginosa* (if neutropenic), *Salmonella* species, *Staphylococcus aureus, Pneumocystis jirovecii* (pneumonia)
Intravascular devices	*Staphylococcus aureus, Staphylococcus epidermidis*
Nosocomial infections	MRSA, *Staphylococcus epidermidis, Enterococcus* species, resistant gram-negatives, *Candida* species

Abbreviations: CLL = chronic lymphocytic leukemia; AIDS = acquired immunodeficiency syndrome; MRSA = methicillin-resistant *Staphylococcus aureus*.

of the enhanced neutrophil respiratory burst, a promising diagnostic test that might be useful in early severe sepsis because it may signal an increased risk of organ failure, especially if levels are persistently high in the first 48 hours.

When suspecting fungal sepsis, blood cultures and/or histopathologic evidence are considered gold standards, although blood cultures are rarely positive. Fortunately, other options are now available, such as 1,3 β-D-glucan (for invasive fungal infections, e.g., candidiasis and aspergillosis, plus *Pneumocystis jirovecii*), galactomannan antigen enzyme immunoassay (for both invasive aspergillosis and mycoses), serum capsular antigen for *Cryptococcus*, and urine polysaccharide cell wall antigens for *Histoplasma* and *Blastomyces*. Invasive pulmonary aspergillosis may be diagnosed using galactomannan antigen detection in bronchoalveolar lavage fluid. When positive, colonization should be distinguished from disease based on clinical features.

Depending on clinical suspicion, other lab tests may be useful. Rapid influenza antigen testing should be done during influenza season. In our institution, we prefer Influenza A and B, plus respiratory syncytial virus (RSV) PCR because processing time is just 6 hours, and the sensitivity and specificity of the tests are excellent. Inflammatory biomarkers, such as procalcitonin (PCT) and C-reactive protein (CRP) may have some utility to differentiate sepsis-associated inflammation versus other causes of generalized inflammatory states.

Computed tomography (CT) scan of the abdomen can reveal previously overlooked fluid collections that may be accessible by needle aspiration. Certain infections prevalent in intravenous drug users, such as epidural abscesses and psoas muscle abscesses, may be diagnosed by magnetic resonance imaging (MRI). Ultrasonography is useful for detecting ascites and biliary, hepatic, and pancreatic pathologic conditions. A portable (bedside) ultrasound can be obtained for critically ill patients who are too unstable to be transported to the radiology department.

Patients with diarrhea should have stool sent for *Clostridium difficile* toxin A and B identification, which used to be done using a cytotoxin assay. Enzyme immunoassay (EIA) testing for toxins A and B is faster but less sensitive. The two-step method of EIA to detect glutamate dehydrogenase then cell cytotoxicity assay or toxigenic culture for confirmation increases sensitivity. In our institution, we use *C. difficile* PCR to detect the toxins, which is much more sensitive and specific. Testing should only be done on symptomatic patients, since many are colonized.

A lumbar puncture for cell count, protein, glucose, bacterial antigens, Gram stain, and culture should be performed on septic patients with unexplained altered mentation or in meningitis suspects.

Despite the above, diagnosing sepsis is still not optimal. Studies have estimated that doctors were correct in diagnosing sepsis between 73% and 77% of the time. This unsatisfactory rate of diagnosis is why numerous biomarkers have been under investigation, with the hope of finding one that will assist clinicians in reliably distinguishing sepsis from other inflammatory conditions, and early enough to improve clinical outcomes.

CRP, cytokines, and chemokines (such as TNF and interleukins [ILs]), activated prothromboplastin time (aPTT), triggering receptor expressed on myeloid (TREM-1), and PCT are potential biomarkers for sepsis. CRP and PCT are the most widely used. TREM-1 appears to be more predictive of poor survival versus PCT and CRP in the ED. The latest meta-analysis on PCT as a sepsis biomarker (2013) gave it a sensitivity of 77% and specificity of 79%, which are lower than

previously believed. Using a cutoff between 1.0 and 2.0 ng/mL may help distinguish sepsis from other inflammatory conditions. Studies have shown that following PCT levels may be useful in reducing excessive antibiotic use by becoming a "marker" as to when antibiotics can be discontinued, particularly in initially septic patients who no longer have evidence of infection.

TREATMENT OF SEPSIS

Early goal-directed therapy (EGDT) emphasizes a timely and coordinated approach to sepsis management, with a significant mortality benefit when efforts are made for early diagnosis, risk stratification, fluid resuscitation, early administration of antibiotics and hemodynamic optimization, specifically within the first 6 hours of disease presentation. Throughout the years, studies have refined and improved EGDT, which should be initiated for hypotension despite an initial fluid challenge or when serum lactate is $\geq$4 mmol/L regardless of blood pressure.

The sepsis "bundles" (recommendations that when performed together produce improved outcomes) include interventions or lab tests to be done within 3 hours: serum lactate; blood cultures before starting antibiotics; starting broad-spectrum antibiotics; infusing 30 mL/kg of crystalloid fluids for hypotension or lactate $\geq$4 mmol/L. To be done within 6 hours are: starting vasopressors for hypotension that is unresponsive to initial fluid resuscitation, and aiming to maintain a mean arterial pressure (MAP) $\geq$65 mm Hg; measuring central venous pressure (CVP) or central venous oxygen saturation (S_{CVO2}) if there is persistent hypotension despite fluid resuscitation, and/or initial lactate $\geq$4 mmol/L (36 mg/dL); and repeating lactate if elevated initially.

Source control should be done early (within 12 hours of diagnosis), keeping in mind the risks and benefits of both surgical and medical interventions.

All these interventions are done to correct global tissue hypoxia that can lead to more severe stages of sepsis, and have been shown to improve outcomes and decrease healthcare resource utilization.

Antimicrobial therapy: selection and duration

Antibiotics form the cornerstone of therapy for sepsis. Outcome is improved if the diagnosis is suspected early and appropriate antibiotics are started without delay. Giving effective antimicrobials within the first hour of hypotension increases survival to hospital discharge in adults with septic shock. Each hour of delay beyond the initial 6 hours after the onset of hypotension is associated with an average decrease in survival of 7.6%; effective antimicrobials should be started within the first hour of severe sepsis or septic shock diagnosis. Empiric antibiotics should be active against likely pathogens, and should penetrate and reach good levels into the tissue that is considered to be the source of infection. Appropriate surgical intervention (surgical source control) often is as important as antibiotics.

Recommendations for empiric antibiotic therapy are in Table 2.4. A few principles are worth emphasizing. Antipseudomonal agents should be used for empiric therapy for nosocomial infection. Antibiotic dosages should be optimized for the site of infection, usually the highest allowable dosage adjusted for organ dysfunction. Intravenously administered antibiotics often result in higher serum and tissue levels than oral antibiotics, which should not be used for patients with compromised gut absorption. Community-acquired infections are likely to be caused by organisms different from those in the hospital. For example, *P. aeruginosa* is unlikely in community-acquired infections, with few exceptions (e.g., intravenous drug users); consequently, antipseudomonal coverage is not warranted routinely. In contrast, *Streptococcus pneumoniae* is one of the most common causes of community-acquired sepsis and should be covered adequately. Aminoglycosides offer rapid killing of gram-negative aerobic bacteria in a concentration-dependent fashion, and toxicity depends on the time that serum levels are above the toxicity threshold. The risk of nephrotoxicity and ototoxicity, the poor penetration of aminoglycosides into abscesses and lung parenchyma, and the lack of data to indicate that the addition of aminoglycosides affects outcomes in sepsis call for their judicious use. We suggest aminoglycosides be used as follows: (1) large single daily doses (e.g., 5 mg/kg of tobramycin daily) in hemodynamically unstable patients; (2) small doses (e.g., 1 to 1.5 mg/kg of tobramycin every 8 hours) when used for synergy against streptococcal and enterococcal infections; (3) use only in the first few days for empriric coverage of aerobic gram-negative bacteria, especially *P. aeruginosa*. Important potential advantages of combination therapy over monotherapy include a higher probability

Table 2.4. Recommended initial antibiotic regimens for septic patients with normal renal function[a]

Clinical situation	Regimen
Empiric coverage for nosocomial infections or neutropenia[b]	(Piperacillin–tazobactam[c] 4.5 g IV q6h) OR (cefepime 2 g IV q8h) OR (imipenem 0.5 g IV q6h or meropenem 0.5–1g IV q6h[d]), with or without an aminoglycoside (e.g., tobramycin[e,f] 5 mg/kg IV q24h) Add vancomycin 15 mg/kg IV q12h if with risk for MRSA (central venous catheter in place, other indwelling hardware, known colonization with MRSA, recent [within 3 months] or current prolonged [>2 weeks] hospitalization, transfer from a nursing home or subacute facility, IV drug use). A carbapenem may be preferable for gram-negative coverage in places where there is a high prevalence (e.g., >20%) of ESBL-producing organisms.
Community-acquired pneumonia[g]	(Ceftriaxone 1 g IV q24h or ampicillin–sulbactam 3 g IV q6h) plus azithromycin 500 mg IV or PO q24h or a fluoroquinolone (e.g., levofloxacin 750 mg or moxifloxacin 400 mg IV or PO qd)
Community-acquired urosepsis	(Ciprofloxacin 400 mg IV q12h or levofloxacin 750 mg IV q24h) OR (aminoglycoside, e.g., gentamicin 5–7 mg/kg IV q24h, with or without ampicillin 2 g IV q6h for *Enterococcus faecalis*) OR (ceftriaxone 1 g IV q24h, with or without ampicillin) OR ertapenem 1 g IV q24h (if with history of ESBL-producing organism)
Meningitis	Vancomycin 30–45 mg/kg divided into q12h–q8h plus ceftriaxone 2 g IV q12h (plus dexamethasone 0.15 mg/kg q6h for 2–4 days, with first dose 10–20 min. before, or at least concomitant with the first dose of antimicrobial in suspected or proven pneumococcal meningitis) Add ampicillin 2 g IV q4h if *Listeria* is a likely pathogen (e.g., elderly, neonates, immunosuppressed)
HIV+ with pneumonia[h]	Trimethoprim–sulfamethoxazole, 5 mg/kg IV q6h or pentamidine 4 mg/kg IV q24h, either with ceftriaxone 1 g IV q24h and with or without azithromycin 500 mg IV or PO q24h. When treating for *Pneumocystis* pneumonia, add prednisone (or equivalent) 40 mg PO q12h for room air $PaO_2 \leq 70$ mm Hg or alveolar–arterial gradient >35 mm Hg

Abbreviations: ESBL = extended-spectrum β-lactamase; HIV = human immunodeficiency virus; IV = intravenous; MRSA = methicillin-resistant *Staphylococcus aureus*.

[a] Antibiotics should be adjusted according to the microbiologic results.

[b] Antipseudomonal agents are recommended for empiric therapy of sepsis in neutropenic patients. Meropenem may be substituted for imipenem, particularly in the elderly, patients with renal failure, patients with seizure disorders, or patients with central nervous system infections.

[c] Recent literature has shown that increasing infusion time leads to better bacterial killing. We recommend infusing the initial dose over 30 min, and subsequent doses over 3 h.

[d] Imipenem dosage should be adjusted according to weight, age, and creatinine clearance. Same with meropenem, which should be given 1 g for high dose, non-meningitis cases and covering for *Acinetobacter baumannii* and *Pseudomonas aeruginosa*.

[e] Amikacin at 15 to 20 mg/kg/day can be substituted for tobramycin at institutions with significant bacterial resistance to tobramycin.

[f] Aminoglycosides should be used in patients with hemodynamic instability because of their rapid killing of bacteria and broad spectrum of activity against aerobic gram-negative organisms. Single daily dosing is recommended when feasible.

[g] A respiratory fluoroquinolone (levofloxacin, moxifloxacin, gemifloxacin) plus aztreonam are recommended for β-lactam allergic patients.

[h] Use the above recommendations for HIV-positive patients with CD4+ cell counts ≤200 cell/mm^3 when *Pneumocystis* is a likely pathogen; otherwise, cover the same as in community-acquired pneumonia without HIV. If Gram stain reveals gram-negative rods, antibiotics appropriate for *Pseudomonas aeruginosa* must be added.

that the infecting pathogen will be covered by at least one of the antimicrobials, a potential synergistic effect, and preventing the emergence of bacterial resistance.

The choice of antibiotic agents depends on multiple factors, including antibiotic penetration to, or efficacy at, the infected site (e.g., ceftriaxone, cefepime, and meropenem for meningitis, or avoidance of daptomycin for pneumonia), underlying medical conditions (e.g., avoidance of trimethoprim–sulfamethoxazole in renal failure, or not using imipenem for patients with seizure disorders), suspected organisms (e.g., carbapenems preferred for infections caused by ESBL and AmpC β-lactamase producing bacteria [the "SPICE" organisms: *Serratia, Providencia,* indole-positive bacteria such as *Proteus*, *Citrobacter,* and *Enterobacter* species] – bacteria with potential to become constitutive producers of β-lactamase; some references include *Acinetobacter baumannii* and *P. aeruginosa*), allergies, and hemodynamic instability (e.g., bactericidal agents preferred over bacteriostatic).

The incidence of nosocomial β-lactam-resistant gram-positive organisms has been increasing, and community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) infections are rising. The routine empiric use of an anti-MRSA antibiotic (e.g., vancomycin, linezolid, or daptomycin) is not advocated because of concerns about the emergence of VRE infections, except if

this pathogen is prevalent (>10–20% of all *S. aureus* isolates) in the community. Thus, physicians should be aware of the patterns of antimicrobial resistance in their place of practice.

Fungi account for 5% of all cases of severe sepsis or septic shock. Therefore, routine antifungal therapy is not recommended in sepsis, unless the patient is at high risk (e.g., neutropenic or post bone marrow transplant). In these patients, delaying antifungal coverage should be avoided. Macronodular skin lesions with biopsies consistent with candidal infection or candidal endophthalmitis are synonymous with dissemination. Because only a fraction of patients with systemic candidiasis will have positive blood cultures, a number of schemes have been developed to stratify the risk of systemic fungal infection in hospitalized patients. In general, when *Candida* species are isolated from three or more non-blood sites, the risk of subsequent infection of the blood by these fungi increases. Initiating therapy in such situations depends on the total clinical picture. In any case, the efficacy of azole antifungals (e.g., fluconazole) and their favorable toxicity profiles have made their empiric use more acceptable, especially in non-neutropenic patients. Nevertheless, a non-azole antifungal (e.g., caspofungin, micafungin) is preferred initially at institutions with high rates of azole resistance, for patients with recent azole exposure, for the moderately severe to severely ill, and for those at high risk for *Candida glabrata* or *Candida krusei*. Aside from echinocandins, lipid formulation amphotericin B is also recommended as first-line empiric therapy for neutropenics.

Duration of antibiotic therapy depends on the clinical response and, occasionally, the infecting pathogen. Recommended duration of antibiotic therapy is 7 to 10 days, but at the same time, ensuring that the patient has been afebrile for 48 to 72 hours, and with no more than one sign of clinical instability. A longer duration is required for patients slow to respond clinically, those with undrained foci of infection, *S. aureus* pneumonia or bacteremia (needs ≥14 days of antibiotic), fungal infections (e.g., candidemia will need 2 more weeks of therapy after documented clearance of *Candida* from the bloodstream) and less common pathogens (e.g., endemic fungi, *Burkholderia pseudomallei*, and even *P. aeruginosa*, since an 8-day course for nosocomial pneumonia had more relapses compared to a 15-day course), patients with *Pneumocystis jirovecii* pneumonia (who should receive 21 days of therapy), and neutropenic patients (those with an absolute neutrophil count [ANC] of ≤500 cells/mm^3) with fever (who should receive continuous antibiotic therapy for, at least, the duration that the patient is neutropenic, and until ANC becomes ≥500, which is a clear sign of marrow recovery, or as needed clinically). If a previously febrile neutropenic patient becomes afebrile and is no longer neutropenic, a shorter course of therapy can be considered. If adequate treatment had been given and a still-neutropenic patient no longer shows signs and symptoms referrable to infection, then therapy can be downgraded to oral fluoroquinolone prophylaxis.

Four weeks or more of antistaphylococcal antibiotic therapy are recommended if bacteremia with *S. aureus* is prolonged (>48 hours) or complicated (e.g., endocarditis [treated for 6 weeks or more], presence of implanted prostheses, repeat blood cultures still positive on specimens taken 2 to 4 days after the initial set, no defervescence of fever within 72 hours of starting effective antimicrobials, and with evidence of metastatic sites of infection).

Antibiotic decisions should be re-evaluated at least daily. Changes need to be considered as culture and susceptibility results become available or as the clinical course dictates. A patient who has not responded or who has relapsed after an initial improvement needs to be re-evaluated thoroughly. Additional diagnostic studies may be indicated, and repeat cultures should be obtained to search for new or resistant pathogens. If the clinical syndrome is determined to be noninfectious, antibiotics should be stopped.

The persistently febrile neutropenic patient presents an especially challenging problem. Empiric antifungal therapy should be started (and testing for invasive fungal infections should be done) if fever persists or is recurrent despite broad-spectrum antibiotic coverage for more than 4 to 7 days, and for febrile neutropenias expected to last more than 7 to 10 days. Pre-emptive therapy can also be done in high-risk neutropenic patients, which means the antifungal choice would be less broad and more targeted based on tests such as chest or sinus CT scans or 1,3-β-D glucan or serum galactomannan testing.

Poor decisions about antibiotic use have immediate and future negative consequences. Long-term antibiotics will not protect patients from infection; rather, this approach will select for resistant organisms. The best way to avoid

widespread resistance is to continuously re-evaluate the need for antibiotic therapy and to de-escalate when microbial susceptibility panels become available. In addition, side effects, such as rashes and *C. difficile* diarrhea, are much more common after long courses of multiple antibiotics.

Supportive therapy

Sepsis is a systemic disease, and proper management requires diligent and prompt attention to resuscitation and supportive care, particularly when multiorgan dysfunction is present. Our recommendation is to aim for normal perfusion parameters. Supernormal perfusion is not warranted and may be harmful. Crystalloids should be the first choice for fluid resuscitation, and used to maintain CVP at 8 to 12 mm Hg. Colloids are an alternative, although one type of colloid, called high-molecular-weight hydroxyethyl starch (HES), has been associated with acute kidney injury in severe sepsis. In trials, crystalloids were equivalent to HES or had fewer adverse outcomes (including mortality, acute kidney injury, and need for renal replacement therapy). Therefore, HES is not recommended in fluid resuscitation. Albumin should only be considered after a significant amount of fluids have been used.

Vasopressors should be added to aim for a MAP of $\geq$65 mm Hg to improve and maintain organ perfusion. Norepinephrine has emerged as the vasopressor of choice for septic shock. Epinephrine is the second choice, or is the next suggested pressor if the first one is not enough. Vasopressin is another add-on option, but should not be the sole or first vasopressor for septic shock. Dopamine has become the alternative, chosen when norepinephrine cannot be used, and given only to patients who have low risk of tachyarrhythmias and bradycardia.

If myocardial dysfunction is identified, or if there is persistent hypoperfusion and/or low MAP despite volume repletion, inotropic therapy with dobutamine (up to 20 μg/kg/min) should be instituted.

In the past, strict glucose control with levels below 150 mg/dL was the recommendation but more recent studies have disputed this and now there has been a shift away from intensive glucose control, with the new target being <180 mg/dL.

Other supportive therapies recommended and their basis for septic patients can be found in Table 2.5.

Adjunctive therapies

Recombinant human activated protein C (rhAPC) was approved by the US Food and Drug Administration (FDA) in 2001. However, studies showed lack of benefit in children, and in less severe forms of sepsis and septic shock in adults. Thus, it was withdrawn from the market.

Corticosteroids have anti-inflammatory and hemodynamic effects, so their use in sepsis has been studied extensively. Based on well-conducted studies, steroids are recommended in proven or suspected meningitis in children and adults, severe typhoid fever, late acute respiratory distress syndrome, moderate-to-severe *P. jirovecii* pneumonia in patients with acquired immunodeficiency syndrome, and in cases of documented adrenal insufficiency. In patients with septic shock and relative adrenal insufficiency (diagnosed as failure to increase serum cortisol level above 9 μg/dL after 250 μg of adrenocorticotropin), corticosteroids effected a 10% absolute reduction in 28-day mortality rate. However, the large CORTICUS European multicenter trial did not confirm any mortality benefit. Also, three systematic reviews did not consistently show a statistically significant decrease in mortality with the use of low-dose hydrocortisone in septic shock, but there was evidence that it was effective in more quickly reversing shock, with better outcomes only in the more severe cases. Thus, intravenous hydrocortisone (200 mg/day in divided doses or by continuous infusion) should only be used in adults who, despite adequate fluid replacement, require vasopressor therapy to maintain adequate blood pressure. Once the vasopressor has been weaned and stopped, the steroid dose must also be tapered before discontinuation.

CONCLUSIONS

The sepsis syndrome is incredibly complex, and the pathophysiology of the more severe forms may not be solely from an uncontrolled inflammatory response, but also from the compensatory anti-inflammatory and dysfunctional immune response. With the failure of therapies focused on curbing inflammation, more efforts are underway to see if countering the anti-inflammatory response will lead to better outcomes. For now, we must continue with our attempts to improve patient survival by aggressively diagnosing the cause of sepsis and promptly treating the syndrome with antibiotics, source control, and supportive/adjunctive therapy.

Table 2.5. Summary of current recommendations for supportive measures for severe sepsis/septic shock

Measure	Recommendations
Blood transfusion	-Transfuse for hemoglobin <7 g/dL, targeting 7 to 9 g/dL, unless with myocardial ischemia, severe hypoxemia, acute hemorrhage, or ischemic coronary artery disease -Transfuse platelet concentrate when counts are $<10\ 000/mm^3$ for non-bleeding patients, and when counts are $<20\ 000/mm^3$ for bleeding patients or those at high risk
Glucose control	-Use a protocol for severe sepsis (in the ICU); start insulin therapy after two successive blood glucose levels >180 mg/dL, and aim for ≤ 180 mg/dL
Sedation, analgesia and neuromuscular blockade	-Sedation should be minimized in mechanically ventilated patients -NMBAs should be avoided in non-ARDS patients; when needed, NMBAs should be given intermittently or continuously, but with train-of-four monitoring -Give only a short course of NMBA (not more than 48 h) for early ARDS secondary to sepsis with $PaO_2/FiO_2 <150$ mm Hg
Renal replacement therapy	-Use either intermittent hemodialysis or CRRT in severe sepsis with acute renal failure (the latter is preferred for hemodynamically unstable patients)
Bicarbonate therapy	-Not recommended to improve hemodynamic status or to decrease vasopressor requirements in lactic acidosis secondary to hypoperfusion with pH ≥ 7.15
Immunoglobulins	-Not recommended
DVT prophylaxis	-Use once-daily SC LMWH rather than $2\times$ or $3\times$/day UFH. Use dalteparin or another LMWH with a low degree of renal metabolism for creatinine clearance of <30 mL/min or UFH -May add intermittent pneumatic (or graduated) compression devices to the above, and should be used for any contraindications to heparin and its derivatives
Stress ulcer prophylaxis	-Use an H_2 blocker or PPI (preferred) for patients with risk factors for upper GI bleeding -Patients with no risk for gastric bleeding need not be given prophylaxis
Nutrition	-Oral or enteral route feeding is preferred in the first 48 hours (instead of complete fasting or IV glucose) -Instead of full caloric feeding in the first week, use low-dose feeding, and progress as tolerated -IV glucose and enteral feeding are preferred to TPN alone in the first week; another option is combining enteral and parenteral nutrition -Nutrition with no immunomodulating supplementation is preferred over nutrition with supplementation
Recombinant human activated protein C (rhAPC)	-Not recommended
Mechanical ventilation of ARDS secondary to sepsis	-Aim for a tidal volume (TV) of 6 mL/kg BW -Measure plateau pressures and initial upper limit should be ≤ 30 cm H_2O -PEEP should be used to prevent alveolar collapse at end expiration (higher PEEP for moderate to severe ARDS) -May use recruitment maneuvers for severe refractory hypoxemia -May use prone positioning in patients with $PaO_2/FiO_2 \leq 100$ mm Hg in institutions experienced with this method -Head of the bed in mechanically ventilated patients should be 30–45° to decrease aspiration and VAP risk -May use noninvasive mask ventilation (NIV) in some patients if benefits outweigh the risks -Use a weaning protocol so that mechanically ventilated patients (who are arousable, hemodynamically stable, off vasopressors, with no new serious conditions, low ventilatory and end-expiratory pressure requirements, and low FiO_2 requirements) will have regular spontaneous breathing trials to see if mechanical ventilation can be discontinued and patient extubated -Routine use of pulmonary artery catheter (PAC) not recommended -Use a conservative (rather than liberal) fluid strategy -Beta 2-agonists not recommended if without bronchospasm
Selenium	-Not recommended

Abbreviations: AKI – acute kidney injury; ARDS – acute respiratory distress syndrome; ARF – acute renal failure; AT – antithrombin; BW – body weight; CRRT – continuous renal replacement therapy; DVT – deep venous thrombosis; EPO – erythropoietin; FFP – fresh frozen plasma; GI – gastrointestinal; Hgb – hemoglobin; IV – intravenous; LMWH – low molecular weight heparin; NMBA – neuromuscular blocking agent; PE – pulmonary embolism; PEEP – positive end-expiratory pressure; PPI – proton pump inhibitor; RCT – randomized control trial; rhAPC – recombinant human activated protein C; SBT – spontaneous breathing trial; SC – subcutaneous; TPN – total parenteral nutrition; TV – tidal volume; UFH – unfractionated heparin; VAP – ventilator-associated pneumonia

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3. Chronic fatigue syndrome

N. Cary Engleberg

INTRODUCTION: NATURE OF THE SYNDROME

Chronic fatigue syndrome (CFS) is a syndrome of subjective complaints, most prominently featuring profound and prolonged physical exhaustion. Many experts suggest that this syndrome is the late-twentieth-century formulation of an illness that has been described under various designations in medical literature for centuries, such as *febricula* ("little fevers") in the eighteenth century, *neurasthenia* in the nineteenth century, and *myalgic encephalomyelitis* (ME), in Great Britain and Canada, or *chronic fatigue and immune dysfunction syndrome* (CFIDS), in the United States, during the late twentieth century. The designation *chronic fatigue syndrome* was adopted by the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) because this name does not assume a direct role for infection, inflammation, or immune system dysfunction in the genesis of the symptoms. Indeed, an abundance of research has failed to attribute the syndrome to any specific infection or immunologic disturbance. Nevertheless, CFS concerns infectious disease physicians because it is frequently recognized as a sequel of infection, i.e., as postviral or postinfectious fatigue.

The association of chronic fatigue and infection was first studied systematically in a study of chronic brucellosis. In a 1951 study, Wesley Spink found that 20% of patients with serologic evidence of brucellosis went on to develop persistent fatigue, muscle weakness, myalgia, mental confusion, and depression without evidence of ongoing infection with *Brucella*. He suggested that the symptoms of chronic brucellosis depended on both a previous *Brucella* infection and a psychological predisposition. Evidence for this theory was provided by investigators from Johns Hopkins during the Asian influenza pandemic of 1957–1958. During that epidemic season, these investigators conducted a retrospective cohort analysis of military personnel and their dependents who had completed the Minnesota Multiphasic Personality Inventory (MMPI) prior to the epidemic. Prolonged convalescence after influenza was associated with unfavorable scores on the test. Moreover, the MMPI profiles of subjects with prolonged postinfluenza symptoms were nearly identical to MMPI profiles of the previously studied patients with chronic brucellosis. This observation implies that the persistent fatigue and associated symptoms may reflect a programmed response to a variety of different infections in predisposed subjects.

Acute mononucleosis has also long been recognized as a precipitant of prolonged postinfectious fatigue. Consequently, when two large studies in 1985 reported an association between chronic fatigue and elevated titers of Epstein–Barr virus (EBV) antibodies, EBV became a leading candidate as the etiologic agent, and chronic mononucleosis became a popular designation for fatigue syndrome. As with other attempts to link CFS to a specific infectious agent, the association between active EBV and CFS was not confirmed by subsequent virologic studies. EBV infection is now best understood as one of the infectious precipitants of the syndrome rather than as a chronic infectious agent that is directly causative of the persistent symptoms. A recent prospective study of 301 adolescents diagnosed with infectious mononucleosis found that 13%, 7%, and 4% met criteria for pediatric CFS 6, 12, and 24 months after the onset of symptoms, respectively, regardless of whether steroids were used during the acute illness. Similarly, infections with enteroviruses, cytomegalovirus, Ross River virus, parvovirus, and human herpesvirus 6, *Borrelia burgdorferi*, *Coxiella burnetii*, *Candida albicans*, and *Giardia lamblia* have also been cited as potential triggering events. The notion that CFS is a direct consequence of chronic active infection with any of these agents is not supported by existing evidence. Studies are either inconclusive or definitively negative. Making a distinction between infection as an acute precipitant and as

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Table 3.1 Case definition of chronic fatigue syndrome

Clinically evaluated, unexplained chronic fatigue for more than 6 months' duration, which is not lifelong or the result of ongoing exertion and is not substantially alleviated by rest. The fatigue is associated with a significant reduction in occupational, educational, social, or personal activities.
PLUS
Four or more of the following concurrent symptoms:
Impaired memory or concentration
Sore throat
Tender cervical or axillary lymph nodes
Muscle pain
Generalized or migratory arthralgia
New headaches
Nonrestorative sleep
Prolonged postexertional malaise

Source: Fukuda *et al.*, 1994.

a chronic persistent cause of the syndrome is critical. It explains why attempts to treat the syndrome with antibiotics, antivirals, and antifungals have been uniformly disappointing.

In the absence of a simple etiology or a uniformly applicable diagnostic test for CFS, the NIH and the CDC proposed a consensus definition of the syndrome, intended to serve as a standard for future studies. Because fatigue is one of the most common complaints encountered in general medicine, the definition excluded patients with trivial or medically explainable fatigue states and captured those with illnesses that were characteristic of the syndrome. The 1994 definition of the syndrome (see Table 3.1) has been applied in most studies during the past decade, and it is used for clinical diagnosis in individual patients. However, there are problems with both specificity and sensitivity of a case definition of this kind. Because the syndrome consists of nonspecific, subjective symptoms, the case definition requires a minimal number of these symptoms. If the definition requires too few nonspecific symptoms, it will capture a collection of fatiguing disorders with more than one etiology and/or pathophysiology, a situation that will confound the interpretation of research findings. Alternatively, as the number of symptoms required for defining CFS increases, the definition captures an increasing proportion of patients with somatization disorder. Clinicians who use the case definition for diagnosis face an additional problem. The case definition may formally exclude patients whose illness closely resembles that of the defined cases and who may suffer the same pathophysiology. The authors of the CFS criteria recognized this problem and stipulated that fatigue lasting 6 months but not associated with the required number of associated symptoms should be designated as idiopathic chronic fatigue. Many of those in this category and those whose CFS is as defined in Table 3.1 may have the same disorder. Thus, rigid application of the CFS criteria (e.g., requiring 6 symptomatic months) may exclude patients who might profit from an early intervention.

EPIDEMIOLOGY

Idiopathic chronic fatigue is very common (5%–10% of patients in general medical practice), but very few (≤1%) can be diagnosed with CFS using the 1994 criteria. The US national prevalence of CFS was estimated by the CDC through a network of physicians in four American cities. The prevalence ranged from 3 to 11 per 100 000 population, and the gender and age distribution were similar in all four sites. Most patients were female (7:1) in the fourth and fifth decades of life. Estimates from clinic-based studies in Australia and the United Kingdom yield similar results. However, a population-based survey in San Francisco and other community-based studies elsewhere suggest a prevalence of about 0.2%, with a larger proportion of males, ethnic minorities, and those of lower socioeconomic classes. The discrepancy between community- and clinic-based studies is attributable to the greater utilization of clinical services by middle- and upper-class women. It belies the notion of a "yuppie flu," a pejorative term applied to this disorder in the past.

Illnesses consistent with CFS also occasionally occur in epidemic fashion. In some instances, the outbreaks may be associated with an infectious event; however, in others, the distribution of illness among the populations at risk clearly does not resemble the spread of an infection. Examples of the latter type include the large hospital-based outbreaks in Los Angeles, California, and London, UK, that affected the hospital professional staff but not the hospitalized patients or nonprofessional staff.

PATHOPHYSIOLOGY

Research on the pathophysiology of CFS has been complicated by the definitional problems described above; most importantly by the problem of selecting a homogenous group of subjects for study who have symptoms that are

attributable to the same cause or causes. Many patients have an acute onset of the syndrome. A small proportion can be traced to a diagnosed infectious disease; more often this is presumed based on the history but cannot be confirmed. CFS may also follow other physically and psychologically stressful events, such as surgeries, accidents, deaths, and divorces. Many patients have an insidious onset with no definite precipitating event. Regardless of the onset, the majority of patients have past or current psychiatric disorders, but a large minority has no active or past psychiatric symptoms.

Numerous infections have been associated with CFS, but evidence that the syndrome is not associated with any specific infectious agent is of three main types. First, there is no single infectious agent that is detectable in all cases of CFS; the disorder may occur even in the absence of the most common agents, such as EBV. Second, the development of the same syndrome occurs during convalescence after infections with non-overlapping geographic distribution (e.g., Ross River virus, Q fever, or Lyme disease). Third, attempts to treat CFS with anti-infectives have been uniformly disappointing. It may be true that only a specific type of infection with prolonged duration or severity is necessary to precipitate CFS. Indeed, patients seen in general practice for common, simple infections do not have an increased frequency of prolonged fatigue relative to patients seen for other medical problems. However, postinfectious cases and those with no apparent precipitant are clinically indistinguishable with respect to symptoms and psychosocial features once the defining criteria are met. These observations lead to the conclusion that the syndrome is a nonspecific sequel to a variety of infections or other precipitants. Whether patients who have CFS will reactivate latent viruses more frequently than well individuals is an unsettled issue, but no correlation between viral reactivation (e.g., EBV) and the expression of symptoms has been demonstrated.

From time to time, sensational reports appear linking a persistent infectious agent with the syndrome, as in 1985 with EBV. The latest of these events occurred in late 2010 when an article appeared in *Science* reporting the presence of a xenotropic murine retrovirus (XMRV) in two-thirds of a panel of CFS patients and only ~4% of controls. The putative presence of this virus was later shown to be due to contamination of samples with mouse DNA, and the original article supporting the claim was subsequently retracted. Clinicians should maintain skepticism about claims of this kind, since the attribution of CFS to a single transmissible agent is not easy to reconcile with the clinical and epidemiologic features described above.

Apart from infections, disruptions in various biologic systems associated with CFS have been proposed as inciting or perpetuating factors. These include subtle alterations in immunologic, neuroendocrine, and neuropsychological function. Attempts to correlate cytokine levels with the presence or severity of CFS have been inconsistent. However, interferons are known to activate expression of the enzyme 2′,5′-oligoadenylate synthetase. This enzyme generates 2′,5′-adenylate oligonucleotides that bind to and activate RNAse L, leading to the cytoplasmic degradation of viral and other RNAs. CFS is associated with increased levels of 2′,5′A oligonucleotides, RNAse L activity, and the expression of a low-molecular-weight RNAse L molecule. The pathophysiologic significance of this phenomenon is uncertain, but measurement of this pathway has been suggested as a potential biologic marker for CFS.

The hypothesis that the central nervous system is the principle site of the pathophysiology in CFS has gained support in recent years. This hypothesis is bolstered by the presence of neuropsychological symptoms in the active syndrome, the observation of prior or pre-existing psychiatric disorders in a large proportion of patients, and subtle alterations of hormones regulated at the hypothalamic level. Previous or concurrent depression is frequently present in CFS. When patients in general practice are evaluated for "viral" illnesses, the psychiatric morbidity and the patient's belief structure concerning the illness are better predictors of subsequent chronic fatigue than the severity of symptoms at the time of presentation. More objective evidence of central nervous system involvement includes the observed disruption of the hypothalamic–pituitary–adrenal (HPA) axis. As a group, patients with CFS appear to have lower HPA axis activity than age- and gender-matched controls. Most evidence points to the hypothalamus as the affected element of the axis; however, it is not known whether this defect is primary or secondary to inactivity, sleep disruption, or continuing stress accompanying CFS. Nevertheless, the decreased HPA activity in CFS contrasts with the increased activity of the HPA axis observed in patients with major depressive disorder. It is more consistent with findings in post-traumatic

stress disorder (PTSD), suggesting that CFS may represent a dysfunctional capacity to respond to both physical and psychological stress, either acquired or genetic or both.

Some evidence for a genetic predisposition to CFS has been generated by twin studies. Studies in the United States, Australia, and Great Britain have shown an increased concordance in monozygotic, rather than dizygotic, twins. However, a microarray analysis of the transcriptome of monozygotic twins who are discordant for CFS failed to show any significant differences. These observations and the other findings mentioned above support a pathophysiologic theory of CFS that depends on a predisposition involving genetic or environmental factors or both. In the presence of an acute provocation, such as an infection, the stress response system fails and results in both the production and perpetuation of subjective symptoms (i.e., fatigue, pain, disrupted sleep, poor cognition) and detectable immune alterations.

DIAGNOSIS

CFS is a clinical diagnosis that depends almost entirely on the history and the patient's report of symptoms. There are no characteristic clinical signs. There are no laboratory tests that can be used with any reliability to rule in or rule out the diagnosis. The purpose of the physical examination and basic laboratory testing is to confirm that there is not another medically definable condition that may be causing the symptoms. In the absence of any confounding medical conditions, the diagnosis of CFS may be guided by the published consensus criteria. For reasons explained above, the clinician need not apply these criteria stringently for individual patients.

In postinfectious fatigue, the chronic symptoms may appear to be an extension of the inciting infection. Most often, there is no identifiable precipitating event, and the same flu-like symptoms develop gradually. They include sore throat, low-grade fever, tender cervical lymphadenopathy, generalized myalgia or arthralgia, headache, sleep disturbances, and a perception of impaired cognition. Objective physical findings accompanying these symptoms (e.g., pharyngeal erythema or exudate, fever greater than 100.5°F, muscle weakness, signs of arthritis, or enlarged lymph nodes) are rare. The presence of any of these signs should raise suspicion of an alternative diagnosis.

The cardinal symptom of the syndrome is persistent and disabling fatigue, and the fatigue has several characteristic qualities. Most importantly, it is unrelenting and of long duration (>6 months according to the CDC/NIH criteria in Table 3.1). It is not improved by rest but worsens after physical exertion. Postexertional malaise may persist for hours to days after even a modest expenditure of effort. Many patients perceive a limited allotment of energy to expend each day, and once it is used, they cannot function.

Most patients describe impaired concentration and poor short-term memory. Standard neuropsychological testing typically shows no evidence of an organic syndrome and need not be ordered unless there is objective evidence for cognitive or memory deficit on physical examination. This problem may be the most alarming for the patient who fears a loss of intellectual function; however, such patients can be reassured that the "mental fog" that they experience will lift as the physical symptoms improve.

Most patients will also report either insomnia or excessive sleep. A thorough sleep history is important, because many primary sleep disorders present with chronic fatigue as the chief complaint. If there is a suspicion of sleep apnea or a nocturnal movement disorder, a formal polysomnography is indicated. Similarly, many patients will have symptoms of depression or anxiety. The clinician must determine whether these symptoms are reactive to CFS, or primary, accounting for all of the patient's symptoms. If all of the symptoms can be attributed to major depression or anxiety, then a diagnosis of CFS is excluded.

A laboratory evaluation should exclude unrecognized medical conditions. All patients should have a complete blood count, a chemistry profile, urinalysis, and thyroid function testing. Additional testing may be ordered to rule out other specific medical conditions if the history or physical examination is suggestive. However, certain laboratory tests may be nonspecifically abnormal in patients with CFS. For example, 15% to 54% of patients may have a low-titer antinuclear antibody test. This is usually nonspecific, and anti-DNA antibodies and antibodies to extractable nuclear antigens are typically absent. Patients with CFS are more likely than healthy controls to have small areas of increased single intensity by brain MRI. These are usually nonspecific and easily distinguished from plaques of demyelinating disease. Urinary free cortisol levels may be relatively low in CFS, but this finding is not reliable enough to be of any diagnostic value.

Hormonal testing, other than thyroid-stimulating hormone, should be ordered only when a particular disorder is suspected. Similarly, measurement of the 2′,5′-oligoadenylate synthetase pathway can be ordered from some commercial laboratories. Although opinions differ about the value of these tests, this author finds them insufficiently sensitive and specific to be useful. EBV serologies are uninformative, both for diagnosis and follow-up of CFS.

CFS often overlaps or coexists with other common idiopathic disorders. Patients with CFS may also meet diagnostic criteria for fibromyalgia, irritable bowel syndrome, interstitial cystitis, premenstrual syndrome, migraine, restless leg syndrome, neurally mediated hypotension or postural orthostatic tachycardia, atypical depression, or spastic dysphonia. The pathophysiologic relationship between these entities and CFS is unclear, but it is important to identify these coexisting disorders, because they often respond to treatments that are not necessarily appropriate for use in CFS alone.

TREATMENT

Guiding principles

At present, the pathophysiology of CFS is not sufficiently understood to inform specific therapy. Consequently, specific medical or psychiatric therapy is indicated only when there is an alternate or coexisting diagnosis. There is no rationale for treating infectious agents unless there is clear evidence of an active infection that is producing symptoms. Antivirals and other anti-infective agents are not of value in treating the symptoms of CFS.

In the absence of specific therapy for CFS, treatment should be focused on the remediation of symptoms, nonpharmacologic interventions, and physical rehabilitation. There are only a few treatment modalities that can be recommended based on consistent efficacy demonstrated in well-designed, controlled studies (Table 3.2). Because evidence-based information is inconclusive, clinicians must use their own judgment when using empirical, symptomatic therapies based on the patient's complaints and their own comfort when prescribing the medications. Several other treatments have been proposed, but a preponderance of studies suggests that they are unhelpful or potentially harmful (Table 3.2). Clinicians should also be aware that there is typically a robust placebo effect in trials with CFS patients; therefore, treatment trials that lack appropriate control groups are uninterpretable.

Table 3.2 Treatments for chronic fatigue syndrome

Therapies supported by several randomized controlled trials	Graded exercise program Cognitive-behavioral therapy
Empiric, symptomatic treatments	Nonnarcotic pain relievers Antidepressants Sleep hygiene Sleep aids
Controversial treatments not supported by a consensus of experimental data and not recommended	Anti-infectives Hydrocortisone Galantamine Fludrocortisone Dehydroepiandrosterone (DHEA) IV immunoglobulin Interferons Nutritional supplements and vitamins Restrictive diets

When initiating treatment, it is useful to objectify the symptoms as much as possible. Patients should be asked to rate their symptoms and to keep personal logs so that their response to any treatment can be assessed. This approach is consistent with the principles of one of the known effective treatments, cognitive-behavioral therapy (CBT). Therapeutic interventions should be initiated sequentially so that their positive and negative effects can be assessed. In addition, it is especially important to document unconventional or alternative therapies, because many patients may resort to using these products. Polypharmacy, including alternative treatments, may confuse the patient's ability to assess their response to any particular treatment that may be prescribed. In general, the empirical use of allopathic medications and the patient's experimentation with alternative therapies should both be guided by concerns for safety and cost, and empirical trials of treatment should be undertaken systematically in a manner that allows the patient and the doctor to assess the value of the intervention.

Therapies with demonstrated efficacy

Several studies have demonstrated that graded aerobic exercise is helpful in reducing the symptoms of CFS. A program of exercise tailored to the individual patient's tolerance should be a part of any treatment effort. The form of exercise should be aerobic and quantifiable. An approach that targets a specified exercise duration is likely to

give the best results. The patient should exercise for 5 to 15 minutes at home five times a week and gradually increase the duration up to 30 minutes. A series of physical therapy visits will provide supervision. Adherence to such a program usually requires substantial oversight by the physician and physiotherapist, especially among patients who experience serious postexertional fatigue. In contrast, there is no evidence to support the prescription of bed rest and some suggestion that continuous inactivity may both reinforce illness behavior and lead to complicating myofascial pain syndromes.

CBT is helpful for symptom control in a variety of organic diseases, so it is not surprising that it also benefits CFS patients. CBT involves a restructuring of the patient's beliefs about the illness and encourages objective assessment of the symptoms and disabilities. With ~50% of patients in CBT experiencing substantial improvement in fatigue, this modality appears to be the most efficacious and cost-effective approach to treatment compared with other nonpharmacologic methods. One innovative approach developed by a Dutch research group used an internet-based CBT program for treating adolescents and found it more effective for increasing school attendance than a treatment program based in a tertiary care center. Unfortunately, CBT is not universally available; however, the physician can integrate some of the principles into routine medical care. Educating the patient about the causes and manifestations of CFS is critical, particularly when there are misconceptions that may lead to counterproductive behaviors. Having the patient objectify their symptoms and identify factors that exacerbate or relieve them may also be helpful in management. A rational and sympathetic approach to the patient is essential. Challenging the reality of symptoms or attributing them to some other cause (e.g., depression in the absence of standard criteria) is distinctly unhelpful because these ideas will not be consistent with the patient's own experience and beliefs. Similarly, classical insight-oriented psychotherapy should be reserved for those patients who have significant emotional stress.

Empirical treatment of symptoms

Certain medications may be useful for symptomatic therapy in selected patients. Nonnarcotic pain relievers for myalgia, arthralgia, or headache may be helpful. Some combination of nonsteroidal anti-inflammatory medications, acetaminophen, and tramadol may improve symptoms in some patients with prominent pain symptoms.

Although studies conflict on the value of antidepressant therapy, there are two rationales for their use in selected patients: (1) certain antidepressants are generally considered effective treatment (e.g., for mood disturbances, anxiety, insomnia, pain, poor concentration) and (2) CFS and fibromyalgia frequently coexist or have substantial symptom overlap, and a benefit of tricyclic antidepressants and similar medications has been demonstrated in fibromyalgia. It should be noted that studies that show benefit of these agents in CFS generally report relief of the associated symptoms noted above rather than the cardinal symptom – fatigue. Therefore, a particular antidepressant may be favored for a given patient depending on the intensity of these symptoms. The remarkable safety profile of antidepressants makes them a reasonable choice for an empirical trial.

Many CFS patients also suffer from sleep disturbances. Pharmacologic sleep aids (e.g., eszopiclone, zolpidem, clonazepam) may be helpful short term but risk creating dependency. Various antidepressants (e.g., low-dose trazadone or amitriptyline) may be better suited for long-term use. Melatonin is a popular over-the-counter sleep remedy, but CFS patients have normal levels and timing of endogenous melatonin secretion. A trial of high-dose melatonin improved CFS symptoms in patients with delayed melatonin secretion; however, the trial used historical controls and must be interpreted with caution.

Perhaps as important as pharmacologic agents is some attention to sleep hygiene. All patients should be instructed to keep regular sleep hours. Patients who are sleeping excessively should be encouraged to reduce their hours of sleep gradually. Those with insomnia should be encouraged to reduce daytime napping to less than 1 hour a day.

Controversial or contraindicated therapies

Several specific therapies for CFS have been tried based on a particular pathophysiologic hypothesis. Up to the present, none of these therapies has been shown to have meaningful benefit. As suggested in the pathophysiology section above, a carefully conducted trial of antiherpesvirus therapy with acyclovir to test the hypothesis that EBV replication is associated with ongoing symptoms failed to show any benefit. Similarly, a randomized therapeutic trial of oral nystatin

was conducted to assess the effect on CFS-like symptoms in patients who claimed to have yeast hypersensitivity. The only benefit was a slight reduction in *Candida* vaginitis in the treatment group.

The finding of depressed HPA axis activity prompted a trial of low-dose hydrocortisone and subsequently a trial of galantamine (to stimulate HPA axis activity centrally). Investigators judged that the bone mineral loss and prolonged suppression of the HPA axis that resulted from hydrocortisone therapy was not justified by the minimal benefit gained by treatment. The study of galantamine showed no substantial benefit. Another neuroendocrine hypothesis involves the hormone dihydroepiandrosterone (DHEA). DHEA supplementation in CFS has reportedly improved fatigue and other symptoms in patients with depressed levels of this enzyme at baseline; however, there has been no controlled trial of this treatment, and it should be regarded skeptically. A study connecting neurally mediated hypotension (diagnosed by a 45-minute tilt table protocol) with CFS prompted therapeutic trials of volume expansion with fludrocortisone. Two independent studies showed no significant benefit of this approach.

Using a model of immune dysfunction as a key factor in the production of CFS symptoms, immune modulation with immunoglobulins, and interferons has been studied. One study used rituximab and reported positive results. These therapies are extremely costly, inconvenient, and potentially harmful so the effects should be reproducible and the benefits should outweigh the negative factors. In fact, the preponderance of evidence shows no benefit associated with the use of intravenous immunoglobulin, and studies with interferon are contradictory. Other therapies that have been ineffective or conflicted in randomized controlled trials include the thiamine precursor, sulbutiamine, growth hormone, homeopathic preparations, and essential fatty acids.

Occasionally, patients report relief of symptoms with specialized dietary alterations. A common example is the restrictive diet recommended to reduce intestinal "yeast." There is no experimental evidence to support these diet therapies in CFS, and highly restrictive diets may impair nutrition and general health. Trials of nutritional supplements (e.g., vitamins, liver extract) have also been discouraging. Two small trials of activated NADH showed some benefit, but both can be criticized on methodologic grounds.

Physicians should be aware that there is a lucrative internet market catering to desperate patients with CFS whose primary care physicians are dismissive. Most of the on-line sales involve unproven supplements and remedies. Many are very expensive (such as replacement of all amalgam dental fillings) and some may be hazardous (such as various hormones and ephedra). Some patients with CFS are motivated to take risks and to spend abundantly from their personal resources to achieve relief from their suffering. Sympathetic physicians should attempt to guide patients through this "medicine show" and to protect them from financial exploitation or harm.

SUMMARY

CFS may occur spontaneously or as a result of an acute stressor, such as an infection. However, there is no evidence that a chronic infection is the cause of the chronic symptoms. Diagnostic criteria have been established by expert consensus in an attempt to standardize research on this disorder. Diagnosis based on the patient's subjective report, physical examination, and laboratory tests are useful only to rule out confounding medical conditions. Medical treatments directed at specific symptoms may be helpful in individual patients. Treatments based on a pathophysiologic hypothesis of the disorder have been uniformly disappointing. Consequently, the most important elements of care include (1) educating the patient with restructuring of beliefs and perceptions of the illness, (2) initiating a graded exercise program, (3) evaluating symptomatic treatments, and (4) protecting the patient from physical or financial harm associated with unproven therapies.

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PART II

Clinical syndromes: head and neck

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4. Pharyngotonsillitis

Itzhak Brook

Pharyngotonsillitis (PT) is an inflammation of the pharynx and tonsils characterized by the presence of increased pharyngeal and tonsillar redness and finding of an exudate, ulceration, or a membrane covering the tonsils. Because the pharynx is served by lymphoid tissues of the Waldeyer ring, an infection can spread to include various parts of the ring such as the nasopharynx, uvula, soft palate, tonsils, adenoids, and the cervical lymph glands. Based on the extent of the infection, it can be described as pharyngitis, tonsillitis, tonsillopharyngitis, or nasopharyngitis. The duration of any of these illnesses can be acute, subacute, chronic, or recurrent.

ETIOLOGY

The diagnosis of PT generally requires the consideration of group A β-hemolytic streptococci (GABHS) infection. However, other bacteria, viruses, and other infections and noninfectious causes should be considered. Recognition of the cause and choice of appropriate therapy are of utmost importance in assuring rapid recovery and preventing complications.

Table 4.1 lists the different causative agents and their characteristic clinical features. The occurrence of a certain etiologic agent depends on multiple variables that include environmental conditions (season, geographic location, exposure) and individual variables (age, host resistance, and immunity). The most prevalent agents accounting for PT are GABHS, adenovirus, influenza virus, parainfluenza virus, Epstein–Barr virus (EBV), and enterovirus. However, the exact etiology is generally not determined and the role of some potential pathogens is not certain.

Recent studies suggested that interactions between various organisms, including GABHS, other aerobic and anaerobic bacteria, and viruses, may occur during PT. Some of these interactions may be synergistic (i.e., between EBV and anaerobic bacteria), thus enhancing the virulence of some pathogens, whereas others may be antagonistic (i.e., between GABHS and certain "interfering" α-hemolytic streptococci). Furthermore, β-lactamase-producing bacteria (BLPB) can protect themselves as well as other bacteria from β-lactam antibiotics.

Aerobic bacteria

Because of the potential of serious suppurative and nonsuppurative sequelae, GABHS are the best known cause of sore throat. Occasionally non groups B, and large colony C, and G β-hemolytic streptococci are responsible. However, the other groups are generally not associated with acute rheumatic fever.

The clinical presentation of PT is generally identical for all groups and is characterized by exudation, palatal petechiae, follicles, tender cervical adenitis, and scarlet fever rash. What are generally absent are the classical signs of viral infections such as cough, rhinitis, conjunctivitis, and diarrhea.

There is no symptom or single sign that reliably identifies GABHS pharyngitis. Symptoms in children younger than 3 years of age are atypical and include nasal congestion and discharge, low-grade fever, and tender anterior cervical lymph nodes. GABHS should be suspected in the presence of abrupt onset of fever in a child older than 3 years (with or without "sore throat"), higher temperature, ill appearance, headache, neck muscle pain, tenderness, abdominal pain, nausea, or vomiting, flushed cheeks, circumoral pallor, palatal "petechiae" and semicircular red marks, early strawberry tongue and/or scarlatiniform rash, a history of exposure to the organism, winter season, and the presence of a peculiar, sour-sweet, yeasty breath odor.

The isolation rate of GABHS varies with patient age, with the highest prevalence in school years (15%–30% of all PT). The isolation rate of non-GABHS is higher in adults than in children.

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Table 4.1 Infectious agents of pharyngotonsillitis

I. Bacteria	Clinical lesions	Clinical frequency
Aerobic		
Groups A, B, C, and G streptococci	F, Er, Ex, P	A
Streptococcus pneumoniae	E	C
Staphylococcus aureus	F, ER, Ex	C
Neisseria gonorrhoeae	Er, Ex	C
Neisseria meningitidis	Er, Ex	C
Corynebacterium diphtheriae	Er, Ex	C
Arcanobacterium haemolyticum	Er, Ex	C
Bordetella pertussis	Er, Er	C
Haemophilus influenzae	Er, Ex	C
Haemophilus parainfluenzae	Er, Ex	C
Salmonella typhi	Er	C
Francisella tularensis	Er, Ex	C
Yersinia pseudotuberculosis	Er	C
Treponema pallidum	F, Er	C
Mycobacterium spp.	Er	C
Anaerobic		
Peptostreptococcus spp.	Er, E	C
Actinomyces spp.	Er, U	C
Pigmented *Prevotella* and *Porphyromonas* spp.	Er, Ex, U	B
Bacteroides spp.	Er, Ex, U	C
II. Mycoplasma		
Mycoplasma pneumoniae	F, Er, Ex	B
Mycoplasma hominis	Er, Ex	C
III. Viruses and *Chlamydia*		
Adenovirus	F, Er, Ex	A
Enteroviruses (Polio, Echo, Coxsackie)	Er, Ex, U	A
Parainfluenzae 1–4	Er	A
Epstein–Barr	F, Er, Ex	B
Herpes hominis Human immunodeficiency virus	Er, Ex, U F, Er, Ex	C C
Respiratory syncytial	Er	C
Influenzae A and B	Er	A
Cytomegalovirus	Er	C
Reovirus	Er	C
Measles	Er, P	C
Rubella	P	C
Rhinovirus	Er	C
Chlamydia trachomitis	Er	C
IV. Fungi		
Candida spp.	Er, Ex	B

V. Parasites		
Toxoplasma gondii	Er	C
VI. Rickettsia		
Coxiella burnetii	Er	C

Abbreviations: Clinical lesions: F = follicular, Er = erythematous, Ex = exudative, U = ulcerative, P = petechial; Frequency: A = most frequent (more than 66% of cases), B = frequent (between 66% and 33% of cases), C = uncommon (less than 33% of cases).

There was a marked decrease in the incidence of acute rheumatic fever in the United States over the past 50 years that is correlated with the replacement of rheumatogenic types by nonrheumatogenic types. However, streptococcal tonsillitis is still a potential serious illness because rheumatic fever still occurs, and GABHS is manifesting increased virulence. More cases of sepsis, pneumonia, and toxic shock syndrome due to streptococci have been observed in recent years. Streptococci can be involved in suppurative complications of tonsillitis such as peritonsillar and retropharyngeal abscesses.

Streptococcus pneumoniae can also be involved in PT that can either subside or spread to other sites.

Corynebacterium diphtheriae can cause a "bull neck," as can *Arcanobacterium hemolyticum*, and both can cause an early exudative PT with a grayish-green thick membrane that may be difficult to dislodge and often leaves a bleeding surface when torn off. The infection can spread to the throat, palate, and larynx. It is rare in developed countries where children are vaccinated against it. *Arcanobacterium hemolyticum* produces a lethal systemic exotoxin.

Arcanobacterium hemolyticum incidence of causing PT is 2.5% to 10%, and occurs mostly in 15- to 18-year-old individuals, and about half of the patients have a scarlatiniform rash.

Neisseria gonorrheae is common in homosexual males and can be detected in sexually active adolescents with pharyngitis. The infection is often asymptomatic but can exhibit ulcerative or exudative pharyngitis, may result in bacteremia, and can persist after treatment. *Neisseria meningitidis* can cause symptomatic or asymptomatic PT that can be a prodrome for septicemia or meningitis.

Nontypeable *Haemophilus influenzae* and *Haemophilus parainfluenzae* can be recovered from inflamed tonsils. These organisms can cause invasive disease in infants and elderly persons, as well as acute epiglottitis, otitis media, and sinusitis.

Staphylococcus aureus is often recovered from chronically inflamed tonsils and peritonsillar abscesses. Methicillin-resistant *S. aureus* (MRSA) was isolated from 16% of recurrently infected tonsils. It can produce the enzyme β-lactamase that may interfere with the eradication of GABHS. High tissue concentration of *H. influenzae, S. aureus*, and GABHS correlates with recurrent infection and hyperplasia of the tonsils.

Francisella tularensis infection (tularemia) is rare and should be considered in patients unresponsive to penicillin. It can be contracted by ingestion of contaminated water such as in poorly cooked wild animal meat. Clinical presentation of PT includes fever, painful ulcerative-exudative pharyngitis, and cervical lymphadenitis.

Other rare causes of PT are *Treponema pallidum, Mycobacterium* spp., and *Toxoplasma gondii*.

Anaerobic bacteria

The anaerobic species that have been implicated in PT are *Actinomyces* spp., *Fusobacterium* spp., and pigmented *Prevotella* and *Porphyromonas* spp.

The role of anaerobes is supported by their predominance in tonsillar or retropharyngeal abscesses and Vincent's angina (*Fusobacterium* spp. and spirochetes). Furthermore, patients with non-GABHS tonsillitis as well as infectious mononucleosis respond to antibiotics directed only against anaerobes (metronidazole), and elevated serum levels of antibodies to *Prevotella intermedia* and *Fusobacterium nucleatum* were found in patients with recurrent non-GABHS tonsillitis and peritonsillar cellulitis and abscess.

Fusobacterium necrophorum has been recovered in recent studies from the United Kingdom and Denmark of adolescents and young adults with nonstreptococcal PT. Other studies also suggest a role for *F. necrophorum* in recurrent or persistent sore throat. It is also the etiology of most cases of

Lemierre's syndrome, which generally occurs in previously healthy adolescents and young adults. The syndrome includes necrotizing tonsillopharyngitis associated with *Fusobacterium* bacteremia, septic internal jugular vein thrombophlebitis, and metastatic pulmonary infection. Clinical findings include fever (>39°C), rigors, respiratory symptoms, and unilateral neck pain and/or swelling.

Mycoplasma

Mycoplasma pneumoniae and *Mycoplasma hominis* can cause PT usually as a manifestation of a generalized infection. Mycoplasma accounts for 5–15% of cases of PT, and most cases occur in those older than 6 years.

Chlamydia

Chlamydia pneumoniae may cause PT in young adults, often accompanying pneumonia or bronchitis.

Viruses

Viral PT is generally characterized by the absence of an exudate, the presence of ulcerative lesions, minor nontender adenopathy, enanthems, cough, rhinitis, hoarseness, conjunctivitis, or diarrhea.

The viruses known to cause PT are adenovirus (concomitant conjunctivitis), Coxsackie A virus, influenza and parainfluenza viruses (seasonal with high fever, cough, headache, and myalgias), coronavirus, enteroviruses (posterior pharyngeal vesicles or ulcers, vesicles on palms and soles in summer), Epstein–Barr virus (exudative pharyngitis, liver and spleen enlargement, cervical adenopathy), herpes simplex (or HSV, most caused by HSV-1, anterior oral and lip ulcers, fever), rhinovirus, respiratory syncytial virus (RSV), rubeola (oral erythema and Koplik spots prior to exanthema), and cytomegalovirus (CMV).

Primary human immunodeficiency virus (HIV) infection may cause an acute retroviral syndrome which is similar to infectious mononucleosis. The symptoms usually occur within days to weeks after exposure and infection includes fever, weight loss, rash, lymphadenopathy, and splenomegaly.

Mixed infections

PT can be caused by multiple pathogens. *Mixed viral/bacterial* pathogens were found in 26 of 127 patients (20.5%) and none of the controls ($p < 0.0001$). Combined pathogens included double bacterial infection with GABHS plus *C. pneumoniae* or *M. pneumoniae* plus *C. pneumoniae* with *M. pneumoniae*; and viral and bacterial infection with GABHS plus RSV, adeno and influenza B and parainfluenza type 1 viruses, *C. pneumoniae* plus RSV or adeno virus, and *M. pneumoniae* plus adeno virus.

A concomitant GABHS and influenza A virus PT, as evident by increased antistreptolysin O (ASO) and anti-DNase B titers, was found in 4 of 12 (33%) patients who had both of these organisms isolated in their upper airways.

CLINICAL FINDINGS

PT has generally a sudden onset, with fever and sore throat, nausea, vomiting, headache, and rarely abdominal pain. At an early stage redness of throat and tonsils is observed, and the cervical lymph glands become enlarged. The clinical manifestations may vary by causative agent (see above and also Table 4.1) but are rarely specific. Erythema is common to most agents; however, the occurrence of ulceration, petechiae, exudation, or follicles varies. The common features are exudative pharyngitis in GABHS infection, ulcerative lesions in enteroviruses, and membranous pharyngitis in *C. diphtheriae*. Petechiae can often be seen in GABHS, Epstein–Barr, measles, and rubella viruses infections.

Viral disease is generally self-limited, lasts 4 to 10 days, and is generally associated with the presence of nasal secretions. Bacterial illness lasts longer if untreated. The most unique features of anaerobic tonsillitis or PT are enlargement and ulceration of the tonsils associated with fetid or foul odor and the presence of fusiform bacilli, spirochetes, and other organisms on Gram stain.

DIAGNOSIS

Determining if GABHS is the cause of the PT is very important. This is because early antimicrobial therapy shortens the illness, prevents suppurative and nonsuppurative complications, reduces transmission of the pathogen, and prevents misuse of antimicrobials.

GABHS PT can be diagnosed by either a positive throat culture or rapid test. Culture is obtained when microbiologic isolation is needed. Throat culture should be obtained before initiation of antimicrobial therapy. Vigorous swabbing of both tonsillar surfaces and the posterior pharyngeal wall, and plating the specimen on sheep blood

agar media is the standard. Incubation in anaerobic condition and use of selective media can increase the recovery rate of GABHS. More than 10 colonies of GABHS per plate are considered to represent a true infection rather than colonization. However, using the number of colonies of GABHS in the plate as an indicator for the presence of true infection is difficult to implement, as there is overlap between carriers and infected individuals. A single throat culture has the sensitivity of 90% to 95% in detection of GABHS in the pharynx. False-negative results can occur in patients who received antibiotics. Throat cultures that generally identify GABHS by direct growth may take 24 to 48 hours. Re-examination of plates at 48 hours is advisable. The use of a bacitracin disk provides presumptive identification. Attempts to identify β-hemolytic streptococci, other than group A, may be worthwhile in older individuals. Commercial kits containing group-specific antisera are available for identifying the specific streptococcal group.

Rapid methods for detection of GABHS that take 10 to 60 minutes are available. They are more expensive than the routine culture but allow for rapid administration of therapy and reduction of morbidity. Antigen tests depend on the detection of the surface Lancefield group A carbohydrate. Newer tests use nucleic acid (DNA) probes and polymerase chain reaction (PCR) with greater sensitivity and identify more pathogenic serotypes of GABHS. Early kits showed low sensitivity, but the current ones have 85% to 90% sensitivity but are still associated with 5% to 15% false-negative results. It is therefore recommended that a bacterial culture be performed in instances where the rapid streptococcal test is negative. Unfortunately, neither rapid test nor throat culture can differentiate patients with PT due to GABHS from viral infection in a GABHS carrier.

A rise in antistreptococcal antibody titers (e.g., antistreptolysin O, antideoxyribonuclease B, streptokinase, hyaluronidase, or nicotinic acid dehydrogenase) after 3 to 6 weeks can provide retrospective evidence for GABHS infection and assist in differentiating between the carrier state and infection.

Other less common pathogens should be identified in specific situations, when no GABHS is found or when a search of other organisms is warranted. Because many of the other potential pathogens are part of the normal pharyngeal flora, interpretation of these data can be difficult. When tularemia is suspected serologic testing is advisable. Pharyngeal cultures for *N. gonorrhoeae* require special media (Thayer–Martin agar). Attempts to identify corynebacteria should be made whenever a membrane is present in the throat. Cultures should be obtained from beneath the membrane, using special moisture-reducing transport media. A Loeffler slant, a tellurite plate, and a blood agar plate should be inoculated. Identification by fluorescent antibody technique is possible. *Arcanobacterium haemolyticum* grows slowly on sheep blood agar plates and produces a tiny zone of beta hemolysis after at least 3 days of incubation.

Viral cultures or rapid tests for some viruses (i.e., influenza, respiratory syncytial and herpes simplex viruses) are available. A heterophile slide test or other rapid tests for infectious mononucleosis can also provide a specific diagnosis. Laboratory features of primary HIV infection may include lymphopenia and increased transaminase levels. HIV viral load and HIV antibodies tests may be helpful.

THERAPY

Many antibiotics are available for the treatment of PT caused by GABHS. However, the recommended optimal treatment for GABHS infection is penicillin administered three times a day for 10 days (Table 4.2). Oral penicillin VK is used more often than intramuscular (IM) benzathine penicillin G. However, IM penicillin can be given as initial therapy in those who cannot tolerate oral medication or to ensure compliance. An alternative medication is amoxicillin, which is as active against GABHS, but its absorption is more reliable, blood levels are higher, plasma half-life is longer, and protein binding is lower, giving it theoretical advantages. Furthermore, oral amoxicillin has better compliance (better taste). Amoxicillin should not be used, however, in patients suspected of infectious mononucleosis, where it can produce a skin rash.

The frequently reported inability of penicillin to eradicate GABHS from patients with PT despite its excellent in vitro efficacy is of concern. Although about half of the patients who harbor GABHS following therapy may be carriers, the rest may still show signs of infection and represent true clinical failure. Studies have shown that the recommended doses of either oral penicillin V or IM penicillin failed to eradicate GABHS in acute-onset pharyngitis in 35% of patients treated with oral penicillin V and 37% of those treated with IM penicillin.

Table 4.2 Oral antibiotics for 10-day course of treatment of acute GABHS pharyngotonsillitis

	Dosage (in mg)		
Generic name	**Pediatric (mg/kg/d)**	**Adult**	**Frequency**
Penicillin V	25–50	250	q6–8 h
Amoxicillin	40	250	q8 h
Cephalexin[a]	25–50	250	q6–8 h
Cefadroxil[a]	30	1000	q12 h
Cefaclor [a]	40	250	q8 h
Cefuroxime-axetil[a]	30	250	q12 h
Cefpodoxime-proxetil[a]	30	500	q12 h
Cefdinir [a,d]	7 mg 14 mg	300 600	q12 h q24 h
Cefprozil[a]	30	250	q12 h
Cefditoren	NA	200	q12 h
Azithromycin[c,d]	12	250[c]	q24 h
Clarithromycin	7.5	250	q12 h
Cefixime	8	400	q24 h
Ceftibuten	9	400	q24 h
Erythromycin estolate	40	250	q8–12 h
Amoxicillin-calvulanate[b]	45	875	q12 h
Clindamycin[b]	20–30	150	q6–8 h

Abbreviations: NA = not approved for children younger than 12 years.
[a] Effective also against aerobic β-lactamase-producing bacteria (BLPB).
[b] Effective also against aerobic and anaerobic BLPB.
[c] First day dose is 500 mg.
[d] Duration of therapy 5 days.

Penicillin failure in eradicating GABHS tonsillitis has several explanations (Table 4.3). These include noncompliance with 10-day course of therapy, carrier state, reinfection from another person or object, and penicillin tolerance. Some postulate that bacterial interactions between GABHS and members of the pharyngotonsillar bacterial flora can explain these failures. These explanations include the "shielding" of GABHS from penicillins by BLPB that colonize the pharynx and tonsils, the absence of normal flora organisms that interfere with the growth of GABHS, and the coaggregation between *Moraxella catarrhalis* and GABHS. Repeated penicillin administration can induce many of these changes. It can result in a shift in the oral microflora with selection of β-lactamase-producing strains of *S. aureus, Haemophilus* spp., *M. catarrhalis, Fusobacterium* spp., pigmented *Prevotella* and *Porphyromonas* spp., and *Bacteroides* spp.

Table 4.3 Possible reasons for antibiotic failure or relapse in GABHS tonsillitis

Bacterial interactions • The presence of β-lactamase-producing organisms that "protects" GABHS from penicillins • Coaggregation between GABHS and *Moraxella catarrhalis* • Absence of members of the oral bacterial flora capable of interfering with the growth of GABHS (through production of bacteriocins and/or competition on nutrients)
Internalization of GABHS (survives within epithelial cells, escaping eradication by penicillins)
Resistance (i.e., erythromycin) or tolerance (i.e., penicillin) to the antibiotic used
Inappropriate dose, duration of therapy, or choice of antibiotic
Poor compliance with taking medication
Reacquisition of GABHS from a contact or an object (i.e., toothbrush, dental retainer, or dental braces)
Carrier state, not disease

It is possible that BLPB can protect the GABHS from penicillin by inactivating the antibiotic. Such organisms in a localized soft-tissue infection may degrade penicillin in the area of the infection, protecting not only themselves but also penicillin-susceptible pathogens such as GABHS. Thus, penicillin therapy directed against a susceptible pathogen can be rendered ineffective. An increase in in-vitro resistance of GABHS to penicillin was observed when GABHS was inoculated with *S. aureus*, *Haemophilus* spp., and pigmented *Prevotella* and *Porphyromonas* spp. *Bacteroides* spp. protected a penicillin-sensitive GABHS from penicillin therapy in mice. Both clindamycin and the combination of penicillin and clavulanic acid (a β-lactamase inhibitor), which are active against both GABHS and *Bacteroides* spp., eradicated the infection.

Penicillin therapy can also reduce the number of aerobic and anaerobic bacteria that can interfere with the growth of GABHS. The oropharyngeal flora of over 85% of individuals who are not tonsillitis prone contains numerous types of organisms that are capable of interfering with the in vitro growth of potential pathogens. In contrast, only 25% to 30% of children who suffer from recurrent tonsillitis harbor interfering organisms.

Acute pharyngotonsillitis

Oral penicillin given for 10 days is still recommended as the antibiotic of choice given its proven efficacy, safety, narrow spectrum,

Table 4.4 Indications for the use of antimicrobials other than a penicillin for GABHS tonsillitis

Presence of β-lactamase-producing bacteria (recent antibiotic exposure, winter, region)
Absence of "interfering flora" (recent antibiotic therapy)
Recurrent GABHS tonsillitis
Past failures to eradicate GABHS
High failures of penicillins in the community
Comorbidities
When failure is a medical, economical, or social hardship
Penicillin allergy (non-type I)

and low cost. Other effective antibiotics included cephalosporins, lincomycin, clindamycin, macrolides, and amoxicillin–clavulanate. Some of these agents were more effective than penicillin in acute (cephalosporins, macrolides) and others in recurrent (lincomycin, clindamycin, and amoxicillin–clavulanate) GABHS PT.

There are patients where more effective antimicrobials that are less likely to fail to eradicate GABHS should be considered. Individual medical, economical, and social issues should be considered in each patient prior to selecting an antimicrobial for the treatment of GABHS PT (Table 4.4). These include the existence of a high probability for the presence in the pharyngotonsillar area of BLPB and the absence of interfering organisms, the recent failure of penicillin therapy, or a history of recurrent GABHS PT.

The macrolides are also an alternative choice in therapy of PT. Compliance with the newer macrolides (clarithromycin and azithromycin) is better compared with erythromycin, because of their longer half-life and reduced adverse gastrointestinal side effects. However, the increased use of macrolides for the treatment of various respiratory and other infections has been associated with increased GABHS resistance to these agents. Resistance of GABHS to macrolides has reached 70% in Finland, Italy, Japan, and Turkey. Of concern is the significant increase of such resistance in the United States that reached 48% in specific populations. The current resistance of GABHS to macrolides in the United States is 5% to 16%. It is therefore advisable to avoid the routine use of macrolides for GABHS PT and save these agents for those patients who are type I penicillin allergic.

The success rate of treatment of acute GABHS tonsillitis was consistently found to be higher with cephalosporins than with penicillin. The cephalosporins' increased efficacy may be due to their activity against aerobic BLPB such as *S. aureus, Haemophilus* spp., and *M. catarrhalis*. Another possible reason is that the nonpathogenic interfering aerobic and anaerobic bacteria that compete with GABHS, and help to eliminate them, are less susceptible to cephalosporins than to penicillin. These organisms are therefore more likely to survive cephalosporin therapy.

The length of therapy of acute tonsillitis with medication other than penicillin has not been determined by large comparative controlled studies. However, certain new agents have been administered in shorter courses of 5 or more days (Table 4.2). Early initiation of antimicrobial therapy results in faster resolution of signs and symptoms. However, spontaneous disappearance of fever and other symptoms generally occurs within 3 to 4 days, even without antimicrobials. Furthermore, acute rheumatic fever can be prevented even when therapy is postponed up to 9 days.

Prevention of recurrent tonsillitis due to GABHS by prophylactic administration of daily oral or monthly benzathine penicillin should be attempted in patients who suffered from rheumatic fever. American Heart Committee guidelines on the prevention of rheumatic fever should be followed, and if any family members are carrying GABHS, the disease should be eradicated and the carrier state monitored.

Macrolides are the drugs of choice for *A. haemolyticum* which is unresponsive to penicillin. When *C. diphtheriae* infection is suspected, erythromycin is the drug of choice, and penicillin or rifampin are alternatives. Supportive therapy of PT includes antipyretics and analgesics, such as aspirin or acetaminophen, and attention to proper hydration.

Pharyngeal *N. gonorrheae* infection appears to be more difficult to treat and can serve as an important reservoir of infection. The recommended treatment is a single injection of ceftriaxone (250 mg IM) plus azithromycin (1 g PO). Doxycycline (100 mg PO BID for 7 days) is an alternate therapeutic option as a second agent to administer with ceftriaxone. HSV infection is treated with acyclovir.

Antiviral therapy may be provided to those with influenza virus if the diagnosis is made early in the course of illness and the symptoms are severe.

Table 4.5 Oral antimicrobials in treatment of GABHS tonsillitis

Acute	Recurrent/chronic	Carrier state
Penicillin (amoxicillin)	Clindamycin, amoxicillin-clavulanate	Clindamycin
Cephalosporins[b]	Metronidazole plus macrolide	Penicillin plus rifampin
Clindamycin	Penicillin plus rifampin	
Amoxicillin-clavulanate		
Macrolides[a]		

[a] GABHS may be resistant.

[b] All generations.

Remark: For dosages and length of therapy see Table 4.2.

Recurrent and chronic pharyngotonsillitis

Penicillin failure in treatment of recurrent and chronic tonsillitis is even higher than the failure of therapy of acute infection. Several clinical studies demonstrated the superiority of lincomycin, clindamycin, and amoxicillin–clavulanate over penicillin. These antimicrobial agents are effective against aerobic as well as anaerobic BLPB and GABHS in eradicating recurrent tonsillar infection. Clindamycin also provides coverage against many MRSA that can resist other antimicrobials such as amoxicillin/clavulanate. However, no studies showed them to be superior to penicillin in treatment of acute tonsillitis. Other drugs that may also be effective in the therapy of recurrent or chronic tonsillitis are penicillin plus rifampin and a macrolide (e.g., erythromycin) plus metronidazole (see Table 4.5). Referral of a patient for tonsillectomy should be considered only after these medical therapeutic modalities have failed.

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5. Infectious thyroiditis

Jeanne Carey and Stephen G. Baum

INTRODUCTION

Acute suppurative thyroiditis (AST) is a rare but potentially life-threatening infection. AST is usually bacterial in etiology, although fungal, parasitic, and mycobacterial organisms have also been documented causes. The routes of infection are predominantly hematogenous or lymphatic; however, thyroid infections may also be the result of direct spread from an adjacent deep fascial space infection, an infected thyroglossal fistula, or anterior perforation of the esophagus. Thus, infectious thyroiditis may occur either as a local infection or as part of a disseminated systemic infection. Because prognosis is dependent on prompt diagnosis and treatment, it is important to differentiate AST from the noninfectious inflammatory conditions of the thyroid and other inflammations in the neck that it may closely resemble.

PATHOGENESIS

The thyroid gland is rarely infected, and several protective factors have been postulated to explain why the gland is relatively resistant to infection. First, there is a rich blood supply to and extensive lymphatic drainage from the thyroid. Second, the high iodine content of the gland may be bactericidal; however, there are no data to show that the concentration of iodine present in the thyroid would be enough to inhibit the growth of microorganisms. Third, in addition to being surrounded by a complete fibrous capsule, the thyroid is separated from the other structures of the neck by fascial planes.

Primary infections of the thyroid are most likely to occur in individuals with pre-existing thyroid disease or with certain congenital anomalies. Goiters, Hashimoto's thyroiditis, or thyroid cancer have been present in up to two-thirds of women and one-half of men with infectious thyroiditis. With respect to congenital anomalies, which are associated with AST more frequently in children than in adults, transmission of infective organisms via a pyriform sinus fistula is the most common direct route of thyroid infection (Figure 5.1). The fistula arises from the apex of the pyriform recess and often ends in, or near, the thyroid gland, allowing bacterial infection to develop in or around the thyroid.

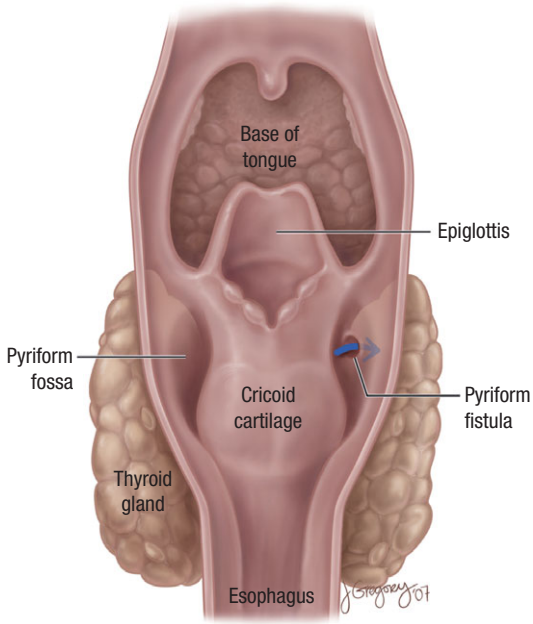

Figure 5.1 Anatomy of the thyroid gland and oropharynx, demonstrating the relationship to a pyriform fistula, anterior view.

Episodes of AST are often preceded by an upper respiratory infection or another factor (e.g., injury or obstruction of the fistula by food or foreign bodies) that may induce inflammation of a pyriform fistula and thus facilitate transmission of pathogens to the thyroid. Particularly in children, the left lobe is more commonly involved, reflecting the observation that pyriform sinus fistulas predominantly occur on the left.

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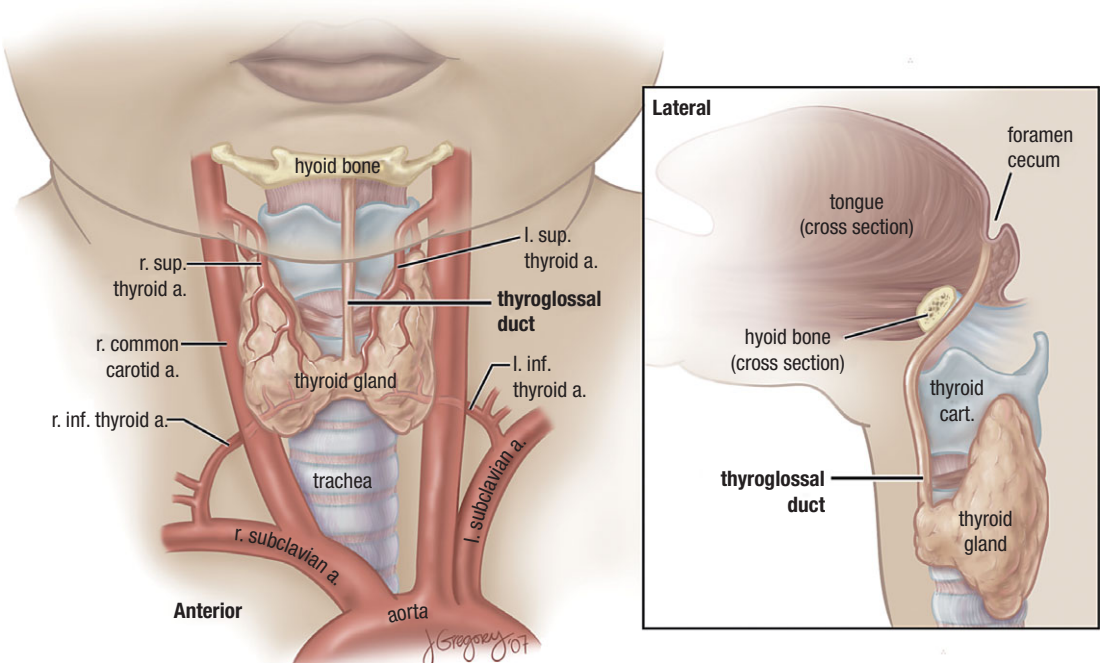

Figure 5.2 Anatomy of the thyroid gland and neck. A thyroglossal duct fistula is shown in frontal and lateral views.

Infected embryonic cysts of the third and fourth branchial pouches have also been identified as causes of AST. Infectious organisms may also spread directly to the thyroid via a patent thyroglossal duct fistula (Figure 5.2). AST may be caused by spread of microbes from adjacent sites of infection, such as the oropharynx and middle ear, although this occurs infrequently, presumably because the thyroid is encapsulated within its fibrous sheath. Perforation of the esophagus may also result in direct spread of infection to the thyroid gland.

Bacterial AST may also result from trauma to the anterior neck. One of us (SGB) has seen a single case of direct spread of infection to the thyroid from a neck wound. The patient was a mechanic who scraped his anterior neck while working on his back underneath an automobile. The wound appeared superficial, but infection spread to the thyroid with abscess formation. The offending organism was a staphylococcus. Even fine-needle aspiration (FNA) of thyroid nodules has resulted in thyroid infection.

Immunosuppressed patients, such as those with human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS) or hematologic malignancies, as well as patients with autoimmune diseases or organ transplants treated with immunosuppressive agents, are at risk for suppurative thyroiditis, which can occur as part of a disseminated infectious process. These infections arise when pathogens reach the thyroid hematogenously or through the lymphatic system.

MICROBIOLOGY

Gram-positive organisms are the most common etiologic pathogens in AST, although a wide variety of bacteria have been isolated as causative agents in case reports (Table 5.1). In a review of 224 cases of thyroid infections reported between 1900 and 1980, staphylococci, found in 23 of 66 (35%) of culture-positive specimens, were the most frequently identified organisms; *Staphylococcus aureus* was the predominant species. *Streptococcus pyogenes*, presumably acquired after a recent pharyngeal infection or colonization, *Streptococcus pneumoniae*, and other streptococci were also commonly recovered. In a subsequent review of an additional 191 cases of AST reported between 1980 and 1997, in which 130 microorganisms were isolated, Yu *et al*. found that the most common bacterial isolates were gram-positive aerobes (39%), gram-negative aerobes (25%), and anaerobes (12%, mostly in mixed culture).

Table 5.1 Microbiology of infectious thyroiditis

Nonimmunocompromised host
Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pyogenes
Other streptococcal species
Klebsiella species, especially in diabetic patients
Other Enterobacteriaceae
Anaerobic oral flora (foul smell on needle aspiration may give hint of this)
Other gram-negative bacteria free-living in water secondary to upper respiratory tract infection
Mycobacterium tuberculosis
Mycobacterium bovis
Actinomyces species
Immunocompromised host
Mycobacterium avium-intracellulare
Nocardia species
Pneumocystis jirovecii

Modified from Shah and Baum, 2000.

The true involvement of anaerobic bacteria in AST is unknown because past studies have not used uniform methods for the recovery of anaerobes. Because anaerobes are more difficult to isolate, it is possible that culture-negative cases of AST may represent purely anaerobic or mixed infections, an important consideration when choosing empiric therapy for AST.

The bacterial pathogens implicated in AST in children are similar to those found in adults. *S. aureus, S. pyogenes, Staphylococcus epidermidis*, and *Streptococcus pneumoniae* are the most commonly isolated organisms in pediatric cases of AST.

Following bacteria, fungi are the second most common microorganisms to infect the thyroid, representing 15% of cases of AST in the review by Yu and colleagues. Fungal thyroiditis most commonly occurs in immunocompromised patients, such as those with leukemia, lymphoma, and autoimmune diseases and in organ transplant patients on immunosuppressive therapy. In a review of 41 fungal thyroiditis cases published between 1970 and 2005, Goldani *et al*. found that *Aspergillus* species (spp.) were the most commonly reported cause of fungal thyroid infection. Thyroid involvement by *Aspergillus* spp. was found at autopsy as part of disseminated aspergillosis in 13 (62%) of 21 patients, most of whom lacked clinical manifestations and laboratory evidence of thyroid dysfunction. After *Aspergillus* spp., *Candida* spp. were the second most common cause; other fungal etiologies reported include *Cryptococcus neoformans, Coccidioides immitis, Histoplasma capsulatum*, and *Pseudallescheria boydii*.

Pneumocystis jirovecii (then called *Pneumocystis carinii*), now classified as a fungus, was not included in the review by Goldani *et al*.; however, *P. jirovecii* has been found to be a cause of thyroid infections, almost exclusively in patients with AIDS. Yu *et al*. identified *P. jirovecii* as the causative agent in 16 of 19 cases of fungal thyroiditis in their literature review.

Mycobacterium tuberculosis as well as atypical mycobacteria have been described as causes of thyroid infection. Thyroidal tuberculosis occurs in the setting of miliary or disseminated disease. Disseminated *Mycobacterium avium-intracellulare* infection in AIDS patients has resulted in thyroidal infection. In their literature review, Yu *et al*. found that mycobacterial organisms were isolated in 12 of 130 (9%) cases of culture-positive AST. Unlike patients with pyogenic bacterial AST, those with mycobacterial thyroiditis are typically symptomatic for months and are much less likely to experience pain, tenderness, and fever.

Involvement of the thyroid gland by parasites is extremely rare and typically occurs in the setting of disseminated disease. In the United States, only nine cases of echinococcal (tapeworm) thyroiditis have been reported. These patients had chronic symptoms (1.5 to 35 years in duration), were generally diagnosed as having goiters, and were discovered to have thyroidal echinococcosis at the time of surgery. *Strongyloides stercoralis*, which is endemic in the southeastern United States and tropical climates, has been reported as a cause of thyroid infection only in the setting of disseminated disease in immunocompromised patients.

Viral infection causing thyroiditis has never been definitively proven. In postmortem studies of patients with AIDS, cytomegalovirus (CMV) inclusions have been found in thyroid tissue in association with disseminated CMV infection. However, symptomatic thyroiditis due to CMV has not been reported in these patients.

CLINICAL MANIFESTATIONS

The symptoms and signs of AST may be indistinguishable from those of a variety of both infectious and noninfectious inflammatory conditions of the anterior neck. Most patients with AST present with fever, pain, and a tender, firm swelling in the

Table 5.2 Causes of painful anterior neck mass

Thyroid-related
Subacute, nonsuppurative thyroid inflammation (Hashimoto's thyroiditis)
Grave's disease
Thyroid cancer, with or without hemorrhage
Hemorrhage into the thyroid secondary to trauma
Radiation damage to thyroid
Acute suppurative thyroiditis
Nonthyroid-related
Cervical lymphadenitis due to infection or malignancy
Cellulitis
Infections of thyroglossal duct remnant, branchial cleft cyst, or cystic hygroma

Modified from Shah and Baum, 2000.

anterior aspect of the neck that moves on swallowing and develops over days to a few weeks. In this clinical scenario, the differential diagnosis includes such entities as subacute thyroiditis, Grave's disease, thyroid cancer, hemorrhage into the thyroid, cervical lymphadenitis, and cellulitis (Table 5.2).

Other typical signs and symptoms of AST include dysphagia, dysphonia (both of which have been attributed to compression of local structures, including the recurrent laryngeal nerve), and concurrent pharyngitis. On examination the thyroid is tender with warmth and erythema of the overlying skin and, in the case of abscess formation, fluctuance. Suppurative areas may include one lobe, both lobes, or only the isthmus of the gland. Because a firm nodule may progress to become fluctuant over the course of 1 to 3 days, repeated physical examinations are advisable.

Children with AST present similarly; however, there are a few noteworthy differences. The left lobe of the thyroid gland is more frequently involved in pediatric cases, because pyriform fossa fistulas are predominantly observed on the left. Neonates and infants are more likely than adults to present with stridor and respiratory distress from tracheal compression by an enlarged thyroid gland.

Suppurative thyroiditis that occurs as part of a disseminated infectious process differs from locally spread bacterial thyroiditis in several important ways. First, suppurative thyroiditis due to a systemic infection often occurs in the absence of any clinical manifestations of thyroiditis. Second, the etiologic organisms are typically opportunistic pathogens, such as fungi, *P. jirovecii*, and mycobacteria, which tend to present with a chronic, insidious course. Finally, in contrast to bacterial thyroiditis, pre-existing thyroid disease is not a significant risk factor for suppurative thyroiditis that occurs as part of a disseminated infection; rather, patients who are immunocompromised are those who are at particular risk for the latter type of infectious thyroiditis.

DIAGNOSIS

Leukocytosis and an elevated erythrocyte sedimentation rate and C-reactive protein level are nonspecific, but are commonly seen in AST. Although thyroid function test results are within normal limits in the majority of patients with AST, destruction of glandular tissue with release of preformed thyroid hormone into the circulation can lead to transient thyrotoxicosis. Hypothyroidism has also been reported. Although most patients with bacterial AST are euthyroid, Yu *et al*. found that those with fungal infections were often hypothyroid (63%) and that half of patients with mycobacterial infections were hyperthyroid.

Imaging studies help to differentiate AST from other causes of anterior neck pain and fever (Table 5.2). Plain neck radiography may reveal tracheal deviation or soft-tissue gas formation, indicative of infection with anaerobic gas-forming organisms, such as *Clostridium* spp. Computed tomography (CT), ultrasonography (US), and magnetic resonance imaging (MRI) often reveal unilobular thyroidal swelling and are extremely useful in the identification of parathyroidal abscesses and spread of infection to contiguous structures (Figure 5.3). For acutely ill patients with suspected AST, the preferred initial imaging modality is CT, which provides a comprehensive view of the neck and upper mediastinum and can thus be used to identify potential extrathyroidal involvement.

In a review of imaging studies performed on 60 patients with AST, Masuoka and colleagues found that, during the acute stage of AST, both CT and US may show nonspecific inflammation in and around the affected thyroid lobe, which may lead to an erroneous diagnosis of subacute thyroiditis. US may be very helpful in leading to the correct diagnosis, as specific US findings differ between AST and subacute thyroiditis; for example, in cases of AST, hypoechoic lesions are typically unifocal and the hypoechoic lesions seen in subacute thyroiditis are usually multiple and often bilateral.

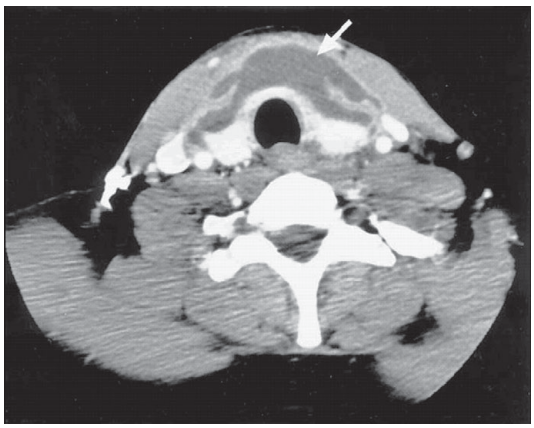

Figure 5.3 Computed tomographic scan of neck with contrast showing an abscess of the left lobe of the thyroid gland (arrow). Published in Jacobs A, David-Alexandre CG, Gradon JD. Thyroid abscess due to *Acinetobacter calcoaceticus*: case report and review of the causes of and current management strategies for thyroid abscesses. *South Med J*. 2003;96:300–307.

The most useful test in AST is FNA, which will frequently be diagnostic. FNA is especially helpful when there is no associated bacteremia or fungemia and when the patient's tenderness is limited to a localized area. Specimens for cytology, Gram stain, and aerobic and anaerobic cultures should be obtained. In the appropriate clinical setting, mycobacterial and fungal cultures as well as special stains for *P. jirovecii* and acid-fast bacilli should also be performed.

MANAGEMENT

Antimicrobial treatment must be targeted at the underlying etiology of AST. In cases of bacterial AST high-dose parenteral antibiotics should be started promptly, as early treatment may prevent complications such as bacteremia and abscess formation. Given the great variety of bacterial species that can cause AST, broad-spectrum antibiotics should be administered while cultures are pending.

In adults, because *S. aureus* and streptococci are the most common causative pathogens, empiric therapy should cover gram-positive cocci. An antistaphylococcal β-lactam (e.g., nafcillin and cefazolin) combined with an aminoglycoside (e.g., gentamicin) or monotherapy with a third-generation cephalosporin are appropriate initial regimens. Until culture results are available, patients who are penicillin-allergic or who may be at risk for infection with methicillin-resistant *S. aureus* (MRSA) should receive vancomycin. Because oral anaerobes may be involved in AST, antibiotic regimens for most patients should also include anaerobic coverage (e.g., clindamycin or β-lactam/β-lactamase inhibitor).

In pediatric or recurrent cases of AST, it is particularly important to cover oral anaerobes, which are commonly involved in these infections. Empiric antibiotic therapy for children with AST should also provide adequate coverage for *S. aureus* and *S. pyogenes*.

If clinical examination or radiographic findings are consistent with an abscess or gas formation, surgical drainage is indicated. If an infection persists despite antibiotic treatment (e.g., continued leukocytosis and fever, progressive local inflammation) or involves extensive necrosis, lobectomy may be required.

Patients with AST should be evaluated for the presence of predisposing conditions. Any pre-existing thyroid pathology that is discovered, such as a goiter or adenoma, should be treated. Because a pyriform sinus fistula is the most common route of infection in bacterial AST, most patients with their first episode and all patients with recurrent episodes should undergo a barium swallow, CT scan, or MRI of the neck to exclude the presence of a communicating fistula. Because the tract may be obscured by inflammatory material during an acute phase of infection, imaging studies may not reveal a fistula until after the completion of antibiotic therapy. Surgical excision or cauterization treatment of such fistulas is necessary to prevent recurrent infections.

With appropriate treatment the prognosis of AST is excellent and the vast majority of patients recover completely. Rarely, however, episodes of AST are followed by hypothyroidism, which is almost always transient, vocal cord paralysis, and recurrent infection. As a result of severe, diffuse inflammation and necrosis of the gland, some patients may develop transient or prolonged hypothyroidism requiring L-thyroxine replacement therapy. Management of AST also includes diagnosing and treating any pre-existing thyroid pathology, such as a goiter or adenoma, which may have served as a predisposing condition.

Suppurative thyroiditis due to pathogens other than bacteria generally occurs in the setting of a disseminated infection, most commonly in immunocompromised hosts. In such cases, systemic therapy for the underlying disease

(e.g., fungal infection, mycobacterial infection) usually results in treatment of the thyroiditis.

CONCLUSION

Acute suppurative thyroiditis is a rare disease, but one that carries considerable morbidity unless promptly treated. Modern imaging techniques are very useful in demonstrating a focus of infection in the thyroid. This infection can occur as a result of systemic infection, in which case hematogenous or lymphatic spread settles in the thyroid. It can also be a result of direct spread from a surface wound or through local invasion from infected congenital anomalies of the neck. In view of the multiplicity and variability of the potential pathogens and their antimicrobial sensitivities, every attempt should be made to identify the offending pathogen. In the case of systemic infections (e.g., bacteremias, fungemias, and disseminated tuberculosis), cultures of blood and other infected sites may be sufficient to establish the etiology. When AST is the single site of infection, prompt FNA should be used to identify the organism and dictate appropriate therapy.

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6. Otitis media and externa

Stephen I. Pelton

INTRODUCTION

The clinical burden from acute (AOM) and chronic suppurative otitis media (CSOM) and their associated morbidities is substantial, especially in children. In industrialized countries, AOM remains the most frequent reason for pediatric office visits and recurrent otitis media (ROM); persistent middle ear fluid and associated hearing loss reduces quality of life. In developing nations, infectious complications of AOM include suppurative intracranial infection and CSOM with severe hearing loss.

The prescription of antimicrobials increases bacterial resistance, so the role of antimicrobials in AOM has been re-evaluated, using an evidence-based approach.

ROM and CSOM usually begin in the first year of life, due to *Streptococcus pneumoniae*, nontypeable *Haemophilus influenzae* (NTHi), or *Morexalla catarrhalis*. Studies of children undergoing tympanostomy report biofilms on middle ear mucosa and positive PCR assays for otopathogens despite negative cultures. Although pneumococcal conjugate vaccine (PCV7) reduced office visits for AOM by ~15%, a multidrug-resistant nonvaccine serotype, 19A, emerged as a prevalent cause of AOM and mastoiditis. A second-generation conjugate vaccine (PCV13) that included pneumococcal polysaccharide 19A (as well as 1, 3, 5, 6A, and 7F) was introduced in 2010, and observational studies report a decline in AOM due to serotype 19A in young children. In children at risk for CSOM, the impact of PCV7 has been more modest. Although disease due to the seven serotypes in PCV declined, disease due to nonvaccine serotypes increased.

DIAGNOSIS

Current American Academy of Pediatrics (AAP) guidelines recommend diagnosing AOM in children who present with moderate to severe bulging of the tympanic membrane or new onset of otorrhea not due to otitis externa (Figure 6.1). Children with mild bulging of the tympanic membrane and recent (less than 48 hours) onset of ear pain (holding, tugging, rubbing of the ear in a nonverbal child) or intense erythema of the tympanic membrane should also be diagnosed with AOM. Older children with AOM usually describe rapid onset of ear pain. However, in young children, otalgia is suggested by tugging/rubbing/holding of the ear, excessive crying, fever, or changes in the child's sleep or behavior pattern. The combination of a "cloudy," bulging tympanic membrane with impaired mobility was the best predictor of AOM. A tympanic membrane that was hemorrhagic, strongly red, or moderately red also correlated with the presence of AOM, but a tympanic membrane that was only "slightly red" was not helpful diagnostically.

Clinical symptoms and signs do not differentiate specific otopathogens. The one clinical finding

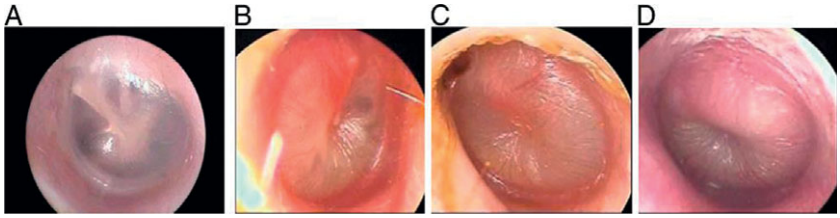

Figure 6.1 A, Normal tympanic membrane. B, tympanic membrane with mild bulging. C, tympanic membrane with moderate bulging. D, tympanic membrane with severe bulging. (Courtesy of Alejandro Hoberman.)

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that is consistently associated with a specific pathogen is conjunctivitis with NTHi.

MICROBIOLOGY OF AOM IN THE ERA OF UNIVERSAL IMMUNIZATION WITH PNEUMOCOCCAL CONJUGATE VACCINE

The pathogenesis of AOM reflects that nasopharyngeal otopathogens ascend the Eustachian tube into the middle ear. Therefore, although the etiology of individual episodes can only be established by sampling the middle ear (tympanocentesis), the spectrum of otopathogens colonizing the nasopharynx will define the microbiology of AOM.

The introduction of PCV7 reduced invasive pneumococcal disease due to the seven vaccine serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F), decreased episodes of vaccine serotypes pneumococcal otitis media as well as overall clinical episodes and tympanostomy tube insertion, and impacted substantially on pneumococcal serotype distribution in the nasopharynx. In clinical trials of PCV7 (FinOM) a 34% overall reduction in pneumococcal otitis was reported; the reduction in vaccine serotype AOM was greater but an increase in episodes due to nonvaccine serotypes of *S. pneumoniae* was observed, providing initial evidence that "replacement" disease (that due to nonvaccine serotypes or alternative otopathogens) was significant. Initially replacement of disease due to vaccine serotype with nonvaccine serotype reduced episodes of AOM due to penicillin-nonsusceptible pneumococci. This was a result of the clustering of resistance among a limited number of pneumococcal serotypes, primarily the vaccine serotypes.

Subsequently nonvaccine serotypes, dominated by serotypes 19A and 6A, emerged. Specifically, serotype 19A became the most commonly recovered pneumococcal serotype in studies of nasopharyngeal colonization and in invasive pneumococcal disease and was a frequent cause of treatment failure in children with acute AOM. In 2010 a 13-valent pneumococcal conjugate vaccine was introduced (serotypes 1, 3, 5, 6A, 7F, and 19A), in part due to the burden of pneumococcal disease due to multidrug-resistant 19A. A decline in both nasopharyngeal colonization and invasive pneumococcal disease with serotype 19A has been observed; however, specific data on AOM is limited. Dagan has reported a decline in AOM due to the PCV13 unique serotypes in observational studies of children undergoing tympanocentesis as part of clinical management in Israel.

Knowledge of the current distribution of pathogens in children with AOM and the prevalence of penicillin-nonsusceptible *S. pneumoniae* or β-lactamase production among NTHi is limited. Studies of nasopharyngeal isolates in the postPCV13 ear demonstrate high prevalence of penicillin-nonsusceptible isolates of *S. pneumoniae* and β-lactamase production among isolates of NTHi; however, strains highly resistant to penicillin and/or ceftriaxone appear to be decreasing. Reports of isolates of NTHi with altered penicillin-binding proteins and increased minimal inhibitory concentrations for amoxicillin–clavulanate have appeared; however, such strains remain uncommon in the United States.

TREATMENT

Pain is a common symptom in AOM. Antibiotic therapy, even when effective, does not appear to provide symptomatic relief over the first 24 hours. Analgesics are effective for pain relief and should be prescribed regardless of whether initial management included antibiotics. Ibuprofen or acetaminophen is effective, and topical agents such as Auralgan may offer symptomatic relief. *For children with severe pain, myringotomy is an effective method to attain relief.* The treatment of otalgia is reviewed in Table 6.1.

The role of antibiotics in the treatment of AOM continues to undergo re-evalution. Multiple questions must be addressed to formulate a strategy for treatment of AOM.

Do children treated with antimicrobial therapy improve more quickly than those assigned to analgesia alone?

Antimicrobial therapy for AOM has reduced suppurative complications dramatically, specifically mastoiditis, over the past five decades. Similarly, in special populations such as Native Americans and Eskimo children, the prevalence of CSOM has declined in association with both the introduction of antimicrobial therapy and the improvement in public health and socioeconomic conditions. Today, AOM resolves in the majority of children without complications with or without antimicrobial therapy.

The observation that 20% to 30% of episodes are culture negative and that a proportion of children with acute bacterial otitis spontaneously clear the pathogen (approximately 15% of those with pneumococcal disease, 40% of those due to

Table 6.1 Treatment of otalgia

Modality	Comments
Acetaminophen, ibuprofen	• Effective analgesia for mild to moderate pain • Readily available • Mainstay of pain management for AOM
Home remedies: (no controlled studies that directly address effectiveness) Distraction External application of heat or cold Oil	• May have limited effectiveness
Topical agents: Benzocaline (Auralgan®, Americaine Otic®) Naturopathic agents (Otikon Otic Solution®)	• Additional, but brief, benefit over acetaminophen in patients >5 years of age • Comparable to amethocaine/phenazone drops (Anaesthetic®) in patients >6 years of age
Homeopathic agents	• No controlled studies that directly address pain
Narcotic analgesia with codeine or analogs	• Effective for moderate or severe pain • Requires prescription • Risk of respiratory depression • Altered mental status • Gastrointestinal upset and constipation
Tympanostomy/myringotomy (EBOM 227–240)	• Requires skill and entails potential risk

NTHi, and up to 75% of those with AOM due to *M. catarrhalis*) led some experts to suggest that symptomatic therapy should be the initial approach. Historically, Engelhard and associates reported greater than 70% failure in children with AOM who received myringotomy alone and Kaleida and colleagues observed a 2-fold higher failure rate among children with temperature greater than 103°F treated with myringotomy plus placebo compared with antibiotics (23.5% vs. 11.5%). They also observed an approximately 2-fold greater failure rate in children with nonsevere episodes who were treated with placebo compared with those who received amoxicillin (7.7% vs. 3.9%). However, studies by Little and coworkers challenged the impact of antimicrobial therapy on AOM symptoms. Their studies compared the outcome of AOM in children initially treated with amoxicillin with those given a prescription to be filled only if symptoms persisted for 72 hours. The authors concluded that immediate antibiotic prescription provided symptomatic benefit mainly after the first 24 hours, when symptoms were already resolving. For children who are not very unwell systemically, a wait and see approach was feasible and acceptable to parents and should substantially reduce the use of antibiotics for acute otitis media. However, both the enrollment criteria and the accuracy of diagnosis in their study were criticized. McCormick and colleagues evaluated "watchful waiting" as a strategy for children with nonsevere AOM. Increased treatment failures and persistent symptoms were observed, especially in those younger than 2 years old assigned to delayed antibiotic treatment. Although delayed resolution was observed in the cohort assigned to watchful waiting, parent satisfaction was not different among the early treatment and the initial observation groups. Increased rates of mild adverse events as well as increases in the prevalence of nonsusceptible *S. pneumoniae* in the nasopharynx were observed in the early treatment group.

Two recent randomized trials of initial antimicrobial therapy vs. placebo for infants and toddlers concluded that treatment reduced the time to resolution of symptoms and the overall symptom burden. Treatment failure with "rescue" antibiotic treatment and signs of persistent acute infection on otoscopic examination were more prevalent in the placebo group (Table 6.2). Table 6.3 summarizes the potential benefits and harms of initial antimicrobial therapy for AOM and provides the current recommendation from the American Academy of Pediatrics.

Does persistence of bacterial infection within the middle ear correlate with persistence of clinical signs or symptoms?

The outcome measure selected is critical for determining the impact of antimicrobial treatment on the course of AOM. If outcome parameters such as resolution of signs and symptoms by day 7 to 10 or persistence of middle ear fluid at day 14 or 28 are selected, no differences between antimicrobial treatment and watchful waiting strategies can be consistently established. Effective antimicrobial therapy sterilizes the middle ear, resulting in a more rapid resolution of clinical signs (bulging and erythema) and symptoms (fever, earache, irritability). Therefore, evaluating outcomes within the first 3 to 5 days is necessary to demonstrate improved outcomes in antibiotic-treated cohorts as well as between antibiotic regimens.

Table 6.2 Comparison of outcomes between initial treatment with amoxicillin–clavulanate and placebo in children with acute otitis media

Outcome	Amoxicillin–clavulanate	Placebo ($n = 158$)	Difference (95% CI)
Treatment failure	30 (18.6%)	71 (44.9%)	−26.3 (−36.5 to −16.1)
No improvement by day 3	12 (7.5%)	22 (13.9%)	−6.5 (−13.2 to 0.3)
Worsening of condition	15 (9.3%)	32 (20.3%)	−10.9 (−18.7 to −3.2)
Tympanic membrane perforation	1 (0.6%)	5 (3.2%)	−2.5 (5.5 to 0.4)
"Rescue" treatment	11 (6.8%)	53 (33.5%)	−26.7 (−35.5 to −17.9)
Use of antipyretics/analgesic	133 (84.2%)	134 (85.9%)	−1.7 (−9.6 to 6.2)%

Modified from Tähtinen *et al.* A placebo-controlled trial of antimicrobial treatment for acute otitis media. *N Engl J Med.* 2011;364:116–126.

Table 6.3 AAP recommendations for antimicrobial treatment of AOM adapted from Lieberthal AS. The diagnosis and management of acute otitis media. *Pediatrics* 2013;131;e964

Condition	Potential for benefit	Potential for harm	Denouement
Severe symptoms	Increased likelihood of more rapid resolution of symptoms. Increased likelihood of resolution of AOM	Adverse events attributable to antibiotics, such as diarrhea, diaper dermatitis, and allergic reactions. Overuse of antibiotics leads to increased bacterial resistance. Cost of antibiotics	Preponderance of benefit over harm
Nonsevere bilateral AOM in young children	Increased likelihood of more rapid resolution of symptoms. Increased likelihood of resolution of AOM	Adverse events attributable to antibiotics, such as diarrhea, diaper dermatitis, and allergic reactions. Overuse of antibiotics leads to increased bacterial resistance. Cost of antibiotics	Preponderance of benefit over harm
Nonsevere unilateral AOM in young children	Moderately increased likelihood of more rapid resolution of symptoms with initial antibiotics. Moderately increased likelihood of resolution of AOM with initial antibiotics	Adverse events attributable to antibiotics, such as diarrhea, diaper dermatitis, and allergic reactions. Overuse of antibiotics leads to increased bacterial resistance. Cost of antibiotics	Observation becomes an alternative as the benefits and harms approach balance
Nonsevere AOM in older children	Slightly increased likelihood of more rapid resolution of symptoms; slightly increased likelihood of resolution of AOM	Adverse events attributable to antibiotics, such as diarrhea, rashes, and allergic reactions. Overuse of antibiotics leads to increased bacterial resistance.	Observation is an option as the benefits and harms approach balance

Both Dagan and Carlin observed greater improvement in signs and symptoms in children with bacterial AOM when the middle ear fluid was sterilized by days 4–6 compared to children who had persistent middle ear infection. Figure 6.2 details the changes in clinical symptom score in children with effective antimicrobial therapy and sterilization of the middle ear compared to those with ineffective antimicrobial therapy and persistence of middle ear infection. The results also demonstrate that many children with persistent middle ear bacterial infection have decreased symptoms at days 4–6 compared to initial presentation.

Is the risk of recurrence greater in children who are not initially treated with antimicrobial therapy?

Patients with clinical improvement or cure on days 4–6 but culture-positive middle ear fluid were shown to have an increased rate of recurrent AOM compared to those with culture-negative middle ear fluid and clinical improvement or cure (Figure 6.3). Molecular analysis of the otopathogens isolated at recurrence and those identified on days 4–6 found concordance in 66% of patients. These observations emphasize the benefit of bacteriologic eradication in AOM.

Does amoxicillin remain the initial drug of choice when the decision to use antimicrobial therapy has been made?

The selection of antimicrobial therapy should be based on knowledge of the microbiology of AOM, pharmacodynamic principles, and clinical trials using both clinical and microbiologic outcomes. Eighteen antibiotics are currently approved by the US Food and Drug Administration (FDA) for treatment of AOM; however, the emergence of otopathogens with reduced susceptibility to β-lactam antibiotics (SP and

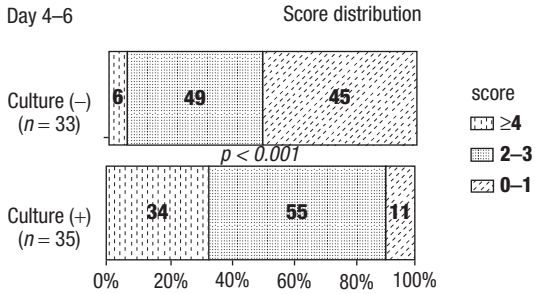

Figure 6.2 Symptoms score in children with AOM.

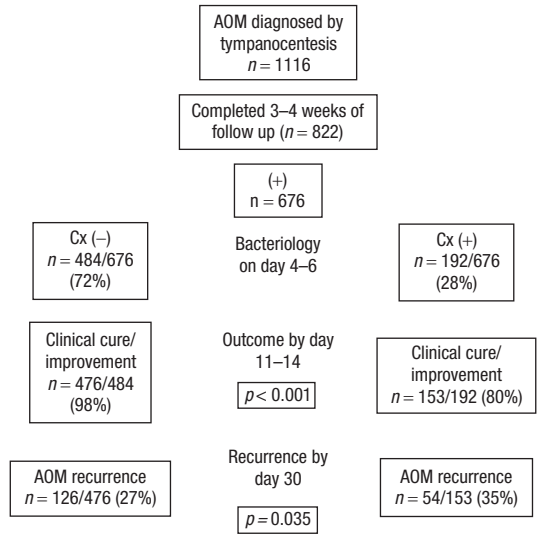

Figure 6.3 Association between eradication of middle ear pathogens during Rx and improvement in clinical symptoms. Cx = culture.

NTHi) has limited the efficacy of some antimicrobials. In the majority of cases of AOM, the specific pathogen is unknown, and presumptive therapy is based on the potential pathogens and their in vitro susceptibility. The proportion of isolates of NTHi-producing β-lactamase has slowly risen to nearly 50% over a 25-year period. A very limited number of β-lactamase-producing, amoxicillin-clavulanate-resistant isolates have also been reported in the United States. The recent emergence of nonvaccine serotypes of pneumococci with reduced susceptibility to β-lactam agents as well as macrolides and trimethoprim–sulfamethoxazole must also be considered in selection of antimicrobial therapy. Because there are no clinical differences between cases with resistant and susceptible pathogens, epidemiologic risk features must be assessed and tympanocentesis employed when a specific microbiologic etiology is needed.

Children with infrequent episodes of OM, without recent antimicrobial therapy, without conjunctivitis, older than 2 years, or not in day care are at low risk for drug-resistant *Streptococcus pneumoniae* (DRSP) or β-lactamase-producing NTHi. For these children the AAP guidelines recommend amoxicillin (Table 6.4).

Children with recent antimicrobial therapy or conjunctivitis are at higher risk for disease due to nonsusceptible *S. pneumoniae* or β-lactamase-producing NTHi. In these children only oral high-dose amoxicillin and intramuscular ceftriaxone achieve middle ear concentrations high enough to exceed the minimal inhibitory concentration (MIC) of all *S. pneumoniae* that are intermediately sensitive to penicillin and of many, but not all, highly resistant strains as well as strains of NTHi that do not produce β-lactamases. Cefuroxime axetil, cefprozil, and cefpodoxime represent alternatives to high-dose amoxicillin; however, each achieves sufficient middle ear concentration to be effective against only approximately 50% of *S. pneumoniae* isolates that are intermediately susceptible to penicillin. Also, cefprozil has limited activity against NTHi. Macrolides are very effective when fully susceptible isolates of *S. pneumoniae* are present. Because amoxicillin clavulanate resists destruction by β-lactamase, it effectively eradicates middle ear infection caused by NTHi. Although the AAP guidelines recommend the consideration of amoxicillin clavulanate as initial therapy only for children with severe disease, the increasing prevalence of AOM due to NTHi warrants consideration for broader use of amoxicillin clavulanate as first-line therapy in selected children.

Initial therapy for children with type I allergy to penicillin (urticaria, laryngeal spasm, wheezing, or anaphylaxis) is limited. Alternatives to β-lactams are limited because of substantial resistance among otopathogens. Macrolides, including azithromycin and clarithromycin, are active against most pneumococcal isolates; however, up to 40% of *S. pneumoniae* have MIC that are beyond the breakpoints for these agents. Resistance to trimethoprim sulfamethoxazole among *S. pneumoniae* and NTHi also is frequent. In the current era, β-lactamase-producing NTHi has emerged as the most common pathogen in children failing initial therapy with amoxicillin (Figure 6.4). The current distribution of pneumococcal serotypes found in the nasopharynx and reported from middle ear cultures includes

isolates with reduced susceptibility to β-lactam antibiotics and macrolides (Table 6.5); however, the prevalence of MDR and specifically penicillin-resistant (MIC > 2.0 μg/mL) isolates has declined. For these children, a three-dose regimen of ceftriaxone (50 mg/kg/day) has demonstrated efficacy (Table 6.6). Anecdotal data support the efficacy for clindamycin and linezolid against nonsusceptible SP; however, neither is active against *Haemophilus influenza*. High-dose amoxicillin in combination with cefixime or ceftibuten and standard-dose amoxicillin in combination with amoxicillin-clavulanate are also appropriate. Clinical studies of quinolones (specifically gatifloxacin and levofloxacin) demonstrate rapid sterilization and clinical resolution of middle ear infection due to both *S. pneumoniae* and NTHi. Currently, quinolones are not licensed for use in children for the treatment of AOM.

Table 6.4 AAP/AAFP recommended antibacterial agents

Temperature ≥ 39°C and/or severe earache	At diagnosis for patients being initially treated with antibacterial agents or clinically defined treatment failure at 48–72 hours after initial management with observation	
	Recommended	Alternative for penicillin allergy
No	Amoxicillin 80–90 mg/Kg/day	Non-type I: Cefdinir Cefuroxime Cefpodoxime Type I: Azithromycin Clarithromycin
Yes	Amoxicillin-clavulanate 90/6.4 mg/Kg/day	Ceftriaxone 1 or 3 days

AAP/AAFP Clinical Practice Guideline: Diagnosis and Management of Acute Otitis Media 2004.

PREVENTION OF RECURRENT ACUTE OTITIS MEDIA

Middle ear disease has been identified as the most common reason for ambulatory healthcare visits, and persistent middle ear fluid with conductive hearing loss is frequent.

Prevention of recurrent AOM can be achieved by preventing nasopharyngeal colonization with otopathogens, preventing viral respiratory infection, or providing specific antibacterial immunity. Insertion of tympanostomy tubes does not reduce the frequency of acute episodes substantially; however, the presence of such tubes shortens the duration of middle ear effusion and restores the conductive hearing loss frequently associated with such effusions. Antimicrobial prophylaxis lowers the frequency of colonization with respiratory otopathogens and decreases the number of acute episodes. Mandel and colleagues found a decrease in acute episodes from 1.04 per child per year in the placebo group to 0.28 in a group

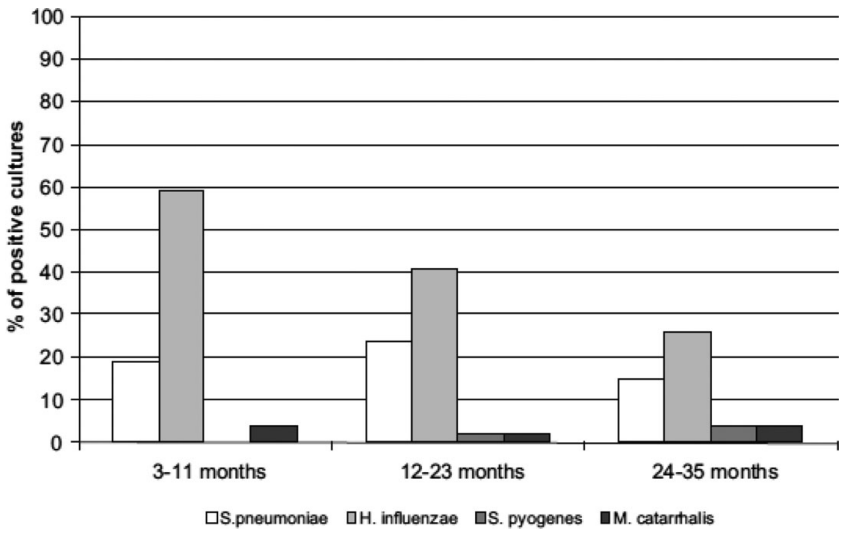

Figure 6.4 Microbiology of bacteria causing recurrent acute otitis media (AOM) and AOM treatment failure in young children in Spain: Shifting pathogens in the post-pneumococcal conjugate vaccination era. (Reprinted with permission from Pumola F, *et al. International Journal of Pediatric Otolaryngology* 2013.)

Table 6.5 Antibiotic susceptibilty patterns among isolates recovered by tympanocentesis from children with recurrent episodes of acute otitis media.

		S. pneumoniae			
		19A (*N* = *9*)	**Other (*N* = *16*)**	**NTHi (*N* = 54)**	***M. catarrhalis* (*N* = 3)**
Antibiotic/test	Resistant (MIC)	*n*(%)	*n*(%)	*n*(%)	*n*(%)
Cefotaxime	≥4	3(33)	0(0)	0	0
Erythromycin	≥1	8(89)	6(38)	–	–
Penicillin G	≥8	0	2(13)	–	–
Amoxicillin	≥8	7(78)	3(19)	–	–
Ampicillin	≥4	–	–	8(15)	–
Cefpodoxime	≥2	2(78)	2(13)	0	0
Amoxicillin/clavulanic acid	≥8/4	–	–	7(13)[a,b]	0
Multidrug resistance	–	7(78)	3(19)	0	2(67)

N = number of isolates; *n*(%) =number(percentage of resistant isolates); – = not tested.

[a] Two were β-lactamase producing.

[b] All were also ampicillin resistant.

MIC, mean inhibitory concentration.

Table 6.6 AAP/AAFP recommended antibacterial agents.

Temperature ≥ 39°C and/or severe earache	**Clinically defined treatment failure at 48–72 hours after initial management with antibacterial agents**	
	Recommended	**Alternative for penicillin allergy**
No	Amoxicillin-clavulanate 90/6.4 mg/Kg/day	Non-type I: Ceftriaxone 3 days Type I: Clindamycin
Yes	Ceftriaxone 3 days	Tympanocentesis Clindamycin

AAP/AAFP Clinical Practice Guideline: Diagnosis and Management of Acute Otitis Media 2013.

receiving prophylactic amoxicillin. The reduction in acute episodes was accompanied by a reduction in persistent MEF. The greatest benefit occurs in otitis-prone children who have multiple episodes per year and in whom recurrences continue despite increasing age; however, chemoprophylaxis offers short-term benefits only. Most otitis-prone children continue to have recurrent episodes once prophylaxis is discontinued, until their immune systems and Eustachian tube function have matured.

The pathogenesis of AOM involves coinfection with respiratory viruses in more than 85% of episodes. Immunization with influenza vaccine reduces febrile AOM episodes as well as insertions of tympanostomy tubes during a winter season. Annual immunization is recommended for children with risk factors for ROM, such as attendance at out-of-home child care, family history of recurrent AOM, or early onset of disease. Seven-valent pneumococcal conjugate vaccines (PCVCRM and PCVOMP), administered at 2, 4, and 6 months with a booster at 12 to 15 months of either 7-valent PCV or 23-valent pneumococcal polysaccharide vaccine have been demonstrated to reduce AOM due to vaccine serotypes of *S. pneumoniae* by approximately 60%, and all episodes of pneumococcal otitis media by one-third. However, the overall reduction in clinical episodes of AOM was more modest (6% to 10%). A critical concern in the studies was the small increase in episodes of AOM due to nonvaccine serotypes and NTHi. Postlicensure studies have confirmed an increase in the proportion of AOM due to nonvaccine serotypes of SP. Follow-up of the original clinical trials of PCV7 in both the Northern California Kaiser Permanente cohort and the FinOM cohort identified significant reductions in tympanostomy tube insertions in the children immunized in infancy with PCV7. Studies of PCV7 in children with frequent recurrences of otitis media or those at risk for CSOM have failed to demonstrate a significant reduction in recurrent episodes. Veenhoven observed that disease due to vaccine serotypes of *S. pneumoniae* was only a small proportion of overall episodes

in children with a history of ROM. Leach and colleagues found a nonsignificant reduction in episodes of chronic suppuration in the first year of life in Aboriginal children immunized with PCV7.

In 2010, PCV13 was introduced as a second-generation pneumococcal conjugate vaccine to broaden coverage against serotypes more commonly causing disease outside of North America (serotypes 1, 3, and 5) as well as replacement serotypes, specifically 19A, 7F, and 6A. Early observational data have demonstrated a further decline in overall pneumococcal AOM episodes including those due to serotype 19A.

COMPLICATIONS OF ACUTE OTITIS MEDIA

Perforation of the tympanic membrane is the most common complication of AOM and occurs most frequently in younger children. Certain ethnic groups, such as Alaskan Eskimos and Native Americans, have a higher rate of spontaneous perforation. Differentiation between AOM with perforation and acute otitis externa can be difficult. In general, the history of increasing pain with relief when otorrhea occurs is found with AOM, whereas increasing pain without relief in the face of otorrhea is seen with otitis externa. The microbiology of AOM in children with acute perforation reports a greater proportion of episodes due to group A streptococcus (GAS) and *Staphylococcus aureus*. However, *S. pneumoniae*, NTHi, and *M. catarrhalis* remain predominant. The natural history of AOM with perforation is usually complete resolution with healing of the tympanic membrane. A small proportion of patients can have persistent dry perforation or experience CSOM (otorrhea persisting for more than 6 to 12 weeks). *Streptococcus pneumoniae* and NTHi are the most common pathogens in infants and toddlers whereas *S. aureus* and *Pseudomonas aeruginosa* are frequent pathogens in older children and during the summer months. An increasing proportion of the *S. aureus* isolates, even those acquired in the community, are resistant to methicillin. Topical otic suspensions, either ofloxacin or ciprofloxacin, is the preferred therapy for uncomplicated episodes of acute otorrhea through a tympanostomy tube. Both of the quinolones are active against pseudomonas as well as the respiratory otopathogens. Amoxicillin is generally effective for acute otorrhea through a tympanostomy tube when disease is due to respiratoy pathogens, and results in rapid clearing of bacterial pathogens and a resolution of otorrhea. When methicillin-resistant *S. aureus* (MRSA) is the pathogen, fluoroquinolone and sulfacetamide ototopical medications were found to be effective. Adjunctive therapy with oral antibiotics, bactrim and clindamycin respectively, did not improve resolution rates. Topical vancomycin (25 mg/mL) drops or the use of trimethoprim–sulfamethoxazole orally in combination with gentamicin otic has also been reported as successful. Caution with both of these regimens is necessary as safety has not been established.

Facial palsy as a complication of AOM has become less prominent with the routine use of antibiotic therapy. Facial weakness and earache are the predominant symptoms. Management with antimicrobial agents and myringotomy (with or without tube insertion) is usually sufficient to achieve complete resolution.

An unusual complication, inflammatory cast of the tympanic membrane causing hearing loss, may occur after AOM with perforation. Patients present with unilateral persistent hearing loss. The diagnosis is suspected by comparison of the affected and unaffected tympanic membranes. On the affected side, a thin, hard cast is observed. Removal results in improvement in hearing.

The incidence of mastoiditis has decreased dramatically with the routine use of antimicrobial therapy. However, it remains the most common suppurative complication of AOM. Although the potential for re-emergence of mastoiditis when antimicrobial agents are withheld for AOM has been a concern, there are few convincing data to suggest an increase in incidence. The management of acute mastoiditis depends on disease classification. *Acute mastoiditis with periostitis* results from an obstruction of the connection between the middle ear and mastoid space (aditus ad antrum). Postauricular erythema, tenderness, and edema are the clinical manifestations. AOM is often but not universally present. *S. pneumoniae*, GAS, and NTHi are most common but *Pseudomonas aeruginosa* was found in 29% and *Staphylococcus epidermidis* in 31% of cases in one large series. *Pseudomonas* and *Staphylococcus* should be suspected when a history of otorrhea precedes development of acute mastoiditis.

Labyrinthitis develops when AOM spreads (through the round window) into the cochlear space. The process may be suppurative or serous (due to toxins). The onset of labyrinthitis is often sudden, with vertigo and hearing loss being

characteristic. Acute surgical intervention (myringotomy with tube insertion) with antimicrobial therapy is the treatment of choice. Additional rare complications of AOM are brain abscess, lateral sinus thrombosis, and otic hydrocephaly.

Gradenigo's syndrome is a rarely seen complication of AOM where infection spreads to the apex of the petrous temporal bone. A triad of symptoms consisting of unilateral periorbital pain due to trigeminal nerve involvement, diplopia due to sixth nerve palsy, and persistent otorrhea is present. This classical triad has become very uncommon in the antibiotic era.

OTITIS EXTERNA

Acute otitis externa (AOE) is primarily a pediatric disease occurring most frequently in children 6 to 12 years of age. The disease results from a disruption of integrity of the ear canal and the normal self-cleaning process of epithelial migration toward the external os. Swimming, local trauma, accumulation of debris from dermatologic conditions, or the wearing of hearing aids are predisposing factors. The early manifestations are itching, pain, and erythema of the canal but the disease can progress with severe swelling and obstruction of the external canal or extension to the bony external canal or even the base of the skull in the elderly or in patients with comorbidity (see discussion of malignant external otitis in Chapter 148, *Pseudomonas*, *Stenotrophomonas*, and *Burkholderia*).

Early in the course, minimal, odorless secretions and erythema of the external canal in association with mild pain and pruritus are present. As the disease progresses, erythema increases and edema of the canal becomes manifest. Seropurulent secretions may be present and acute pain is elicited by movement of the auricle or direct pressure on the tragus. Severe disease is noted by edema of the canal wall obstructing the lumen, intense pain, and extension to cervical adenitis or auricular cellulitis.

The diagnosis of AOE requires rapid onset of symptoms over several days with evidence of inflammation of the external ear canal manifest by otalgia, itching, tenderness of the tragus or pinna, and/or diffuse erythema. Systemic manifestations such as cervical adenitis or cellulitis of the pinna may be present. Distinguishing AOE from AOM is critical as the therapy is markedly different. Identification of complications that may be manifest by facial paralysis, vertigo, or meningeal signs or cranial nerve palsy or the presence of granulation tissue at the junction of the boney and cartilaginous portions of the canal is critical. A furuncle may be observed in the external canal. Often referred to as localized otitis externa, this represents an infected hair follicle in the outer third of the external canal. History is helpful in discriminating AOE from AOM. Often the pain in AOE is progressive whereas in AOM the pain will usually abruptly improve when perforation occurs. The tympanic membrane in both AOM and AOE is frequently erythematous but in AOE pneumatic otoscopy reveals normal motility. Otomycosis may manifest as thick otorrhea, white debris with hyphae in the canal (*Candida*), or a white plug with dark debris (*Aspergillus niger*).

Topical therapy is the initial choice for diffuse, uncomplicated AOE as there is no need for systemic antimicrobials unless there are comorbid conditions that are associated with disease complications, there is progression to cellulitis of the pinna or adenitis, or topical therapy is contraindicated. AOE is primarily a bacterial disease with *Pseudomonas aeruginosa* the dominant pathogen followed by *S. aureus*. Fungal infection is uncommon except in those who have failed initial topical therapy. Mild disease can be treated with 2% acetic acid with or without a steroid. Compliance may be poor as acetic acid is irritating and frequently causes stinging when administered topically. Topical antimicrobial preparations containing an aminoglycoside, polymyxin B, or a quinolone with or without a steroid are effective but should only be used when the tympanic membrane is intact. These topicals achieve local tissue concentrations 1000-fold that of systemic administration. No significant difference in clinical outcome has been established for antiseptic vs. antimicrobial preparations, for quinolone vs. nonquinolone formulations, or for steroid-antimicrobial preparations compared with antimicrobials alone. However, when a perforation of the tympanic membrane is suspected, a tympanostomy tube is in place, or the tympanic membrane has not visualized, only quinolone formulations are approved for use. Critical for topical therapy to be successful is the delivery. Self-administration is difficult and often unsuccessful. Ototopical formulations should be administered with the patient lying on his/her side. The canal should be filled and, if necessary, the pinna pulled forward and back to assist filling. Some clinicians use aural lavage for removal of debris either initially or, if necessary, repeatedly. Pain may limit the ability to perform

aural lavage or suction. If edema is present, a wick of either compressed cellulose or ribbon gauze will enable complete delivery of the ototopical agent. Once the edema resolves, the wick may be removed and therapy continued to complete 7 to 10 days. Adverse events with topical therapy are not common; however, sensitization especially to those formulations that contain neomycin can occur. If infection has spread beyond the ear canal, or in patients at risk of rapid progression, or if signs and symptoms fail to improve, systemic antimicrobial therapy should be added based on the results of susceptibility testing of external ear canal culture.

Fungal disease, most commonly *Candida* or *Aspergillus*, is most often found in patients failing initial topical therapy. Two approaches have been used successfully: ketoconozole cream can be applied to the external canal directly once with follow-up examination in 5 to 7 days and repeat application if needed or Cresylate otic is applied three times a day. Both treatments achieve greater than 80% cure rates. Most recently, community-acquired methicillin-resistant *S. aureus* (CaMRSA) has emerged as an increasing cause of AOE. Treatments used successfully in the treatment of MRSA otitis externa were aural toilet and fusidic acid-betamethasone 0.5%. Most CaMRSA are susceptible to quinolones and it would be expected that ofloxacin or ciprofloxacin formulations should be effective.

Pain management is an integral part of treatment of AEO. Nonsteroidal anti-inflammatory agents and benzocaine otic have been used successfully to manage the discomfort of AOE.

In children with recurrent otitis externa, strategies such as the use of acidifying ear drops before or after swimming, the use of a hair dryer to dry the ear canal after swimming or bathing, or the use of ear plugs while swimming have all been used successfully. If recurrences persist, allergies or underlying inflammatory dermatologic conditions should be sought and the underlying causes addressed.

Necrotizing otitis externa is a complication of otitis externa in which infection extends from the external auditory canal to the base of the skull. It is seen commonly in elderly patients with diabetes and immunocompromised hosts, often in those with advanced HIV. The most common pathogen is *Pseudomonas aeruginosa*; however, a spectrum of pathogens including *Aspergillus* species, *S. aureus, Proteus mirabilis, Klebsiella oxytoca, Burkholderia cepacia*, and *Candida parapsilosis* has been reported. The presentation is characterized by severe pain; cranial nerve involvement is reported in a significant proportion. On physical exam granulation tissue is often visible at the bone–cartilage junction of the external auditory canal. Systemic fluoroquinolones, third-generation cephalosporins, and surgical debridement are the mainstay of treatment.

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7. Sinusitis

Charles D. Bluestone and Todd D. Otteson

Sinusitis is commonly diagnosed, yet criteria for its diagnosis vary and a standard treatment protocol is nonexistent. The majority of patients with acute sinusitis improve without any therapy or with over-the-counter remedies. The temptation to treat an upper respiratory infection with antimicrobials should be avoided, especially in light of increasing bacterial resistance profiles. An understanding of the anatomy, pathophysiology with predisposing factors, and common microbiology helps drive therapeutic decision making.

SINUS ANATOMY

The paranasal sinuses consist of paired maxillary, ethmoid, sphenoid, and frontal sinuses. The maxillary and ethmoid sinuses are present at birth and fully pneumatize during childhood. The paired sphenoid and frontal sinuses appear in childhood and continue to pneumatize into early adulthood in some cases. The maxillary, anterior ethmoid, and frontal sinuses drain into the osteomeatal complex (OMC). The OMC is a functional physiologic unit comprising the ethmoid infundibulum, middle meatus, and surrounding structures. The OMC and its patency are the keys to normal sinus drainage and the maintenance of physiologic mucociliary clearance.

PATHOPHYSIOLOGY

Any anatomic anomaly, environmental exposure, or disease process, acute or chronic, that prevents the normal mucociliary clearance either by functional obstruction or by thickening of nasal secretions may result in pathogen overgrowth and sinusitis. Typically these processes or exposures affect not only the paranasal sinus mucosa but also the intranasal mucosa, prompting use of the term rhinosinusitis. Table 7.1 outlines causes of obstruction, thickened secretions, and dysfunction of mucosal cilia. Rarely, direct inoculation of bacteria from odontogenic infection or during swimming or diving may cause acute sinusitis as well.

The bacteriology of sinusitis has been well documented. The results have been consistent for decades, with the most common organisms isolated in acute sinusitis being *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Since the vaccination of children with the seven-valent pneumococcal vaccine became commonplace after its introduction in 2000, there has been a decline in the recovery rate of *S. pneumoniae* and a corresponding increase in *H. influenzae*. Individual resistance to antibiotics has increased. The spectrum of organisms widens in chronic sinusitis to include anaerobic bacteria, *Staphylococcus aureus*, and gram-negative organisms, particularly *Pseudomonas aeruginosa*. Much research has been dedicated to the role of biofilm formation in the pathophysiology of chronic rhinosinusitis. A biofilm is a complex polysaccharide matrix synthesized by bacteria that is protective of bacterial colonies and renders them somewhat resistant to antibiotic therapy. *Pseudomonas aeruginosa* is a known biofilm former in patients with chronic rhinosinusitis. Anaerobic isolates are more common when the etiology of the infection is thought to be odontogenic.

DIAGNOSIS

Diagnosis of sinusitis is based on history and physical examination with radiographic support in certain cases. The physical examination consists of anterior rhinoscopy before and after topical decongestion. Any purulent drainage or edema in the area of the middle meatus should be documented as well as the general appearance of the nasal mucosa. Nasal endoscopy allows a more detailed examination of the nasal cavity. Palpation of the paranasal sinuses may elicit focal tenderness. Transillumination of the sinuses may be helpful in adults if the exam is normal or completely absent but is not reliable in children.

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Table 7.1 Conditions precipitating sinusitis

OMC obstruction
Concha bullosa
Mucosal edema secondary to rhinitis
Nasal foreign body
Nasal septal deviation
Nasogastric/nasotracheal tubes
Polyps
Secretion thickness
Allergic rhinitis
Cystic fibrosis
Viral upper respiratory infection
Ciliary dysfunction
Ciliary dyskinesia

Distinguishing between bacterial sinusitis and viral upper respiratory infection may be difficult but is important in planning a treatment strategy. A set of standardized definitions for rhinosinusitis based on symptom profile and duration is well accepted. Symptoms are described as major or minor and include facial pain, nasal obstruction, nasal discharge/postnasal drip, hyposmia/anosmia, purulence on examination (major), and headache, halitosis, dental pain, fatigue, cough, and ear pain/pressure (minor). Rhinosinusitis is acute when symptoms last 4 weeks or less, subacute when symptoms are present for 4 to 12 weeks, and chronic for symptoms present longer than 12 weeks. Recurrent acute rhinosinusitis occurs in patients with four or more episodes per year with disease-free intervals in between. An acute exacerbation of chronic sinusitis is defined as a sudden worsening of symptoms with return to baseline after treatment. If the onset of an acute sinusitis is severe, with fever of at least 39°C and purulent nasal discharge for at least 3 to 4 consecutive days at the beginning of the illness, consideration to starting treatment earlier than the usual 7 to 10 days of symptoms should be entertained.

Plain films add little to the diagnosis, especially if sinuses other than the maxillary sinuses are involved. If the clinical situation warrants it, the suspicion of sinusitis is confirmed by computed tomography (CT), which can demonstrate characteristic changes in the paranasal sinuses and especially the OMC. The best time to obtain a CT scan is at the end of a treatment course when the patient is not acutely ill. The CT scan is crucial if any surgical intervention is required. If there is concern for invasive fungal sinusitis in an immunocompromised patient, a CT and an MRI should both be obtained. Figure 7.1A shows the paired maxillary sinuses (M) with dependent fluid in the right maxillary sinus. Note also the right nasal septal deviation. Figure 7.1B shows the ethmoid sinuses (E) with some right anterior ethmoid opacification. Note also the proximity of the ethmoid sinuses to the orbit (O); the lamina papyracea is a layer of thin bone separating these structures. The sphenoid sinuses posteriorly are also present in this image. Figure 7.1C shows the frontal sinus (F).

TREATMENT

The treatment of acute sinusitis involves appropriate antibiotic therapy and should improve the patency of the sinus ostia. Topical decongestants, such as oxymetazoline, may alleviate nasal obstruction and decrease nasal mucosal edema but they can only be used for a short time. Systemic decongestants and mucolytics may assist with clearance of secretions. While treatment with these adjunctive therapies may provide some temporary symptomatic relief in some patients, there is no evidence supporting the use of antihistamines, decongestants, nasal steroids, mucolytics, or nasal irrigations for an acute sinusitis.

Ideal antimicrobial therapy eliminates the common bacteria that cause acute sinusitis with as narrow a spectrum as possible. Current antibiotic treatment recommendations for acute bacterial rhinosinusitis take into account emerging antimicrobial resistance patterns. In children, the first-line antibiotic therapy for acute sinusitis is amoxicillin–clavulanate dosed 45 mg/kg/day twice a day. High-dose amoxicillin–clavulanate dosed 90 mg/kg/day twice a day is recommended for children from locations with high rates of penicillin-nonsusceptible *S. pneumoniae*, who were recently hospitalized, or who were treated with another antibiotic course in the past month. For penicillin-allergic patients, levofloxacin is an alternative to amoxicillin/clavulanate. Treatment failure after 72 hours may require directed cultures and treatment with a broader-spectrum second-line agent.

Treatment of chronic sinusitis is aimed at alleviation of symptoms and diminishing sinus inflammation. Irrigation of the nasal cavity with normal saline as well as treatment with topical steroids, systemic antihistamines, or systemic

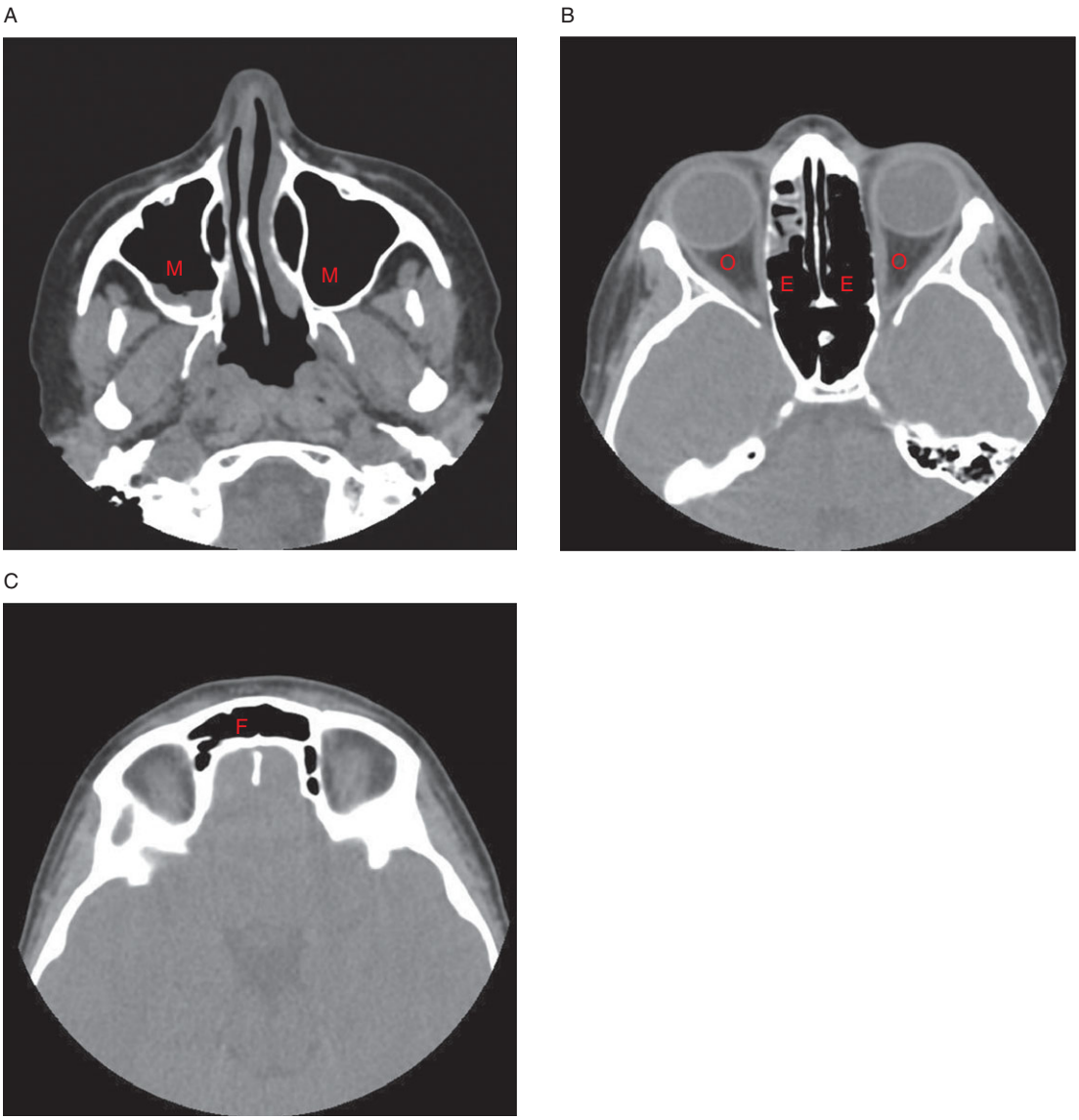

Figure 7.1 (A) Paired maxillary sinuses (*M*) with dependent fluid in the right maxillary sinus. (B) Ethmoid sinuses (*E*) with some right anterior ethmoid opacification and orbit (*O*). (C) Frontal sinus (*F*).

decongestants, may be attempted but data supporting them are inconclusive. Longer-term antimicrobial therapy lasting 4 weeks with a second-line antibiotic may improve symptoms when shorter courses have failed.

If patients with either chronic sinusitis or recurrent acute sinusitis fail to respond to these medical measures, consultation with an otolaryngologist should be considered. Investigation into the etiology of the inflammation causing rhinosinusitis, including any anatomic or physiologic source, should be undertaken and surgical management considered. The goal of surgical intervention is to restore sinus drainage while preserving as much paranasal sinus and nasal mucosa as possible.

COMPLICATIONS

Complications of sinusitis are almost exclusively a phenomenon of acute sinusitis and involve spread of infection to adjacent structures. Acute ethmoid sinusitis may cause orbital infection that ranges from preseptal cellulitis to orbital cellulitis to subperiosteal orbital abscess to orbital abscess

with possible secondary cavernous sinus thrombosis. Frontal sinusitis may precipitate meningitis or intracranial abscess. Therapy involves intravenous antibiotic therapy and possibly surgical drainage of the affected sinus or sinuses.

FUNGAL SINUSITIS

Fungal sinusitis typically occurs in patients with immunodeficiency for any reason, including uncontrolled diabetes mellitus and patients taking immunosuppressive medications after transplant or hematologic malignancy. Treatment in these cases involves intravenous antifungal medications and aggressive surgical debridement. Reversal of the immunosuppression is advised if possible. A less aggressive form of chronic invasive fungal sinusitis has been described in immunocompetent patients.

Allergic fungal sinusitis is characterized by an allergic inflammation of the sinonasal mucosa from colonizing fungi. Tissue samples show no mucosal invasion. The allergic response of the mucosa is immunoglobulin E (IgE)-mediated inflammation. The production of thick, tenuous, allergic mucin is pathognomonic. Histologic examination of the mucosa reveals chronic inflammation with eosinophils. The mucin demonstrates fungal hyphae characteristic of the species involved and Charcot–Leyden crystals. Treatment consists of conservative surgical debridement, either topical or systemic antifungal therapy, and topical or systemic steroids depending on the clinical situation.

A fungal ball, or mycetoma, typically involves a single sinus, is not considered invasive, and may masquerade as chronic sinusitis. Treatment is surgical, addressing only the sinus(es) in question with no subsequent medical therapy required.

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8. Dental infection and its consequences

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ANATOMY

The treatment of odontogenic infections requires an understanding of the fascial spaces surrounding maxillomandibular dentition (Figure 8.1). Although both maxillary and mandibular teeth can become infected, infections of mandibular dentition are more common. Anatomic spaces involved by maxillary infections include the canine and buccal spaces, with the orbit and cavernous sinus less commonly affected. If untreated, odontogenic infections tend to erode through the thinnest, closest cortical plate. The thinner bone in the maxilla is on the labial-buccal side, the palatal cortex being thicker. The canine space is that region between the anterior surface of the maxilla and the levator labii superioris (Figure 8.2). Infection of this fascial space usually results from maxillary canine tooth infection. The buccal space is located between the buccinator muscle and the skin and superficial fascia. Infections of this space usually result from maxillary molar processes with the premolars as the rare culprits. Orbital cellulitis or cavernous sinus thrombosis are unusual but serious manifestations of maxillary infection. Under such circumstances, the infection most likely spreads both by direct extension as well as hematogenously.

In the mandible, the thinnest region is on the lingual aspect around the molars and the buccal aspect anteriorly. The primary mandibular spaces include the submental, sublingual, and submandibular fascial spaces. The submental space is that area between the anterior belly of the digastric muscle, the mylohyoid muscle, and the skin. Infection here usually results from the mandibular incisors (Figure 8.3). Medially, the sublingual and submandibular spaces are typically affected by the mandibular molars. Whether the infection is in the sublingual or submandibular space is determined by the relationship between the area of perforation and the mylohyoid attachment. Specifically, if the apex of the offending tooth is superior to that of the mylohyoid (e.g., premolars, first molar, and occasionally second molar), the sublingual space is affected; if the infection is inferior (e.g., third molar and occasionally second molar), the submandibular space is involved. Multiple fascial spaces can be infected simultaneously. For example, the sublingual space lies between the oral mucosa and the mylohyoid and communicates along the posterior boundary of the mylohyoid muscle with the submandibular space. When infection involves the primary

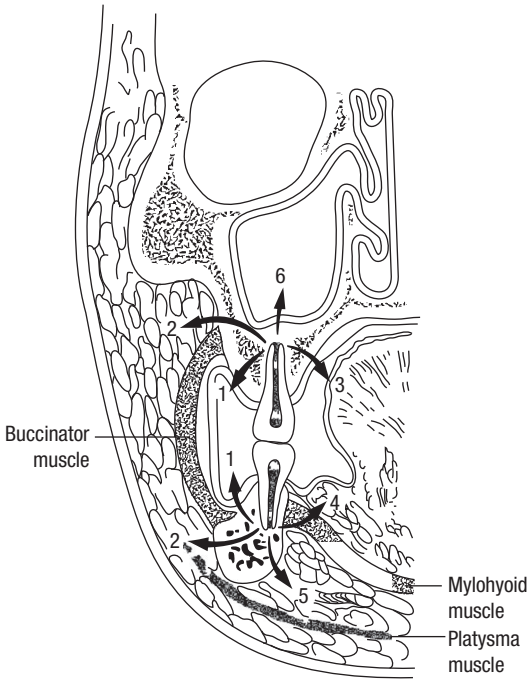

Figure 8.1 An odontogenic infection can express itself after erosion through jaw bone, depending on the thickness of the overlying bone and the nature of the surrounding soft tissues. This illustration displays six possible locations: (1) vestibular abscess, (2) buccal space, (3) palatal abscess, (4) sublingual space, (5) submandibular space, and (6) maxillary sinus. Cummings: *Otolaryngology: Head & Neck Surgery, 4th ed.*, Copyright © 2005 Mosby, Inc.

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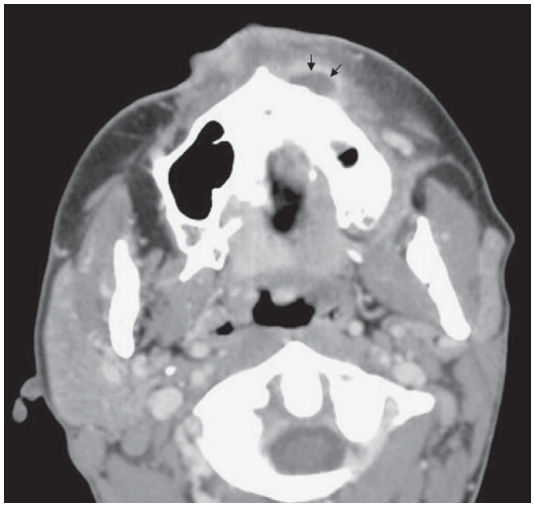

Figure 8.2 CT image demonstrating an abscess of the canine space (black arrows).

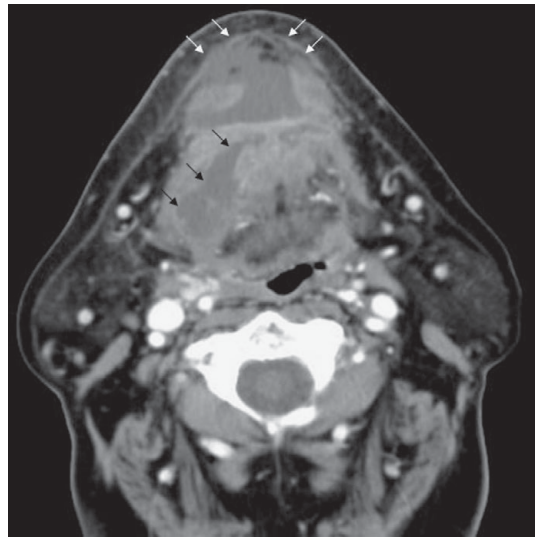

Figure 8.3 CT image demonstrating an abscess of the floor of mouth (black arrows) and submental space (white arrows).

mandibular spaces bilaterally it is known as Ludwig's angina.

Odontogenic infection can extend beyond the mandibular spaces to the neck to involve the cervical fascial spaces. The secondary mandibular spaces include the pterygomandibular, masseteric, and temporal spaces. These fascial spaces become infected as the result of secondary spread from more anterior spaces, including the buccal, sublingual, and submandibular spaces. The pterygomandibular space lies between the medial aspect of the mandible and the medial pterygoid muscle. The masseteric space is that area between the lateral mandible and the masseter muscle, and the temporal space is superior and posterior to the pterygomandibular and masseteric spaces. Infection of these areas almost uniformly produces trismus resulting from inflammation of the muscles of mastication.

Infection in these spaces may progress to the deep neck spaces, which include the lateral pharyngeal (parapharyngeal) space, the retropharyngeal space, and the prevertebral space. Infections of these spaces are discussed in detail in Chapter 10, Deep neck infections. One should keep in mind, however, that up to 30% of deep neck infections may result from odontogenic processes. Deep neck infections may spread distally into the mediastinum.

PATHOPHYSIOLOGY

Odontogenic infections and their complications may be encountered by any clinician who treats diseases of the mouth and throat. Most infections are minor and self-limited, confined to the offending tooth and its apex. Under certain circumstances, however, the infectious process may break through the bony, muscular, fascial, and mucosal barriers and spread to contiguous spaces, resulting in soft-tissue infections.

Typically, infections originate within the dental pulp, periodontal tissue, or pericoronal tissue from a carious tooth. This results in bacterial invasion and a local inflammatory response, which includes vasodilatation and edema leading to increased pressure, which exacerbates the pain and decreases the blood supply. This sequence of events exacerbates the periapical necrosis, with subsequent bacterial invasion into bone and erosion of the bony cortex into surrounding soft tissues. The spreading infection can result in a chronic sinus tract or, under the appropriate circumstances (e.g., perforation of the cortical bone above the muscular attachment), a fascial space collection. Alternatively, infections involving the maxillary dentition may spread to involve the maxillary sinus and present as unilateral maxillary sinusitis.

The microbiology of odontogenic infection reflects the normal endogenous oral flora. A large number of bacteria are contained in the mouth, particularly around the dental crevices. It has been estimated that 40% to 70% of all oral bacterial species have yet to be cultivated and phenotypically characterized. Infections that

result from the spread of these organisms into surrounding soft-tissue spaces are often polymicrobial. Anaerobic bacteria are dominant in odontogenic infections. Techniques for isolating and identifying anaerobic bacteria tend to be labor- and time-intensive. Molecular biology techniques including PCR and pyrosequencing have enhanced our understanding of the microbiology of the oral flora and odontogenic infections.

The phyla *Firmicutes* (e.g., genera *Streptococcus*, *Dialister*, *Filifactor*, and *Pseudoramibacter*) and *Bacteroidetes* (e.g., genera *Porphyromonas*, *Prevotella*, and *Tannerella*) comprise more than 70% of the species found in dental abscesses. Other species frequently identified belong to the phyla *Fusobacteria* (e.g., genera *Fusobacterium* and *Leptotrichia*), *Actinobacteria* (e.g., genera *Actinomyces* and *Propionibacterium*), *Spirochaetes* (e.g., genus *Treponema*), *Synergistetes* (e.g., genus *Pyramidobacter*), and *Proteobacteria* (e.g., genera *Campylobacter* and *Eikenella*).

DIAGNOSIS

Odontogenic infections commonly present with pain and swelling around the infected tooth. As the infection progresses, a sinus tract may develop as detected by drainage and usually decreased discomfort. If the infection spreads into the surrounding soft tissues and fascial spaces, the signs and symptoms may become systemic and include fever, leukocytosis, and dehydration. It should be noted that with the spread of the infection, local signs and symptoms of odontogenic infection may diminish and the origin of the space infection may seem remote or obscure.

Signs and symptoms of fascial space involvement include swelling of the face and lateral neck, trismus, dysphagia, and airway compromise. To assess the airway for impending compromise, one should note tongue mobility, floor-of-mouth edema, uvular deviation, and lateral pharyngeal swelling. The presentation of infection of the floor of the mouth, or Ludwig's angina, deserves special mention. Patients may develop this widespread fascial space infection as a result of second or third molar infection or widespread periodontal disease. Cellulitis of the floor of mouth rapidly becomes a spreading, gangrenous process producing elevation and displacement of the tongue and brawny induration of the entire submandibular region. Airway compromise can occur precipitously (Table 8.1), hence appropriate precautions should be undertaken.

Table 8.1 Emergency considerations

Presence of subcutaneous air Consider necrotizing fasciitis
Ludwig's angina – progressive severe soft-tissue edema Consider tracheotomy

Information regarding the causative dentition as well as the extent of infection may be gained through radiographic evaluation. A panoramic radiograph (panorex) of the maxilla and mandible is useful to examine the bone morphology and presence of impacted teeth or caries. When there is clinical suspicion of infection extending to the soft tissues of the head and neck, computed tomography (CT) or magnetic resonance imaging (MRI) is warranted. CT with contrast is generally considered to be the first-line imaging modality given its lower cost, greater availability, and patient tolerance relative to MRI. However, in a prospective study of 47 patients, Muñoz *et al*. concluded that MRI was superior to CT in the initial evaluation of odontogenic infections in terms of anatomic discrimination, lesion conspicuity, and extension of the processes. MRI was also more precise in identifying the number of spaces involved. However, CT is more sensitive in detecting intralesional gas. It is yet unclear whether these advantages of MRI translate into improved patient outcomes to warrant its routine use in this setting.

THERAPY

Initial evaluation should seek to determine the site and nature of the infectious process. In the presence of palpable fluctuance on physical exam or radiographic evidence of abscess, treatment is surgical drainage.

It is often not difficult to obtain material for Gram stain and culture. One approach is needle aspiration. However, precautions should be taken to obtain the material in a sterile fashion, process it under anaerobic conditions, and make an effort to evaluate the Gram stain before starting antibiotics. The administration of antibiotics is necessary under most circumstances to control the infection. Antibiotics should be administered before surgical drainage or if the process is determined to be in the cellulitic phase. The choice of antimicrobial agent(s) sometimes must be made empirically. In addition, the general condition of the host (e.g., dehydration, predisposing conditions such as diabetes mellitus and immunocompromise)

must be taken into consideration when devising a treatment plan. The presence of palpable subcutaneous air or air on radiographs is an indication of infection by gas-forming organisms and is a hallmark of necrotizing fasciitis, a surgical emergency.

Choosing an effective antibiotic for an odontogenic infection depends on the ability of the clinician to correctly predict the offending organism (s). As noted, these infections are nearly always polymicrobial and caused by endogenous oral cavity flora. Monotherapy is generally preferable because of the reduced cost, fewer potential side effects, and greater ease of administration. The antibiotic should have activity against oral anaerobes and streptococci.

Penicillin G, once a first choice for odontogenic infection, is rarely used for serious infection because of the rising incidence of penicillin-resistant streptococci in the community as well as the frequency of β-lactamase-producing *Bacteroides* species (estimated to be greater than 30%). Amoxicillin or amoxicillin–clavulanate is an acceptable first-line agent for the treatment of early or mild odontogenic infections. Clindamycin is an effective alternative for penicillin-allergic patients. Metronidazole is effective against oral anaerobes, but has no activity against aerobic organisms and must be used in combination with another antimicrobial. If one chooses a cephalosporin, it should be noted that the higher ''generations'' tend to sacrifice gram-positive aerobic activity for gram-negative efficacy. First-generation agents, such as cefazolin and cefoxitin, are likely more effective than other, broader-spectrum drugs.

A study by Salinas *et al*. of antibiotic susceptibility of bacteria causing odontogenic infections found high susceptibility for amoxicillin, amoxicillin/clavulanate, linezolid, and clindamycin. Conversely, a relatively high proportion of bacteria cultured were resistant to metronidazole, erythromycin, and azithromycin. Antibiotics should be administered parenterally for severe infections and in the perioperative period (e.g., 24 to 48 hours). Ampicillin–sulbactam is an appropriate first-line choice for parenteral therapy. Once the drainage catheters are removed and the patient is ready for discharge, the oral route of administration is adequate. Decisions regarding the duration of antimicrobial administration are made empirically, but a 2-week course usually is adequate. Macrolides should be used with caution in patients who are on other drugs that prolong the Q-T interval as this can result in a potentially lethal cardiac arrhythmia (torsades de pointes).

Evacuation of the purulent collection is the standard of care for odontogenic infections. Cellulitis which has not progressed to abscess formation may resolve with antibiotic therapy. However, the patient must be followed closely and surgery undertaken if abscess ensues. Surgery may entail a minor procedure, such as drainage of a periapical abscess, or extensive debridements of adjacent fascial compartments in the case of necrotizing fasciitis.

The route of drainage should be evaluated on an individual basis. General principles to be followed include stabilization of the airway, protection of vital structures, adequate visualization at the time of drainage, copious irrigation of the abscess cavity with saline solution, and postoperative drainage of the wound. Canine and isolated sublingual space infections can usually be drained transorally. Buccal space infections can be drained transorally or extraorally with care taken to identify Stensen's duct and the buccal branch of the facial nerve. The submental space is best approached extraorally via an incision that parallels the inferior border of the mandibular symphysis. Buccal, submandibular, masseteric, pterygomandibular, and sublingual spaces can all be drained extraorally via a horizontal incision parallel to the inferior angle of the mandible.

Drainage catheters are generally used when a transcutaneous route is used and should be left in place until wound drainage has essentially ceased ($\leq$10 mL in 24 hours). In our experience, the catheters do not serve as a route for infection (i.e., to draw bacteria inward). In all cases, special attention should be paid to the status of the airway. Ideally, a team of clinicians with expertise in difficult airway management is involved. In Ludwig's angina, urgent tracheotomy is usually required. Other, less rapidly progressing, maxillomandibular space infections can usually be managed with careful endotracheal intubation. If the airway compromise continues in the postoperative period, the patient should remain intubated or an elective tracheotomy should be performed.

If necrotizing fasciitis is diagnosed based on identification of subcutaneous air or recognition of tissue necrosis at the time of drainage, the wound must be opened widely, necrotic tissue debrided, and the wound packed open for observation and potential further debridement. Hyperbaric oxygen administration may be beneficial in this circumstance.

A recent study by Eisler and colleagues estimated the national cost of inpatient care for odontogenic infections approaches $200 million annually. Increasing access to regular preventative dental care may reduce the morbidity and cost associated with these infections.

The successful treatment of these infections depends on a combination of accurate diagnosis and institution of appropriate therapy in a timely fashion. Adjunctive laboratory and radiographic tests may confirm the diagnosis and help plan the drainage procedure, but a thorough history and physical examination often provides the clinician with sufficient information.

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9. Infection of the salivary and lacrimal glands

Zainab Alhamal, Mary Jordan, and Issam Raad

Sialadenitis is an inflammation of the salivary glands that is usually caused by a virus or bacteria and it can be subdivided into acute, subacute, or chronic forms.

Acute bacterial suppurative parotitis can occur by several mechanisms, including ascending bacterial infection through the ductal system. Salivary stasis can permit retrograde seeding of Stensen's duct by mixed oral flora. Viral infection and obstruction of the duct by calculi and tumor are additional pathogeneses.

There are several predisposing local and systemic generalized factors in the development of sialadenitis (Table 9.1).

Table 9.1 Etiologic classification of sialadenitis

Acute bacterial sialadenitis
Acute purulent parotitis
Acute postoperative parotitis
Acute bacterial submandibular sialadenitis
Chronic bacterial sialadenitis
Chronic recurrent parotitis
Chronic sclerosing sialadenitis of submandibular gland
Obstructive sialadenitis
Viral sialadenitis
Parotitis epidemica (mumps)
Cytomegalovirus infection (salivary gland viral disease)
Other types (Coxsackievirus, infectious mononucleosis, measles, encephalomyocarditis virus, ECHO virus)
Granulomatous sialadenitis
Giant cell sialadenitis
Tuberculosis

ACUTE BACTERIAL SIALADENITIS

Acute bacterial (suppurative) sialadenitis affects predominantly the parotid and submandibular glands. Sialadenitis of the intraoral and sublingual glands is rare. Primary acute bacterial parotitis (ABP) has been reported mainly in elderly, postoperative patients who are intubated or suffering from dehydration, malnutrition, Sjogren's disease, poor oral hygiene or recent intensive teeth cleaning, ductal obstructions due to sialolithiasis, tumor or foreign bodies, chronic tonsillitis, dental infection, neoplasm of the oral cavity, liver cirrhosis, or diabetes mellitus. The use of antisialanogic drugs, including antidepressants, anticholinergics, and diuretics, has been associated with acute bacterial sialadenitis. Bacteria can infect the parotid gland by ascending transmission through Stensen's duct or through bacteremia. Acute postoperative parotitis, as a special type of acute purulent parotitis, is observed particularly after major abdominal surgery and is accompanied by large fluid loss and reduction of salivary secretions. Additional risks include fine-needle aspiration of the parotid and intravascular iodinated radiocontrast agents, especially in older males.

Neonatal suppurative sialadenitis is uncommon. Risk factors include prematurity, decreased saliva production related to prolonged orogastric or nasogastric feeds, dehydration, sialolith, and abnormalities of Wharton's duct.

The most common pathogens associated with acute bacterial infection are *Staphylococcus aureus* and anaerobic bacteria, followed by group A strep, Strep viridans, and strict anaerobes, such as *Fusobacterium nucleatum*, *Prevotella*, and *Porphyromonas*. *Peptostreptococcus anaerobius* may also play a major role. Brook reported 43% of patients with anaerobic infection and 57% with mixed aerobes/anaerobes etiology. Recent reports suggest increasing incidence of gram-negative rods. Less frequently isolated organisms included *Arachnia*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Salmonella* spp., *Pseudomonas aeruginosa*, *Treponema pallidum*, cat scratch bacillus, *Eikenella corrodens*, *Actinomyces israelii*, and *Actinomyces eriksonii*.

Patients present with sudden onset of firm, erythematous swelling of the pre- and post-

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auricular areas that extends to the angle of the mandible, with intense pain and tenderness, trismus, and dysphagia. Fever and chills are common.

Pus can be expressed from the orifice of the Stensen's duct in 50% of cases (Figure 9.1).

Leukocytosis with left shift, elevated sedimentation rate, and increased serum amylase level are frequent.

If purulent discharge is present, it should be Gram stained and cultured, with care to avoid contamination with oral flora. Ultrasound confirms presence of a mass with high sensitivity and can localize disease to the parotid gland. In addition, ultrasound can identify those entities that may not need surgical intervention and can detect stones and differentiate between obstructive and nonobstructive sialoadenitis.

Sialography cannot be used during acute infection and requires the injection of a contrast material.

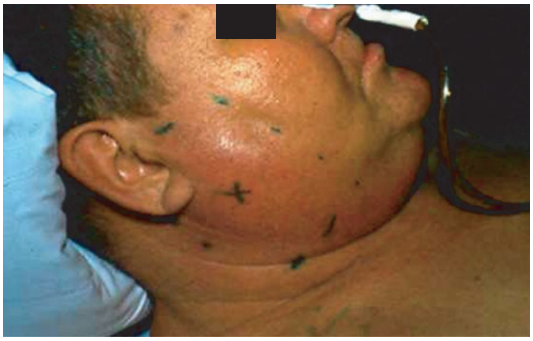

Figure 9.1 Staphylococcal parotitis in a postoperative patient. The enlarged parotid is outlined by ink marks with an X in the center. Note the characteristic diffuse enlargement of the gland, earlobe elevation, and obliterated mandible landmarks. (Courtesy of David Schlossberg, MD.)

Magnetic resonance sialography is promising. The differential diagnosis of an enlarged parotid mass includes viral parotitis, cystic fibrosis, collagen vascular diseases, alcoholism, chronic recurrent parotitis, sarcoidosis, sialolithiasis, and neoplasms.

Treatment of ABP requires elimination of the cause, e.g., mucus plug, by using adequate hydration to increase the salivary flow, and intravenous systemic antibiotics that cover gram-positive cocci, spirochetes, and mouth anaerobes. Immunocompromised patients with neutropenia or neutrophil dysfunction should have additional coverage for Enterobacteriaceae and pseudomonas pending results of cultures. In cases involving abscess, incision and drainage are performed by surgical exposure of the gland and blunt probing. Antistaphylococcal agents (to also cover methicillin-resistant *S. aureus* [MRSA]) plus either metronidazole or clindamycin is adequate empiric treatment in immunocompetent hosts. In immunocompromised patients, vancomycin or linezolid can be used in addition to imipenem, meropenem, or piperacillin–tazobactam (Table 9.2). Antibiotics should be given for 10 to 14 days.

Adjuvant treatment includes optimal oral hygiene, nutritional support, warm compress, discontinuation of anticholinergic drugs that reduce salivary flow or increase the viscosity of the saliva, and use of sialagogic agents such as lemon juice. Irradiation of the glands is no longer recommended. Needle aspiration of the gland should be avoided. Surgical intervention is indicated for lack of improvement after 3 to 5 days of antibiotic therapy, facial nerve involvement, and abscess formation.

A follow-up CT scan or sialogram is recommended after the resolution of the infection to treat the underlying disease such as calculi or stricture to prevent recurrence. Acute bacterial

Table 9.2 Treatment of sialadenitis

	Antibiotic treatment	Surgical treatment
Acute bacterial sialadenitis	Susceptible Gm+ : penicillinase-resistant penicillin or first-generation cephalosporin Resistant Gm+ (MRSA, *S. pneumoniae*): vancomycin Gm− : third-generation cephalosporin, quinolone Anaerobes: flagyl or clindamycin	Parotid drainage may be needed; silolithectomy in submandibular infection
Chronic bacterial sialadenitis	Same as above	Gland extirpation usually required
Viral sialadenitis	None; symptomatic treatment	None
Granulomatous sialadenitis	Director to specific cause	Rarely needed

Abbreviations: Gm+ gram positive; Gm− gram negative; MRSA methicillin-resistant *Staphylococcus aureus*.

submandibular sialadenitis (ABSS), unlike ABP, is frequently associated with ductal obstruction by stones or structures. Medical treatment is the same as for ABP. If ductal calculi are present, excision is necessary. Repeated ductal stone formation may cause chronic submandibular infection, in which case surgical excision of the gland is indicated.

Subacute necrotizing sialadenitis (SANS) is an uncommon self-limiting inflammatory disease of unknown origin that has a male to female ratio of 3:1 and an age range from 15 to 70 years old. It usually affects the palatal salivary glands. Patients present with pain and/or swelling. The cause is infarction of the gland from surgery or trauma.

CHRONIC BACTERIAL SIALADENITIS

Chronic bacterial sialadenitis (recurrent bacterial sialadenitis) involves parotid or submandibular glands and may follow a subclinical course. It occurs via the excretory duct. Inflammation of the oral mucosa and decreased salivary flow cause ascending infection in the major salivary glands. This chronic infection is sometimes associated with Sjogren's disease, with associated xerostomia and systemic autoimmune disease. Chronic juvenile recurrent parotitis is a combination of a congenital malformation of a portion of the salivary ducts and infections ascending from the mouth following dehydration. Boys are more often affected than girls. The clinical course includes recurrent episodes of acute sialadenitis of either parotid or submandibular glands. Although the inflammation may occur bilaterally, painful swelling is often unilateral. In cases involving swelling in the parotid glands area, salivary gland neoplasm should be considered, as well as sialadenosis and lymphadenopathies from diseases such as cat scratch disease, toxoplasmosis, and neoplasm. As in acute parotitis, microbiologic culturing of the saliva is recommended. Several studies have identified *Streptococcus viridans* as the most common causative organism, followed by *S. aureus*, *Streptococcus pneumoniae*, and mixed aerobic-anaerobic oral flora. Involvement of a specific microorganism, such as *Mycobacterium tuberculosis* and *Actinomyces*, is quite rare.

Sialography is the most important diagnostic tool for diagnosis of chronic parotitis. In addition to plain radiographs, CT sialography may provide additional and more detailed information. Scintigraphy is useful, especially when sialography cannot be performed. ESR is commonly elevated. Histologically, parenchymal structures are replaced by fibrosis and fat. The ducts are dilated and surrounded by a dense lymphocytic infiltrate.

The initial treatment should be conservative; patients with chronic parotitis should be instructed to carefully massage the involved gland in a dorsoventral direction four to six times a day and to eat sour foods to stimulate parotic secretion. Systemic antibiotics and proper oral hygiene are helpful, and sialoendoscopy may reduce recurrences of acute episodes of parotitis.

In spite of medical treatment, some cases require surgical management.

CHRONIC SCLEROSING SIALADENITIS (FIGURES 9.2 TO 9.4)

Chronic sclerosing sialadenitis of the submandibular gland (Kuttner's tumor [KT]), is a chronic inflammatory process that produces a firm, sometimes painful, swelling in the submandibular area that mimics malignancy and is difficult to distinguish from tumor. Chronic sclerosing sialadenitis is often diagnosed only after excision of the gland. Submandibular glands are the most involved, but involvement of other major and minor salivary glands has been reported.

In 29% to 83% of cases, it is associated with sialolithiasis and is most commonly seen in the elderly. It is a benign disease and no additional treatment is warranted.

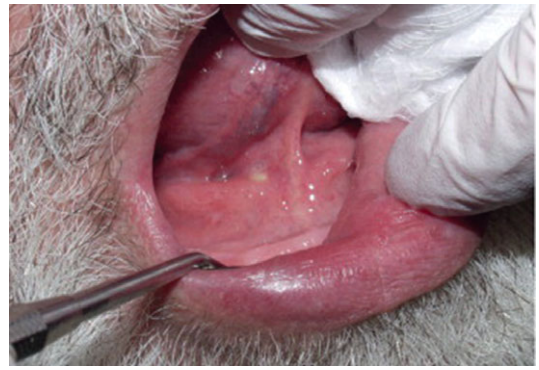

Figure 9.2 An intraoral exam of this patient with chronic sclerosing sialadenitis revealed a white, calcified hard material at the Wharton duct orifice. (Courtesy of Cyril Pandarakalam, BDS, MDS.)

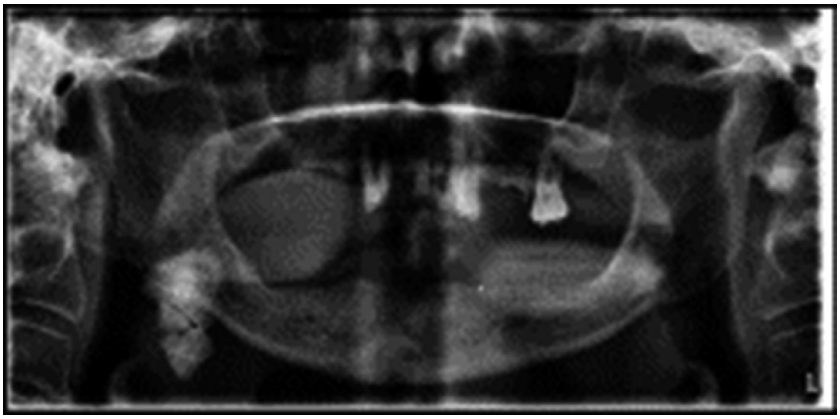

Figure 9.3 In a patient with chronic sclerosing sialadenitis a panoramic radiograph revealed a large, lobulated, radiopaque mass in the right submandibular region corresponding to the sialolith. (Courtesy of Cyril Pandarakalam, BDS, MDS.)

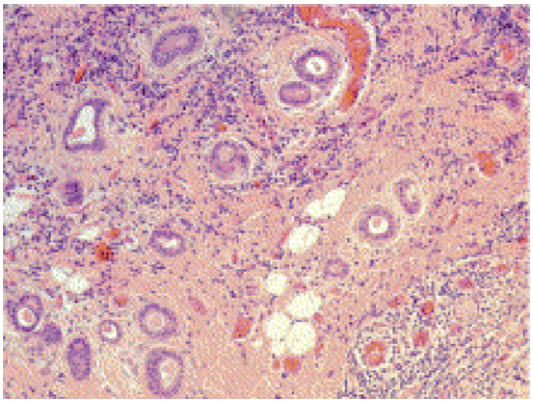

Figure 9.4 In a patient with chronic sclerosing sialadenitis, histopathologic findings revealed chronic inflammatory infiltrate associated with acinar atrophy and periductal sclerosis (hematoxylin–eosin stain, magnification ×10). (Courtesy of Cyril Pandarakalam, BDS, MDS.)

OBSTRUCTIVE SIALADENITIS

Obstructive sialadenitis is the most common type of sialadenitis. Thirty-seven percent of cases are localized in the submandibular gland, 30% in the salivary glands, and 20% in the parotid gland. The remaining 13% are in the sublingual glands. There are two causes of obstructive sialadenitis, mechanical obstruction (cyst, tumor, or lesion of the oral mucosa) and disturbance of the secretory changes in electrolyte concentration resulting in a viscous secretory product.

If a salivary calculus is not removed, the secretory congestion leads to an inflammatory reaction in the salivary gland tissue. Sialography and, more recently, sialoendoscopy are helpful in diagnosis.

VIRAL SIALADENITIS

Viral infection of the salivary glands is a frequent condition mainly affecting the parotid glands. Mumps (a paramyxovirus) is by far the most common virus producing clinically significant parotitis. This disease is contagious and transmitted by droplets of saliva. Mumps is predominantly a childhood disease and is more common in boys than in girls. Young adults may also be affected and have a more aggressive clinical course. Mumps is often preceded by a viral infection in the oral cavity or the nose, leading to viremia and hematogenous infections of the salivary glands. Apart from the major salivary glands, the testes, meninges, pancreas, and mammary glands may become involved. The incubation period is approximately 3 weeks, followed by 1 to 2 days of fever, chills, headache, and jaw pain on chewing, followed by rapid and painful swelling of the parotid gland. The submandibular glands may additionally become involved. In 30% to 40% of the infected patients no clinical symptoms have been noticed. The virus can be isolated from the saliva during the first week of the clinical manifestation of the disease. During this period, leukopenia with relative lymphocytosis and elevation of serum analyses is observed. Serologic diagnosis can be made using a complement-binding reaction or a 4-fold increase in antibody titer, usually at the end of the second week. Apart from vaccination, no effective treatment for mumps is available.

Cytomegalovirus (CMV) sialadenitis is rare and usually presents as painful salivary gland and swelling. The diagnosis is usually based on an elevated complement fixation titer of antibodies to CMV, a positive CMV titer, and detection of CMV in the salivary gland. Other viruses

that produce sialadenitis are Coxsackievirus, infectious mononucleosis, measles, echovirus, influenza A, parainfluenza, human immunodeficiency virus, lymphocytic choriomeningitis virus, adenovirus, human herpesvirus 6, parvovirus B19, and Epstein–Barr virus. Most of these viral infections have a self-limiting condition, which produces lifelong immunity. Chronic hepatitis C virus (HCV) infection has been associated with mild lymphocytic sialadenitis.

GRANULOMATOUS SIALADENITIS

A rare condition, granulomatous sialadenitis is most often secondary to regional lymph node involvement rather than involvement of the gland parenchyma itself. Granulomatous giant cell sialadenitis is localized mostly in the submandibular gland. The inflammatory reaction is caused by obstruction of the ducts and development of granulomas with multinuclear foreign-body giant cells. Many conditions have been reported to cause granulomatous sialadenitis such as tuberculosis, syphilis, tularemia, toxoplasmosis, cat scratch disease, blastomycosis, and coccidiomycosis. Xanthogranulomatous sialadenitis of the parotid gland presenting as B-cell lymphoma has also been reported. Other noninfectious etiologies include sarcoidosis, Wegener's granulomatosis, or Crohn's disease.

Tuberculosis is the most common type of granuloma and starts mostly from the parotid and submandibular lymph nodes. Clinically there is a firm, nontender swelling of the gland-resembling tumor more than parotitis. Most patients have simultaneous pulmonary tuberculosis. The diagnosis may be established by acid-fast bacilli (AFB) smear and culture of the salivary gland drainage if present. Tissue biopsy with culture may be necessary to make the diagnosis.

Treatment, as in other forms of extrapulmonary tuberculosis, consists of a three- to four-drug regimen that usually includes isoniazid, rifampin, ethambutol, and pyrazinamide. The duration of therapy depends on the clinical response but usually is 6 to 9 months. Surgical excision of salivary tissue is rarely needed. A typical *Mycobacterium* infection most often affects children and usually presents as a facial or cervical mass that may drain spontaneously. As in tuberculosis, the diagnosis is based on AFB smears and cultures. Actinomycosis is usually caused by *Actinomyces israelii*, which can be part of the oral flora, particularly in patients with dental caries. It may present as acute suppurative parotitis or have a more chronic course. The diagnosis is based on smears and cultures of draining material or tissue biopsy. Surgical drainage and high dose of penicillin for a prolonged period are indicated.

LACRIMAL SYSTEM INFECTION

Infection of the lacrimal system includes three types: canaliculitis, dacryocystitis, and dacryoadenitis.

Canaliculitis

Canaliculitis is inflammation of the canaliculi that leads to obstruction of the lumen. Primary canaliculitis is almost always a unilateral disease. It presents clinically as conjunctivitis, itching, and burning sensation, mild to severe swelling of the canaliculus, and mucopurulent discharge from the punctum and is associated with excessive tears. *Staphylococcus* species are emerging as the most common organism and *Actinomyces* species and *Arachnia propionica* are commonly implicated as well. Other organisms less frequently causing canaliculitis include *Fusobacterium*, *Enterobacter cloacae*, *Lactococcus lactis*, *Eikenella corrodens*, *Nocardia*, *Candida albicans*, and *Aspergillus*. Viruses such as herpes can also be involved.

The diagnosis is based on isolation of the organism from the lacrimal passage, and fluorescein to see the patency of the duct lumen.

Treatment consists of topical antibiotics. Eyedrops, penicillin, or macrolides may be used (Table 9.3). For others, canaliculotomy is the main mode of therapy to prevent recurrence. Canaliculoplasty with canalicular intubation and one-snip punctoplasty may be safe and efficacious techniques in largely and mildly dilated canaliculum, respectively, with no demonstrable risk of posttreatment epiphora in patients with *Actinomyces* canaliculitis.

Dacryocystitis

Dacrocystitis is a common infection of the lacrimal sac. It can be either an acute or chronic infection. Dacryocystitis often occurs in children as a complication of congenital or acquired nasolacrimal proximal or distal duct obstruction of the drainage system. In the neonate period it is often due to dacryocele and presented as a duct cyst. In older infants and children, nasolacrimal duct obstruction may occur as a consequence of ethmoidal sinusitis or facial fracture. Also, it is common in adults over 40, with obstruction at the opening of the nasolacrimal duct into the inferior

Table 9.3 Treatment of lacrimal system infection

	Antibiotic treatment	Surgical treatment
Canaliculitis	Topical antibiotic drops plus antibiotic irrigation of canaliculi (pen G) plus intravenous/oral pen V or macrolides	Canaliculotomy
Acute dacrocystitis		
Neonatal (duct cyst)	Topical antibiotic drops or IV plus oral cephalosporin antibiotic	Duct probing nasal endoscopy
Preseptal cellulitis	IV antibiotics	Duct probing
Trauma	IV antibiotics	Dacryocystorhinostomy nasolacrimal intubation
Chronic dacryocystitis	IV antibiotics	Endoscopic intranasal, dacryocystorhinostomy
Acute dacryoadenitis	Systemic antibiotic	Incision and drainage if spontaneous resolution does not occur
Chronic dacryoadenitis	Directed toward specific cause	Rarely required

meatus being the most common risk factor. Dacryocystitis can be subdivided to acute and chronic forms.

ACUTE DACRYOCYSTITIS

Presented clinically with swelling, erythema, and/or tenderness of the lacrimal sac. Because dacryocystitis tends to be complicated by preseptal or orbital cellulitis, meningitis, or sepsis, it should be treated with systemic antibiotics.

Because of the great increase in MRSA in many areas of the United States oral clindamycin, or, in more severe cases, intravenous vancomycin, is a first-line treatment, used in combination with a third-generation antibiotic; the duration is usually 7 to 10 days; if culture is then available change accordingly.

CHRONIC DACRYOCYSTITIS

Presented by mucopurulent drainage from the lacrimal punctum, chronic dacryocystitis can be treated with topical antibiotics, which may include topical tobramycin, gentamicin, erythromycin, sulfacetamide, or fluoroquinolones (e.g., moxifloxacin, ciprofloxacin, ofloxacin, etc.).

The most common organisms isolated in the acute stage are *S. aureus*, including MRSA, *S. pneumoniae*, gram-negative rods (*P. aeruginosa*, *H. influenzae*), and rarely *Stenotrophonomas maltophilia,* in which setting quinolones are recommended for the treatment of chronic dacryocystitis. Other rare etiologies of dacryocystitis include mucocutaneous leishmaniasis, *Proteus mirabilis*, *Haemophilus parainfluenzae*, *Peptostreptococcus*, *Propionibacterium*, *Prevotella*, *Fusobacterium*, and *Curvularia*. Acute dacryocystitis may lead to orbital cellulitis, abscess, or fistula.

The diagnosis can be made by culture, radiographically by dacryocystography, CT, or scintillography.

Treatment consists of hot compresses applied to the affected area and systemic antibiotics based on Gram stain and culture results as mentioned above. Surgical intervention is indicated for abscess or when the symptoms do not resolve with medical therapy (Table 9.3). Recently the holmium:YAG laser has been used to decrease the risk of hemorrhage associated with traditional surgery. (See also Chapter 16, Periocular infections.)

Dacryoadenitis

Dacryoadenitis is inflammation of the lacrimal gland. It is usually present as localized tenderness and swelling of the eyelid. Acute bacterial infections can be due to pyogenic bacteria, such as *S. aureus* and streptococci. Viral infections with mumps and infectious mononucleosis are most often implicated as causes. Chronic infection of the lacrimal gland can be associated with various infectious and noninfectious causes. Tuberculosis, syphilis, leprosy, and schistosomiasis, Epstein–Barr virus, *Brucella melitensis*, herpes simplex virus, and varicella-zoster virus have been also reported. It has also been associated with *Acanthamoeba* keratitis, Wegener's granulomatosis, sarcoidosis, and Sweet's syndrome.

Clinically, patients with acute dacryoadenitis complain of severe pain in the lacrimal gland region, edema, and redness and swelling, whereas in chronic dacryoadenitis only minimal eyelid edema and mild tenderness can be observed. Management of dacryoadenitis includes symptomatic treatment with local hot compresses or systemic antibiotics in the case of bacterial cause. The standard treatment for acute idiopathic inflammatory dacryoadenitis is oral corticosteroids. Others report the benefit of intralesional steroid injection.

If symptoms persist, irradiation or cyclosporine may be an option. Surgical drainage is necessary for abscess formation.

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10. Deep neck infections

Jeremy D. Gradon

INTRODUCTION

Infection of the deep spaces of the neck are becoming more common. Hospital admissions for such infections in the United Kingdom more than doubled between 1996 and 2005. These infections are often life threatening, and even stable-appearing patients are at grave risk for sudden clinical decompensation. Clinical severity is related to both the anatomic nature of the space involved, due to the numerous adjacent critical structures, as well as the nature of the hosts themselves (Figure 10.1). The elderly and diabetics are more likely to have complicated infections than their counterparts.

Patients with deep neck infections are frequently either diabetic, human immunodeficiency virus (HIV)-infected (irrespective of antiretroviral therapy status), or immunocompromised in some other way. An example of a deep neck infection of the lateral pharyngeal space in an HIV-infected patient is shown in Figure 10.2. *Nocardia asteroides* grew from the deep neck cultures. In addition, a history of injection drug use (IDU), neutropenia, or exogenous steroid therapy is common. A dental source is frequently present. On rare occasions, deep neck space infection may complicate head and neck cancers. Cases complicating traumatic airway intubation have also been reported.

Management of deep neck infections is very costly. A recent analysis of 71 such patients treated in the United States found that the total cost of care exceeded $1.1 million.

Deep neck infections are usually polymicrobial, reflecting the oral cavity source of most of these infections. When associated with IDU, community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) is the most likely organism to be encountered. The microbiology of these infections is shown in Table 10.1. The increasing prevalence of multidrug-resistant gram-negative rods complicates therapy. Wound botulism as a complication of deep neck infection may occur in IDUs.

RELEVANT ANATOMY OF THE DEEP NECK SPACES

The deep neck spaces are bound by a variety of anatomic landmarks and are anatomically distinct. However, all have the potential for communicating with each other, and thus infection may spread from one region to another during the course of the illness. It is important to delineate

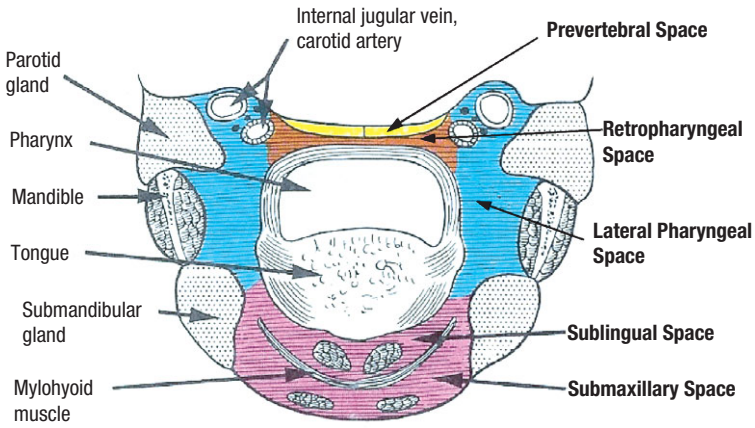

Figure 10.1 Oblique section of top of neck. Note contiguity of spaces and resultant potential for spread. Adapted with permission from Hollingshead WH. *Anatomy for Surgeons. Vol. 1: The Head and Neck*, 2nd edn. New York, NY: Harper & Row; 1968.

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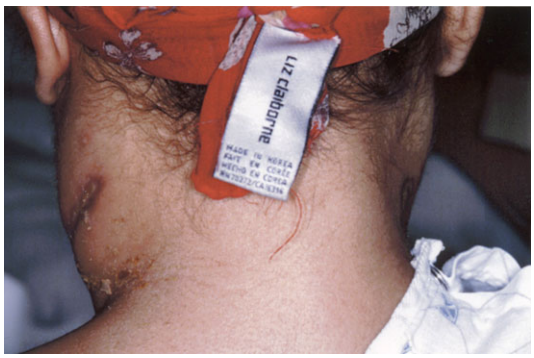

Figure 10.2 Recurring deep neck abscess of lateral pharyngeal space caused by *Nocardia asteroides* in an HIV-infected patient with CD4 count of 86/mm^3.

Table 10.1 Pathogens enountered in deep neck space infections

Common
Viridans and other streptococci
Staphylococcus aureus (including MRSA)
Prevotella, Fusobacterium, Bacteroides, Porphyromonas
Rare
Moraxella
Haemophilus species
Pseudomonas species
Actinomyces species

Table 10.2 Management of deep neck space infections

NEVER LEAVE THE PATIENT UNATTENDED out of a monitored unit
Protect the airway – experienced otolaryngology evaluation is essential
CT or MRI of mouth, neck, mediastinum to evaluate for drainable collections, airway compression, vascular complications, or mediastinal involvement
Dentist/oral surgery evaluation for a (removable) dental source of infection
Correct underlying medical issues – maximize glycemic control, correct neutropenia, taper steroids (if feasible), etc.

the various spaces clinically and radiologically so that appropriate management can be provided. The main spaces are as follows:

- The submandibular space (composed of two spaces separated by the mylohyoid muscle: the sublingual space, which is superior, and the submaxillary space, which is inferior).
- The lateral pharyngeal spaces (anterior and posterior)
- The retropharyngeal spaces (including the retropharynx, the prevertebral space, and the "danger space").

Radiologic testing in deep neck infections

Computed tomography (CT) and magnetic resonance imaging (MRI) are excellent diagnostic tools for deep neck infections. However, it must be appreciated that these patients are critically ill with a risk for acute airway obstruction at any time in their clinical course. Thus, appropriately trained personnel must accompany these patients when they go for such scans. Equipment must be brought along to allow immediate airway protection should acute airway obstruction develop in (or on the way to) the radiology department.

In the postoperative setting, rim enhancement (>50%) of fluid collections in the neck on CT scanning correlates with abscess formation.

Submandibular space infections ("Ludwig's angina")

This bilateral infection of the submandibular space most commonly arises from infection of the posterior two molar teeth. There is the rapid onset of fever, mouth pain, and drooling of oral secretions. Soft-tissue spread of infection causes woody induration of the submandibular space and a stiff neck. Because the tongue may be displaced upward and backward, acute airway obstruction may develop. Tracheal compression due to surrounding edema is another cause of airway failure in this infection. Management is outlined in Tables 10.2 and 10.3 and complications in Table 10.4.

LATERAL PHARYNGEAL SPACE INFECTIONS (ANTERIOR AND POSTERIOR)

These are the most common forms of deep neck space infection. Infections of the lateral pharyngeal spaces can result from pre-existing submandibular space infections or may develop secondary to dental, salivary gland, lymph node, or retropharyngeal space infections. IDU, with the patient attempting to access deep neck (jugular) veins with nonsterile needles, is the most common cause of lateral pharyngeal space infections in the urban setting (Figure 10.3).

Patients present with fever, neck pain, and rigors. If the anterior portion of the lateral pharyngeal space is involved, then trismus may develop. This may mimic the cephalic form of tetanus.

Table 10.3 Antibiotic therapy[a]

Nonimmune compromised host[b]
Penicillin G 3 million units IV q4h plus IV metronidazole 500 mg q6h
or
Ampicillin–sulbactam 3 g IV q6h
or
Clindamycin 600 mg IV q8h plus moxifloxacin 400 mg IV q24h
Immune compromised host[b]
Imipenem–cilastatin 500 mg IV q6h plus vancomycin 1 g IV q12h
or
Piperacillin–tazobactam 4.5 g IV q6h plus vancomycin 1 g IV q12h

[a] These antibiotic recommendations are only examples of appropriate regimens. Multiple other combinations of antibiotics providing polymicrobial coverage for both aerobes and anaerobes are appropriate as well.
[b] In the setting of injection drug use, HIV infection or the recent use of antibiotics (within $\leq$3 months) would add anti-MRSA coverage with either vancomycin, ceftaroline, daptomycin, or linezolid.

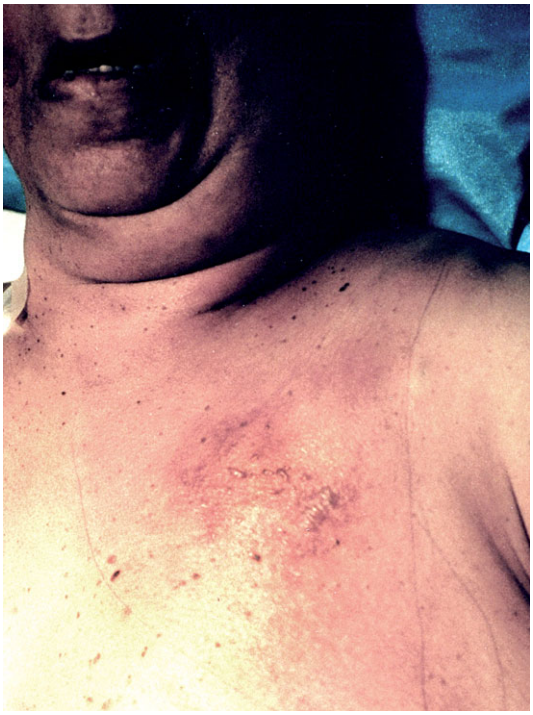

Figure 10.3 Group A streptococcal necrotizing fasciitis of the neck and anterior chest wall: preoperative photo, taken before wide surgical debridement was performed.

However, posterior lateral pharyngeal space infection is not associated with either trismus or visible neck swelling. Management is outlined in Table 10.2 and 10.3 and complications in Table 10.4.

Table 10.4 Complications of deep neck space infections

Submandibular space infection
Acute airway obstruction
Aspiration pneumonia
Tongue necrosis
Carotid artery erosion
Jugular vein thrombosis
Spread to the lateral pharyngeal space
Anterior lateral pharyngeal space
Spread of infection to the parotid gland
Posterior lateral pharyngeal space
Carotid artery erosion
Suppurative jugular vein thrombosis
Cranial nerve palsies (IX–XII)
Retropharyngeal space
Respiratory distress
Spread to cervical vertebrae
Danger space
Spread of infection to mediastinum
Spread of infection to the pleural space
Prevertebral space
Spread of infection along the length of the vertebral column
Lemierre's syndrome
Jugular venous thrombosis
Septic pulmonary emboli
Empyema
Septic arthritis

RETROPHARYNGEAL SPACE INFECTIONS

The retropharyngeal space

Patients present with fever, sore throat, dysphagia, systemic toxicity, and neck stiffness. Inspection of the retropharynx will frequently demonstrate bulging or swelling of the retropharyngeal soft tissues. On occasion, the lesion may penetrate the posterior pharynx and pus may be visible on the anterior wall of the retropharynx. Infection may occur as a complication of local pharyngeal infection or be due to hematogenous seeding from a distal site. On occasion, the infection may be due to direct spread from acute cervical vertebral osteomyelitis, or follow penetrating trauma to the area. The differential diagnosis is shown in Table 10.5.

THE "DANGER SPACE"

The "danger space" is an anatomical potential space that connects the deep neck spaces with the mediastinum. Access to the mediastinum is via the pretracheal fascia to the parietal pericardium and

posterior mediastinum via the "danger space" from the retropharynx. As a result of this connection, acute bacterial mediastinitis may develop as a consequence of deep neck space infection. Other predisposing factors for mediastinal extension of a deep neck infection include older age, involvement of two or more deep neck spaces, and diabetes.

In addition, postoperative mediastinal infections may track up to the retropharynx and present as an apparent primary neck infection.

THE PREVERTEBRAL SPACE

This fascial plane runs from the base of the skull to the coccyx along the anterior borders of the vertebrae. Thus, infection may spread from the retropharyngeal space to the whole length of the vertebral column. Management is outlined in Tables 10.2 and 10.3 and complications in Table 10.4.

LEMIERRE'S SYNDROME

Lemierre's syndrome is an eponym describing internal jugular vein septic thrombophlebitis. It is the most common vascular complication of parapharyngeal space infection. The most commonly encountered cause is the anaerobe *Fusobacterium necrophorum*. Other causative bacteria include *Bacteroides*, MRSA, anaerobic streptococci, and other assorted mouth flora.

This infection classically affects young adults and is preceded by a sore throat, followed by fever, systemic toxicity, and tenderness to palpation along the angle of the jaw and sternocleidomastoid muscle. Trismus is not present. As a consequence of this endovascular infection, bacteremia develops, with associated septic pulmonary emboli, empyema formation, and septic arthritis.

Routine screening of throat swabs for *Fusobacterium* in 15- to 24-year-olds presenting with pharyngitis has been suggested, but is not a standard of care at present.

Lemierre's syndrome can also develop as a complication of attempts to access the jugular vein either for IV line placement or for purposes of IDU. The management of Lemierre's syndrome is outlined in Table 10.6.

CAROTID ARTERY EROSION

This may occur as a complication of almost any deep neck space infection. Initially, this entity may be difficult to recognize due to the tight fascia binding the carotid artery. Once a false aneurysm has developed the patient may develop "herald bleeding" from the nose, mouth, or ears. Once major bleeding occurs death is common. Treatment involves urgent vascular surgical repair, and the risk of stroke is high. Successful cases of treatment with endovascular stenting for infection-induced carotid pseudoaneurysm have been reported.

Table 10.5 Differential diagnosis of retropharyngeal space infections

Bacterial meningitis
Cervical vertebral osteomyelitis
Pott's disease
Calcific tendonitis of the neck muscles
Inflammatory tumor/neoplasm
Mediastinal infection with spread via the "danger space"

Table 10.6 Management of Lemierre's syndrome

IV antibiotics (as shown in Table 10.3)
Drainage of metastatic abscesses (other than septic pulmonary emboli)
Rarely: ligation and resection of involved jugular vein (for unrelenting sepsis)
No clear role for anticoagulation

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PART III

Clinical syndromes: eye

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11. Conjunctivitis

Elmer Y. Tu

Conjunctivitis is a nonspecific term used to describe inflammation of the ocular surface and conjunctiva from either infectious or noninfectious causes. Infectious conjunctivitis is most commonly due to exogenous inoculation of the mucous membranes lining the surface of the eye and eyelid, resulting in an activation of a local inflammatory response. The vast majority of cases are acute but it may also present as chronic or recurrent. Although most cases of acute infectious conjunctivitis are self-limited and result in few long-term sequelae, appropriate evaluation and therapy are indicated with specific presentations.

CLINICAL FEATURES

The hallmark of conjunctivitis is injection or hyperemia of the conjunctival vessels, resulting in a red eye as well as tearing and/or mucopurulent discharge. Conjunctivitis may also result in complaints of irritation, foreign-body sensation, mattering or crusting of the eyelids, and mild visual blurring primarily due to alterations of the tear layer. The local inflammatory response may manifest as conjunctival lymphoid follicles or vascular papillae, eyelid edema, and/or preauricular adenopathy. Complaints of severe eye pain, photophobia, significant visual loss, or referred pain should alert the examiner to the possibility of other, more ominous, etiologies. Similarly, loss of normal corneal clarity, either diffuse or focal, proptosis, pupillary abnormalities, conjunctival scarring, or restriction of eye movement are criteria for a detailed ophthalmic evaluation (Table 11.1).

ETIOLOGY

Numerous studies have demonstrated that, regardless of the etiology, acute conjunctivitis follows a benign course and results in few sequelae even without specific antibiotic therapy. Because characteristic signs and symptoms can distinguish bacterial and viral syndromes, the diagnosis of conjunctivitis is based largely on clinical history and examination. Cultures are normally reserved for neonatal or hyperacute conjunctivitis or in patients with a course greater than 2 to 3 weeks, classified as chronic conjunctivitis. A history of contact with other patients with conjunctivitis, bilateral involvement, or exposure to groups of children is associated with the more contagious viral agents. Signs of preauricular lymph node swelling (with the exception of hyperacute or chlamydial conjunctivitis), a follicular palpebral conjunctival reaction, and clear discharge or copious tearing are also more consistent with acute viral conjunctivitis. A papillary conjunctival reaction, mucopurulent discharge, and the lack of local lymph node swelling is more suggestive of bacterial conjunctivitis. When indicated, diagnostic workup consists of conjunctival swabs for Gram and other histologic stains as well as culture.

VIRAL CONJUNCTIVITIS

Acute conjunctivitis, defined as less than 2 to 3 weeks duration, is most commonly viral, especially in adults. Adenovirus is a commonly identified pathogen in outbreaks of acute viral conjunctivitis. Although usually associated with types 8 and 19, epidemic keratoconjunctivitis (EKC) has been associated with several other serotypes and is highly contagious, spread by direct contact from hand to eye. In addition to the classic signs of viral conjunctivitis, patients with EKC may develop an immune keratitis consisting of corneal subepithelial infiltrates approximately 2 or 3 weeks after the onset of the conjunctivitis. The corneal inflammation results in complaints of foreign-body sensation, photophobia, and, possibly, decreased vision sometimes lasting days to months. Pharyngoconjunctivitis has a similar ocular presentation but is associated with

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Table 11.1 Red eye: differential features

	Conjunctivitis			Keratitis			
	Bacterial	**Viral**	**Allergic**	**Bacterial**	**Viral**	**Iritis**	**Glaucoma (acute)**
Blurred vision	0	0	0	+++	0 to ++	+ to ++	++ to +++
Pain	0	0	0	++	0 to +	++	++ to +++
Photophobia	0	0	0	++	++	+++	+ to ++
Discharge	Purulent + to +++	Watery + to ++	White, ropy +	Purulent +++	Watery +	0	0
Injection	+++	++	+	+++	+	0 to + (limbal)	+ to ++ (limbal)
Corneal haze	0	0	0	+++	+ to ++	0	+ to +++
Ciliary flush	0	0	0	+++	+	+++ to +++	+ to ++
Pupil	Normal	Normal	Normal	Normal or miotic (iritis)	Normal	Miotic	Mid-dilated Nonreactive
Pressure	Normal	Normal	Normal	Normal	Normal	Normal, low or high	High
Preauricular nodes	Rare	Usual	0	0	0	0	0
Smear	Bacteria PMNs	Lymphs	Eosinophil	Bacteria PMNs	0	0	0
Therapy	Antibiotics	Nonspecific	Nonspecific	Antibiotics	Antivirals (if herpes)	Cycloplegia Topical steroids	Medical or surgical

+, Mild; ++, moderate; +++, severe; PMNs, polymorphonucleocytes.

serotypes 3 and 7 and includes fever and pharyngitis. Viral cultures are reserved for tracking large outbreaks because results usually are available after symptoms have subsided. The recent introduction of an in-office, rapid, reproducible adenovirus antigen screening test should prove to be of more clinical utility. The virus may remain viable on surfaces for many days to weeks, making control of outbreaks problematic. True EKC may remain highly transmissible from patient to patient for 2 weeks or more, and, therefore, requires strict hygiene instruction as well as isolation precautions, especially during the phase of copious discharge. Acute hemorrhagic conjunctivitis associated with enterovirus 70 and Coxsackievirus A24 is a highly transmissible follicular conjunctivitis with preauricular adenopathy with the added feature of subconjunctival hemorrhages (Figure 11.1). Currently available topical antivirals are not efficacious in any of these entities, making primary treatment supportive with topical lubricants, cool compresses, and topical nonsteroidal anti-inflammatory drugs (NSAIDs). Topical corticosteroids have been used cautiously in patients with debilitating symptoms of EKC-related keratitis, but their use is controversial.

Either herpes simplex type 1 or 2 may result in a primary follicular conjunctivitis seen in children and young adults. Primary conjunctivitis is normally unilateral with a palpable preauricular lymph node associated with a classic vesicular eyelid or periorbital eruption (Figure 11.2). Systemic antivirals are indicated for primary infection. Because vision-threatening sequelae are associated with corneal involvement, topical trifluridine 1% five to nine times per day or topical ganciclovir five times per day may also be added to either treat or reduce the risk of herpes simplex virus (HSV) keratitis by shortening the duration of the HSV conjunctivitis. Recurrence is common.

Chronic viral conjunctivitis may be associated with molluscum contagiosum, usually seen in children. The chronic follicular conjunctivitis is caused by viral shedding into the eye from an eyelid or periorbital molluscum, characteristically a pearly white nodule with an umbilicated center (Figure 11.3). These lesions are typically small and multiple and spread by direct contact. Immunocompromised individuals may present with much larger lesions. Treatment of the molluscum lesion by incision and curettage of its center or excision is curative of the associated conjunctivitis.

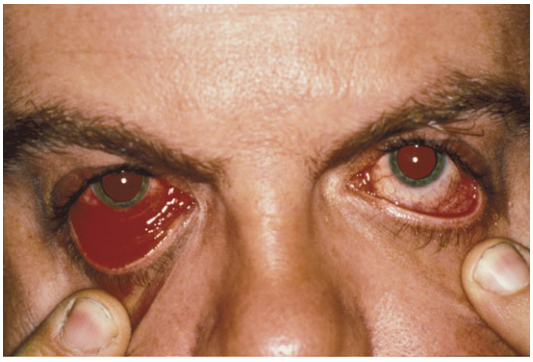

Figure 11.1 Self-limited acute hemorrhagic conjunctivitis.

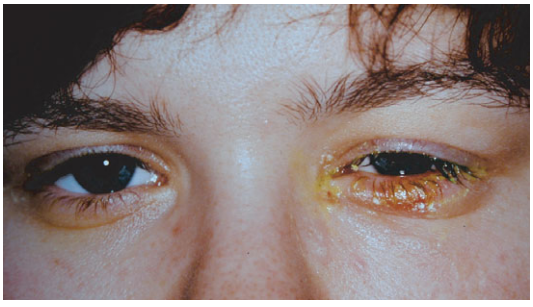

Figure 11.2 Primary herpes simplex blepharitis and conjunctivitis.

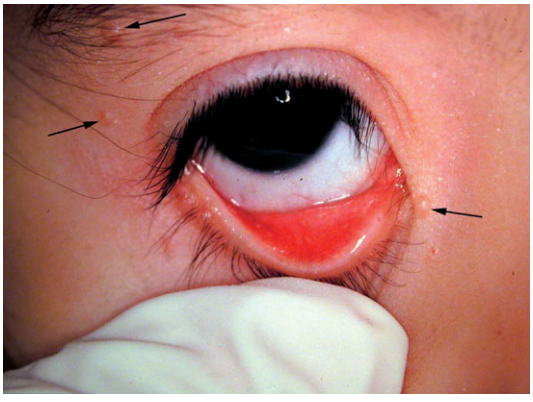

Figure 11.3 Molluscum contagiosum chronic follicular conjunctivitis.

BACTERIAL CONJUNCTIVITIS

Most bacterial conjunctivitides are self-limited, have low morbidity, and respond well to most available topical broad-spectrum antibiotics, obviating the need for microbiologic identification. Definitive evaluation and specific treatment is, however, required in hyperacute conjunctivitis, a rapidly progressive, purulent, destructive infection, and neonatal conjunctivitis to avoid local and systemic complications more common to these two entities.

Table 11.2 Systemic treatment of gonococcal conjunctivitis

Adults	**Dosage**
Ceftriaxone (drug of choice)	1 g IM, single dose
Ciprofloxacin	500 mg PO, single dose
Ofloxacin	400 mg PO, single dose
Spectinomycin	2 g IM, single dose
Children (≤ 45 kg)	**Dosage**
Ceftriaxone	125 mg IM, single dose
Spectinomycin	40 mg/kg IM (max = adult dosage), single dose
Neonates	**Dosage**
Ceftriaxone	25–50 mg/kg IV or IM (max = 125 mg), single dose

HYPERACUTE CONJUNCTIVITIS

Hyperacute conjunctivitis is usually associated with *Neisseria* species, most commonly *Neisseria gonorrhoeae* in newborns and young sexually active adults. A copious, rapidly accumulating mucopurulent discharge, intense redness, and periorbital swelling are characteristic of hyperacute conjunctivitis. It is one of the few acute bacterial conjunctivitides that develops a preauricular lymphadenopathy. Rapid corneal and conjunctival penetration can result in severe corneal ulceration and ocular destruction if left untreated. It is considered a true ocular emergency. This potential for ocular complications and systemic infection with *N. gonorrhoeae* necessitates microbiologic identification as well as systemic antibiotic therapy (see Table 11.2). Local sterile saline lavage can be symptomatically helpful. Because of a significant incidence of coinfection, systemic therapy directed against *Chlamydia* infection is recommended in these cases (see below). Less commonly, *Neisseria meningitidis* may result in hyperacute conjunctivitis in a similar, but muted, presentation. The infection may be a primary conjunctivitis but is more likely secondary to systemic meningococcemia, requiring aggressive systemic therapy to prevent systemic complications.

NEONATAL CONJUNCTIVITIS

Conjunctivitis occurring within the first month of life is termed neonatal conjunctivitis and is either nosocomial or contracted during passage through

the birth canal. The pathogens most commonly identified include *Chlamydia trachomatis* (30–50%), *Staphylococcus aureus*, and *N. gonorrhoeae*, with *Streptococcus pneumoniae*, *Haemophilus* spp., and *Pseudomonas* also identified. Prophylaxis with a single topical application of antibiotic within the hour of delivery has drastically reduced the incidence of neonatal conjunctivitis. The original solution of 1% silver nitrate (*Crede prophylaxis*) has been largely supplanted by topical erythromycin 0.5% or tetracycline 1% ointment both for better coverage for *Chlamydia* and for a lower incidence of toxicity. Signs and symptoms are not helpful in discerning between these infections, necessitating microbiologic identification to direct appropriate therapy.

Infection with *N. gonorrhoeae* causes hyperacute conjunctivitis 1 to 13 days after birth and constitutes an ocular emergency. Clinical signs, symptoms, and treatment are similar to those seen in adults as described above. The proper use of neonatal prophylaxis reduces the incidence of gonococcal conjunctivitis to less than 2% in infected children born to infected mothers.

Neonatal inclusion conjunctivitis is caused by *C. trachomatis* and presents 5 to 14 days after birth. Signs may include lid swelling, redness, water, or mucopurulent discharge. In some cases a pseudomembrane may occur. Diagnostic workup is detailed below. Ocular infection can be associated with pneumonia and/or otitis media in up to 50% of patients, necessitating both topical and systemic therapy consisting of oral erythromycin or erythromycin ethylsuccinate 50 mg/kg/day in four divided doses.

Most other bacterial infections will respond to a topical broad-spectrum antibiotic such as erythromycin, sulfacetamide, aminoglycoside, or fluoroquinolone.

HSV may also result in ophthalmia neonatorum either as an isolated conjunctivitis/keratitis or as part of a serious systemic neonatal infection. Prophylaxis of the mother with acyclovir or valacyclovir has been shown to reduce viral shedding during delivery. This combined with cesarean section, in the presence of active genital herpes, has reduced the incidence of HSV neonatal infection. Transmission may, however, still occur in asymptomatic individuals and should be considered in the differential of neonatal conjunctivitis. Classic vesicular lesions are usually noted on the eyelid with a concomitant follicular conjunctivitis. Dendritic lesions of the cornea indicate HSV keratitis with the potential for loss of vision secondary to corneal scarring. Intraocular involvement may lead to more serious ocular damage. Although HSV type 2 is more common, HSV type 1 has also been isolated. Superficial scraping for smear and culture is helpful but not integral to diagnosis. Treatment includes systemic antivirals as well as topical trifluridine 1% nine times per day or topical ganciclovir five times per day. Other forms of neonatal viral conjunctivitis are otherwise uncommon.

ACUTE BACTERIAL CONJUNCTIVITIS

Overall, the majority of acute conjunctivitis is viral, except in the pediatric population, where more bacterial pathogens are seen. Clinical features include a mild to moderate mucopurulent discharge, a papillary conjunctival inflammatory response, injection (hyperemia), and initial unilaterality. With few exceptions (see hyperacute conjunctivitis, chlamydia in this chapter), routine bacterial conjunctivitis does not result in preauricular adenopathy. Cultures and smears are not normally performed in its management, but, in prospective series, gram-positive bacteria, *S. pneumoniae*, *Streptococcus viridans, S. aureus*, and *Haemophilus* predominate. Gram-negative bacteria are seen less frequently. *S. pneumoniae* may cause a bilateral conjunctivitis with characteristic small petechial hemorrhages of the conjunctiva. Seen more commonly in children, *Haemophilus* may cause discoloration of the involved eyelid described as "violaceous" and create significant upper eyelid edema resulting in a characteristic S-shaped upper eyelid.

Treatment of acute bacterial conjunctivitis with any of a number of broad-spectrum topical antibiotics will achieve local concentrations that can easily overcome even mild to moderate resistance. The average duration of untreated acute bacterial conjunctivitis is 2 to 7 days. Topical antibiotics have been shown to shorten the overall course when administered early in the course of infection and to improve clinical and microbiologic signs of disease. Addition of antibiotics later in the course after day 4 is of limited benefit. Broad-spectrum antibiotics are administered four to six times daily for 5 to 7 days (see Table 11.3). In adults presenting with conjunctivitis, it has been suggested that a delay in treatment for 3 to 4 days, instituted only with a lack of resolution, would significantly reduce the unnecessary use of topical antibiotics in viral or self-limited bacterial cases with no significant impact on overall outcome. Although unnecessary, the use of antibiotic–steroid combinations (Table 11.3) may

Table 11.3 Common topical ophthalmic antibiotics and steroid forms

Antibiotic	Common brand names	Form	Steroid-containing combination product brand name
Sulfacetamide	Bleph-10	Drop/ointment	Blephamide, Vasocidin
Erythromycin	Generic	Ointment	None
Bacitracin	Generic	Ointment	None
Bacitracin–polymyxin B	Polysporin	Ointment	
Polymyxin B–trimethoprim	Polytrim	Drop	None
Neomycin–polymyxin B		Drop/ointment	Maxitrol, Cortisporin
Tetracycline–polymyxin B	Terramycin	Ointment	None
Gentamicin	Garamycin	Drop/ointment	Pred-G
Tobramycin	Tobrex	Drop/ointment	Tobradex, Zylet
Ciprofloxacin	Ciloxan	Drop/ointment	None
Ofloxacin	Ocuflox	Drop	None
Levofloxacin	Quixin	Drop	None
Gatifloxacin	Zymar	Drop	None
Moxifloxacin	Vigamox	Drop	None

speed symptomatic relief but may potentiate serious masquerading conditions and should, therefore, be used with caution if the diagnosis is in question. Because of a relationship between Haemophilus conjunctivitis and acute otitis media or other involvement, the addition of appropriate systemic antibiotics is strongly considered, especially if systemic signs are present.

CHRONIC BACTERIAL CONJUNCTIVITIS

Conjunctivitis persisting for greater than 2 weeks is considered chronic and requires more detailed ophthalmic examination as well as Gram and Giemsa staining and culture. Chronic or recrudescent bacterial conjunctivitis may persist because of characteristics of the causative organism or a persistent local or external reservoir of the organism not exposed to normal ocular surface defense mechanisms. Although contaminated prosthetic devices such as contact lenses may be a source for pathogen reintroduction, the most common reservoir is the eyelids in the form of blepharitis, dacryocystitis, or, rarely, dacryoadenitis.

Blepharitis, or eyelid margin inflammation, is most commonly associated with chronic colonization by *S. aureus* or epidermidis and is characterized by eyelash debris, eyelid margin thickening, and telangiectasias (Figure 11.4). Angular blepharitis refers to infection of the lateral canthus causing inflammation and irritation of the eyelid skin and is associated with *Moraxella lacunata*. Seen more commonly in alcoholics and immunocompromised individuals, it may also result in conjunctivitis and keratitis. Swabs for Gram stain demonstrate the classic "double boxcar" gram-negative organisms. A concomitant conjunctivitis may accompany any form of blepharitis. Signs and symptoms are similar to other forms of bacterial conjunctivitis and respond to lid hygiene and topical antibiotic ointment such as erythromycin, bacitracin, or sulfacetamide at bedtime.

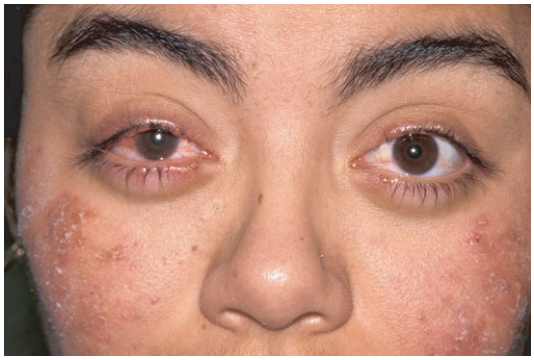

Figure 11.4 *S. aureus*-related chronic blepharoconjunctivitis.

CHLAMYDIAL CONJUNCTIVITIS

Serotypes A to C are associated with trachoma, a follicular bacterial conjunctivitis that because of its chronicity results in scarring of the superior tarsus. These cicatricial changes may lead to

entropion and trichiasis, inward turning eyelashes, resulting in chronic corneal trauma and scarring. Seen primarily in endemic areas of the developing world, it is one of the most common causes of blindness. Diagnostic workup consists of conjunctival swabs/scrapings for culture or direct immunofluorescence. Courses of systemic erythromycin, doxycycline 100 mg twice daily for 7 days, or a single 1-g oral dose of azithromycin are effective and curative, but because of its endemic nature, whole community programs are required to prevent recurrent reinfection. Alternatives include erythromycin, ofloxacin, and levofloxacin.

Adult inclusion conjunctivitis is also caused by *C. trachomatis* (serotypes D through K). The conjunctivitis is concurrent with, but may occur independent of, active genital infection. Transmission to the eye is by direct contact with contaminated secretions. Nonspecific symptoms of tearing, foreign-body sensation, photophobia, and eyelid edema are presenting complaints. *Chlamydia* causes a follicular conjunctivitis with preauricular lymphadenopathy, but unlike trachoma, the lower eyelid is normally more involved. As in trachoma, systemic azithromycin or doxycycline is effective but also requires appropriate evaluation and treatment of sexual contacts.

MISCELLANEOUS CAUSES

In addition to *Neisseria* spp. and *Chlamydia* spp., several other forms of conjunctivitis may be related to systemic infection. Parinaud's oculoglandular syndrome is the association of a follicular conjunctivitis, conjunctival granuloma, and an ipsilateral lymphadenopathy. Cat scratch disease caused by *Bartonella henselae* is the most common cause of Parinaud's and is transmitted by contact with an infected cat. The conjunctival granuloma may be single or multiple and is surrounded by intense inflammation accompanied by ipsilateral head, neck, or axillary lymphadenopathy. Other causes of Parinaud's include tularemia, sporotrichosis, tuberculosis, syphilis, and coccidioidomycosis (Table 11.4). Evaluation should include a detailed history of exposures and appropriate serologic tests and systemic cultures. Treatment is directed toward the underlying process.

Chronic use of any topical ophthalmic medication may result in ocular medicamentosa. Signs and symptoms include tearing, redness, photophobia, and irritation, masquerading as an infectious conjunctivitis. Although it is most commonly associated with over-the-counter vasoconstrictors, it is also seen with topical antibiotics and may cause a self-perpetuating conjunctivitis until medication use is discontinued. Other etiologies should be considered in chronic conjunctivitis, including neoplasm, allergy, toxicity, autoimmune disease, and unusual pathogens.

Table 11.4 Causes of Parinaud's oculoglandular syndrome

Disease	Agents
Cat scratch disease	*Bartonella henselae*
Tularemia	*Francisella tularensis*
Sporotrichosis	*Sporotrichum schenckii*
Tuberculosis	*Mycobacterium tuberculosis*
Syphilis	*Treponema pallidum*
Coccidioidomycosis	*Coccidioides immitis*
Paracoccidioidomycosis	*Paracoccidioides brasiliensis*
Actinomycosis	*Actinomyces israelii*, *A. propionicus*
Blastomycosis	*Blastomyces dermatitidis*
Infectious mononucleosis	Epstein–Barr virus
Mumps	Paramyxovirus
Pasteurellosis	*Pasteurella multocida (septica)*
Yersinia infection	*Yersinia pseudotuberculosis* *Yersinia enterocolitica*
Glanders	*Burkholderia mallei*
Chancroid	*Haemophilus ducreyi*
Lymphogranuloma venereum (LGV)	Chlamydial LGV agent L, L_2, L_3
Rickettsiosis (Mediterranean spotted fever)	*Rickettsia conorii*
Listerellosis	*Listeria monocytogenes*
Ophthalmia nodosa (noninfectious)	Lepidoptera (caterpillars) Tarantula hairs

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12. Keratitis

Elmer Y. Tu, Francis S. Mah, and Jules Baum

Keratitis is an ocular emergency that can lead to severe visual disability and requires prompt diagnosis and treatment. Sequelae can vary in severity from little or no visual loss to corneal scarring, perforation, endophthalmitis, and loss of the eye. Although the corneal surface is awash with microorganisms of the normal flora, an intact corneal epithelium and ocular defense mechanism serve to prevent infection in the normal eye. Although some organisms such as *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Corynebacterium diptheriae*, *Listeria*, and *Shigella* can penetrate an intact epithelium, all others require damage to the epithelial layer to invade the cornea. Several risk factors predispose the cornea to infection. Dry eyes from Sjogren syndrome, Stevens–Johnson syndrome, or vitamin A deficiency can result in bacterial keratitis. Prolonged corneal exposure from ectropion, lagophthalmos, or proptosis can lead to secondary infection. Entropion and trichiasis resulting in epithelial defects put the cornea at risk. Neurotropic keratopathy from cranial neuropathy, prior herpes simplex, or zoster infections predispose to secondary infections. Some systemic conditions such as chronic alcoholism, severe malnutrition, immunosuppressive drug use, immunodeficiency syndromes, and malignancy can impair immune defenses and allow infection by unusual organisms. Prior ocular surgery such as penetrating keratoplasty or refractive procedures is also a risk factor. Trauma is a common predisposing factor of bacterial keratitis, especially for patients at the extremes of age and in developing countries. Injury to the corneal surface and stroma allows invasion of normal flora as well as organisms harbored by foreign bodies.

Contact lens wear is the most common established risk factor for bacterial keratitis in developed countries. All types of contact lenses have been linked to infection, with extended-wear soft lenses conferring greater risk than daily wear hard or soft lenses. Corneal changes from contact lens use include an induced hypoxic and hypercapnic state promoting epithelial cell derangement and allowing bacterial invasion. Contact lenses also induce dry eye and corneal hypesthesia. Overnight rigid gas-permeable lens use for orthokeratology has also been associated with bacterial keratitis, but with a disproportionately high incidence of *Acanthamoeba* keratitis.

Although there are geographic variations in the order of incidence, the most common pathogenic organisms associated with bacterial keratitis include *Staphylococcus* species, *Streptococcus* species, *Pseudomonas aeruginosa*, and enteric gram-negative rods. A 5-year review of bacterial keratitis isolates from Pittsburgh showed a change in distribution with a decrease in gram-positive organisms, whereas gram-negative isolates remained stable (Figure 12.1). In South Florida, an increase in gram-positive isolates with a decrease in gram-negative isolates over a 30-year period has been reported. *Pseudomonas aeruginosa* is commonly associated with contact lens-related bacterial keratitis, causing up to two-thirds of cases, although a decline in the frequency of *P. aeruginosa* isolates in these patients has been noted. Nontuberculous mycobacteria are being reported with increasing frequency as a cause of infectious keratitis after laser *in situ* keratomileusis (LASIK). Although the reported incidence of infection after LASIK is low, this condition is a management challenge requiring proper diagnosis and treatment. Bacterial colonization of the eyelid and conjunctiva is normal and helps reduce opportunities for pathogenic strains from gaining a foothold. Host defense mechanisms can be overcome, however, and this leads to serious ocular morbidity if the pathogen is not treated properly. Although the clinical manifestations of corneal infections may be characteristic of certain pathogens, further laboratory evaluation with cultures and antibiotic susceptibility testing provides a definitive diagnosis and more focused treatment after empirical therapy has been initiated.

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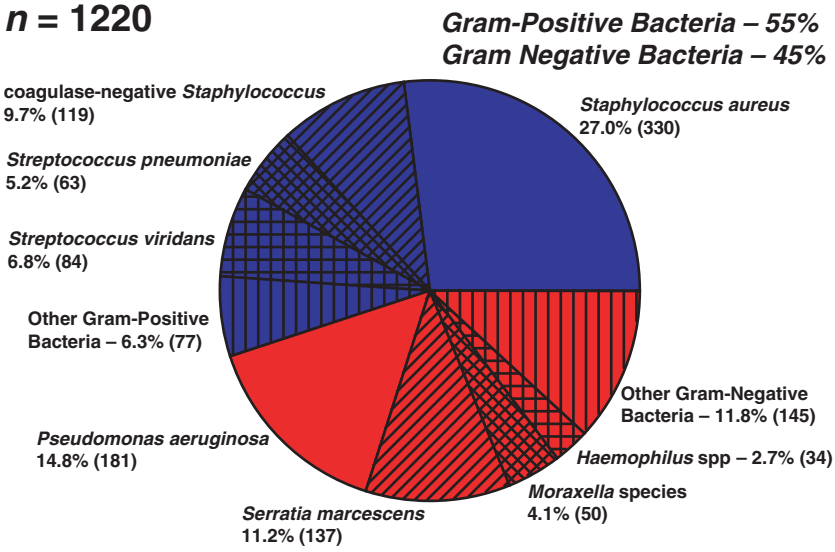


Figure 12.1 Keratitis isolates (1993–2006).

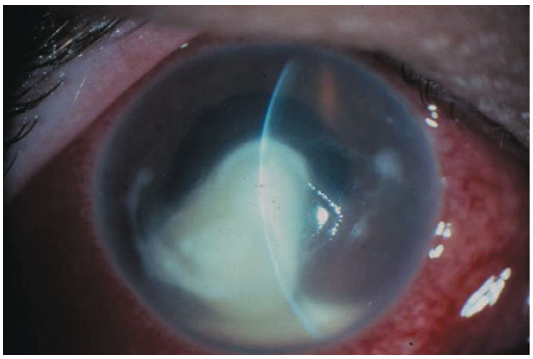


Figure 12.2 Infectious keratitis.

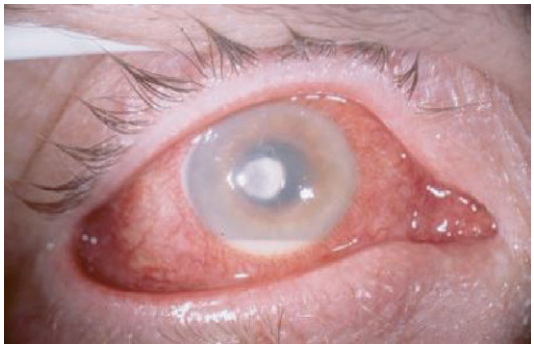
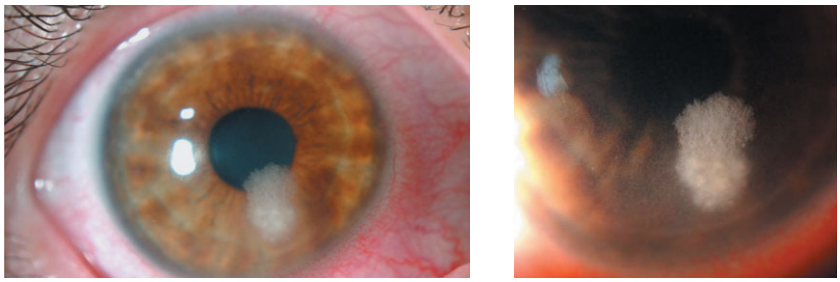


Figure 12.3 Hypopyon.

CLINICAL FEATURES

The presenting symptoms, clinical history, and exam findings may suggest an infectious keratitis but are seldom pathognomonic for a particular organism. The presenting signs of bacterial keratitis vary depending on the virulence of the organism, duration of infection, structural status of the cornea, and host inflammatory response.

Common presenting symptoms include pain, decreased vision, tearing, and photophobia. Eyelid edema, conjunctival hyperemia with a papillary reaction, and chemosis are typical findings. A corneal epithelial defect with adherent mucopurulent exudate and underlying stromal infiltrate is a hallmark sign for infectious keratitis (Figure 12.2). Multiple focal infiltrates can be seen with contact lens use or with polymicrobial infections. Migration of inflammatory cells causes a diffuse cellular infiltration adjacent to and within the ulcerated stroma. An anterior chamber reaction can range from mild cells and flare to a marked hypopyon (Figure 12.3). A cornea damaged from prior disease can present with less distinct signs and symptoms. Pre-existing corneal scars, epitheliopathy, or inflammation confuse the picture as does prior use of antibiotics and corticosteroids. On examination, all ocular abnormalities should be documented in detail to help track the clinical course on subsequent visits. Repeat measurements of the size of the epithelial defect, the depth of the stromal infiltrate, and the severity of inflammation can be used to assess the effectiveness of treatment.



Figures 12.4 (A and B) Infectious crystalline keratopathy.

Nontuberculous mycobacterial keratitis has been reported with increasing frequency after LASIK, including several clusters of cases. In two recent reviews of post-LASIK corneal infections, *Mycobacterium* represented the most common etiologic organism. The isolated subtypes include the fast-growing *Mycobacterium chelonae*, *Mycobacterium abscessus*, *Mycobacterium fortuitum*, and *Mycobacterium mucogenicum*, as well as the slow-growing *Mycobacterium szulgai*. Nontuberculous keratitis after LASIK is characterized by a delayed onset with an indolent course. Time of onset from fast-growing organisms averaged 3.4 weeks after the procedure, whereas the slow-growing *M. szulgai* can present 6 to 24 weeks after surgery. Symptoms can range from a mild foreign-body sensation to pain, redness, photophobia, and decreased vision. The infiltrate, which can be multiple, begins in the interface and spreads to adjacent stroma of the flap and stromal bed. Anterior perforation through the flap can occur with progression of infection. The location can be central, paracentral, or peripheral. In addition to a focal infiltrate, a cracked windshield appearance of infectious crystalline keratopathy has been reported (Figures 12.4A and B).

DIAGNOSTIC TECHNIQUES

Currently, routine culture of corneal infections is not the usual practice in the community. A small peripheral ulcer may be treated empirically, but a large, purulent, central ulcer that extends to the middle to deep stroma should be cultured. In addition, ulcers that are atypical or clinically suspicious for fungal, mycobacterial, or amebic infections or are unresponsive to initial broad-spectrum antibiotics warrant cultures. Topical anesthesia with proparacaine hydrochloride is preferred because it has fewer antibacterial properties than other topical anesthetics that might interfere with culture yields. A sterile platinum spatula is used to scrape the leading edge as well as the base of the ulcer while carefully avoiding contamination from the lids and lashes. Organisms such as *Streptococcus pneumoniae* are more readily recovered from the ulcer edge, whereas other organisms such as *Moraxella* are characteristically recovered from the base. The scrapings are inoculated onto solid media (blood, chocolate, and Sabouraud's agar) by streaking a row of Cs. New material is recovered for each row. Scrapings are also placed on microscope slides and stained with Gram and Giemsa stains. Special stains include Ziehl–Neelsen acid-fast stain for *Mycobacterium*, *Actinomyces*, and *Nocardia*. Acridine orange is a fluorescent dye that may be helpful in identifying bacteria when yields are low, but this stain does not yield classification information that Gram stain provides.

In vivo confocal microscopy may be helpful in atypical, nonbacterial corneal infections where the organisms are larger and not as amenable to culture or identification. In cases of deep stromal suppuration that is not readily accessible or a progressive microbial keratitis unresponsive to therapy, a corneal biopsy may be warranted. A round 2-mm to 3-mm sterile disposable skin trephine is used to incise the anterior corneal stroma, and lamellar dissection is performed with a surgical blade. The specimen is then ground in a mortar with trypticase soy broth and plated on media.

TREATMENT

Routes of administration

The topical application of drugs with eyedrops is the preferred method of treatment of bacterial keratitis. Increased drug penetration can be achieved by higher concentrations, more frequent

applications, and by the typical presence of an epithelial defect. Fortified antibiotics are made by mixing the powdered drug or diluting the parenteral form with artificial tears or balanced salt solution. These freshly prepared solutions remain stable for up to a week without significant loss of activity. Although ointments prolong corneal contact time and lubricate the ocular surface, peak corneal concentrations may be limited when compared with solutions. They also retard the absorption of antibiotics delivered in eyedrop form. Ointments can be used as adjunctive therapy at bedtime in less severe cases.

The need for other routes of antibiotic administration in bacterial keratitis is rare. Subconjunctival injections may not have a therapeutic advantage over topical solutions. However, they may be indicated in certain clinical situations such as imminent perforation or spread of infection to adjacent sclera, especially when patient compliance is an issue. Soft contact lenses and collagen shields can act as drug depot/delivery devices and aid in sustaining high corneal drug levels. These "bandage" contact lenses may also provide protection to promote reepithelialization. Systemic therapy is indicated for gonococcal infections as well as for young children with severe *H. influenzae* or *P. aeruginosa* keratitis. Systemic antibiotics are also indicated for perforations and scleral involvement.

Empiric therapy

Because bacterial keratitis can rapidly progress and threaten vision, treatment should begin when an infectious process is suspected to limit further damage in an effort to preserve vision. Topical broad-spectrum antibiotics are initially used and later modified according to culture results, antibiotic susceptibilities, and clinical response. For severe cases, combination therapy with fortified β-lactam (cefazolin 50 mg/mL) and aminoglycoside (tobramycin or gentamicin 14 mg/mL) (Figure 12.5) provides adequate coverage of both gram-positive and -negative organisms that cause bacterial keratitis. Vancomycin (50 mg/mL) can be substituted for cefazolin in cases of penicillin allergy or resistance in *Staphylococcus* species. Because of a high prevalence of methicillin resistance in some centers, vancomycin instead of cefazolin is utilized as a first-line agent. A loading dose is achieved with a drop every 5 minutes for five applications. Antibiotic is then continued every 30 minutes to 1 hour around the clock for several days and then rapidly tapered once control of the infection has been achieved.

Figure 12.5 Topical aminoglycosides are combined with β-lactam therapy.

Single-agent therapy with fluoroquinolones has previously been shown to be as effective as combination therapy in treating bacterial keratitis. The widespread systemic use of the second (ciprofloxacin and ofloxacin) and third (levofloxacin) generation fluoroquinolones has, however, led to the emergence of resistance in several bacterial species, including *Pseudomonas aeruginosa*. The fourth-generation fluoroquinolones, gatifloxacin and moxifloxacin, have been developed to improve coverage of gram-positive and atypical mycobacterial pathogens. They require two mutations to establish resistance and, therefore, are more effective against gram-positive organisms that already have a single mutation and are resistant to older generation fluoroquinolones. Unfortunately, large surveys have noted that the vast majority of methicillin-resistant *Staphylococcus aureus* is also resistant to all currently available topical ophthalmic fluoroquinolones.

Regardless of the susceptibility profile, a favorable response to empiric therapy merits continuing the treatment. Positive signs of clinical improvement include decreased pain and discharge, consolidation of the stromal infiltrate, decreased anterior chamber reaction, and corneal reepithelialization. Culture and antibiotic susceptibility results can be used to focus therapy against the offending organism or to discontinue

unnecessary drugs. Clinical improvement may not be seen during the first 2 days due to increased inflammation and suppuration from bacterial exotoxins. Toxicity from topical medications can also mask changes. A lack of improvement or clinical worsening after 48 hours may warrant repeat cultures, although concomitant antibiotic therapy will decrease yields. Topical therapy can be tapered as the clinical picture improves.

Management of nontuberculous mycobacterial keratitis after LASIK can be challenging and requires aggressive treatment. The flap should be lifted for smears and culture as well as for soaking of the stromal bed and flap with antibiotics. Fortified amikacin, clarithromycin, and azithromycin are the drugs of choice. Fourth-generation fluoroquinolones have also been shown to be effective against mycobacterial keratitis. Combination therapy is recommended due to emergence of resistance on monotherapy. Lack of clinical improvement warrants repeat culture and tailoring of antibiotics accordingly. Flap amputation may also be necessary to allow increased antibiotic penetration.

Adjunctive therapy

Bacterial keratitis is often associated with severe pain. Pain control with analgesics may provide not only comfort but also better compliance with the difficult regimen of around-the-clock topical drop instillation. Cycloplegic agents should also be used to decrease discomfort from ciliary spasm and to prevent synechiae formation. Cyanoacrylate glue can be used to reinforce an area of corneal thinning, a descemetocele, or a small perforation. A "bandage" contact lens is placed after the glue hardens. This procedure allows for further treatment of the infection and inflammation while postponing surgery. A corneal patch graft is an alternative for small perforations, whereas larger necrotic perforations require a therapeutic penetrating keratoplasty. Surgical interventions are most successful after patients have received therapeutic dosing of antibacterial drugs prior to surgery.

Corticosteroids may play a role in treating bacterial keratitis with their potential for reducing the host inflammatory response and resultant corneal scarring but this must be balanced by their potential to inhibit corneal wound healing. Other adverse effects may include potentiation of microbial replication, recrudescence of infection, steroid-induced glaucoma, and cataract formation. The use of corticosteroids prior to the initiation of effective antimicrobial therapy is associated with a significantly poorer outcome in bacterial keratitis and their use in eyes with pre-existing corneal disease increases the risk of the development of ulcerative keratitis. The only prospective, randomized trial of corticosteroid administration in treated bacterial keratitis failed to show any increase in adverse events with corticosteroid use, but also did not demonstrate a visual benefit at 3 months. General guidelines for the use of corticosteroids include: (1) consider use only in those patients with vision-threatening infections in or around the central cornea, (2) corticosteroids should be used only after establishing effective antibiotic therapy with an appropriate response of the infection, (3) continue use of concomitant antibiotics, and (4) do not use steroids if the infection is not responding appropriately to topical antibiotics or if there is suspicion for an atypical or nonbacterial pathogen.

Herpetic keratitis is the most common cause of corneal blindness in developed nations. Herpes simplex virus (HSV) can manifest as a blepharitis, conjunctivitis, epithelial keratitis, stromal keratitis, limbitis, endotheliitis, uveitis, or retinitis. As elsewhere, in immunocompetent individuals, the infection is usually self-limited, but once established in any facial dermatome will become latent in the trigeminal ganglia. Recurrences may occur for a patient's lifetime in any dermatome including the eye and periocular region and visual loss is strongly associated with the number of recurrences and location within the cornea. Pediatric patients have a high rate of corneal scarring, increasing in severity with the age of first onset. Both HSV-1 and HSV-2 have been detected with HSV-1 marginally more common in eye infections. There is often a history of labial or genital herpes as well as a history of a recurrent, nonspecific red eye or frank vesicular lesions in the periorbital region.

HSV keratitis may be bilateral in a minority of cases (<10%) but is usually unilateral. The initial corneal infection may be minimally symptomatic and is characterized by a dendritic epithelial lesion with terminal bulbs which stain with Rose Bengal but may also be geographic. This usually will leave a ghost imprint on the anterior stroma. Subsequent recurrences may be either epithelial, stromal, endothelial or some combination thereof. Stromal HSV keratitis appears inflammatory with either a diffuse stromal edema and interstitial keratitis or a disciform keratitis reminiscent of *Acanthamoeba* keratitis. Isolated corneal edema

may be characteristic of associated endotheliitis and elevated intraocular pressure seen with HSV trabeculitis. Most patients will have some loss of corneal sensation which may lead to an unstable epithelium and dry eye.

Treatment for the initial and recurrent episodes may be either topical or systemic. Currently available topical agents include trifluridine and ganciclovir as well as acyclovir, which is available outside of the United States. Significant toxicity can be seen with trifluridine and treatment with any topical agent should be limited to 7 to 10 days after which a reassessment should be done as to whether findings are either still due to active infection or due to the complications of neurotropic keratitis or medication toxicity. Systemic therapy consists of acyclovir, valacyclovir, or famivir in the same doses used for dermatologic therapy and is as effective as topical therapy without the local side effects. Treatment has been shown to reduce the duration of the infection by 1 to 2 days but has no preventive effect in reducing recurrences or progression to stromal keratitis. However, long-term maintenance oral antiviral therapy has been shown to reduce the number of recurrences of herpetic eye disease. Corticosteroids may be used in stromal keratitis to reduce pain and discomfort while the patient is on effective antiviral therapy.

Other viruses in the herpes family can also cause keratitis, including herpes zoster (HZV), Epstein–Barr, and cytomegalovirus. Of these, HZV is the most commonly recognized and like HSV may cause a retinitis, uveitis, epithelial keratitis, and stromal keratitis initially occurring within 3 months of an episode of Vth nerve zoster. Clinical findings are similar to HSV, but the pseudodendrites are lacking in terminal bulbs and keratitis may be treated with corticosteroids, which are a contraindication in HSV epithelial keratitis. The neurotropic keratitis seen with HZV is often more profound than with HSV. As in HSV, initial episodes should be treated with dermatologic treatment doses of oral antivirals for zoster. Subsequent "recurrences" are largely inflammatory, but some epithelial lesions may require topical antivirals for resolution. Vaccinations for HZV should be approached with caution in a zoster ophthalmicus patient for fear of reactivation, which has been reported. In other patients, however, vaccinations should prove to partially protect from episodes of shingles.

Acanthamoeba keratitis is a rare opportunistic infection that affects an estimated 18 to 20 patients per million contact lens wearers per year in the United Kingdom and more recently in the United States where there are approximately 36 million contact lens users. Acanthamoebae are ubiquitous protozoa found in both soil and water that exist in two forms: trophozoites (the active form) and cysts (the inactive form). In stressful environments, trophozoites transform into cysts within hours that are resistant to extremes of temperature, pH, and desiccation. Because the cysts are notoriously difficult to kill, the infestation of the corneal stroma is very difficult to eradicate. Indeed, only one class of commonly compounded ophthalmic medications, the biguanides (polyhexylmethylbiguanide [PHMB], chlorhexidine, pentamidine), has cystocidal activity.

The initial report of *Acanthamoeba* keratitis in 1973 occurred in a non contact lens wearer who sustained eye trauma. The infection remained rare until the mass market introduction of soft contact lenses was followed by an outbreak of infection in wearers in the late 1980s, largely attributed to nonsterile homemade saline contact lens care solutions. More than 85% of all acanthamoeba infections are in contact lens wearers with additional risk factors of ocular trauma, corneal transplantation, and exposure to contaminated lake water, sea water, or hot tubs. Starting in 2003, an alarming increase in the rate of *Acanthamoeba* keratitis has been observed, prompting the Centers for Disease Control and Prevention (CDC) and academic centers to attempt to identify a cause which persists despite the identification and recall of an at-risk contact lens solution, AMO Complete Moisture Plus, in 2007.

Acanthamoeba infection presents with similar nonspecific symptoms as bacterial keratitis. Pain that is out of proportion to clinical findings is classic but not universal. Early corneal infection manifests as epithelial involvement, including elevated epithelial lines that may appear as dendritic, punctuate epithelial erosions, microcysts, and epithelial haze (Figure 12.6). Stromal findings, which occur later in the infection, include single or multiple stromal infiltrates and nummular keratitis. Ring infiltrates or satellite lesions usually suggest advanced disease (Figure 12.7). Tropism of the *Acanthamoeba* organism for corneal nerves causes radial keratoneuritis, the reason for the extreme pain (Figure 12.8).

Diagnosis is typically delayed because the clinical appearance mimics other etiologies. Early infections are commonly treated as bacterial keratitis, especially because many practitioners rely

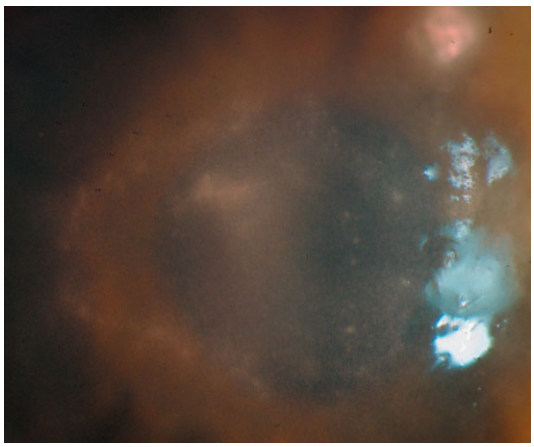


Figure 12.6 Epithelial haze.

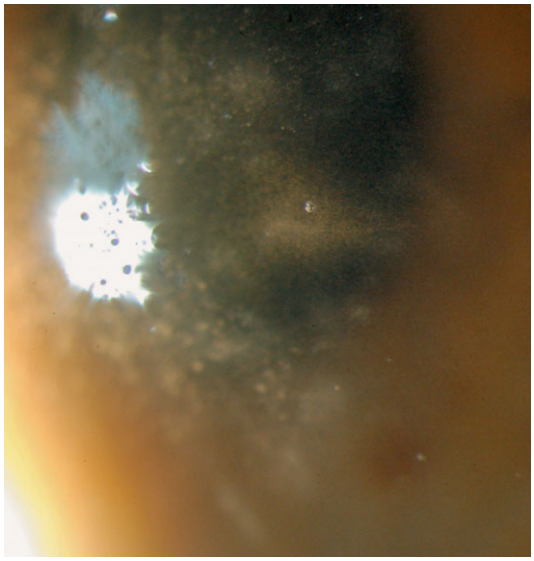


Figure 12.8 Radial keratoneuritis.

on empiric treatment with broad-spectrum topical fluoroquinolones. Early disease is commonly misdiagnosed as herpes simplex, whereas later disease can be confused with fungal keratitis characterized by severe pain and a minimally necrotic deep stromal infiltrate. A significantly poorer prognosis is associated with deeper corneal involvement, which is increasingly likely with this delay in diagnosis.

Treatment of *Acanthamoeba* keratitis may last weeks to years, involves toxic medications, and may be unsuccessful in curing the infection if the infection involves the deep cornea or involves a resistant pathogen. A combination of topical

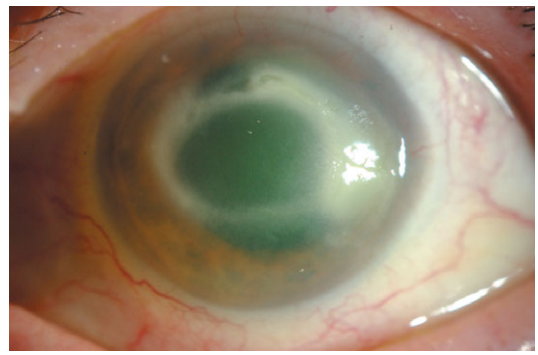


Figure 12.7 Ring infiltrates.

antiamebic agents, including biguanides (e.g., PHMB and chlorhexidine), and diamides (e.g., propamidine) are typically used. Second-line agents include azole and triazole antifungals, specifically voriconazole (oral and/or topical) or clotrimazole, and topical neomycin. Monotherapy with a biguanide alone can be curative. Most of these medications are not available commercially in the United States and they must be either compounded (biguanides, topical azole and triazole antifungals) or imported (diamidines) by a specialty pharmacy before use. Medications are often used for months, starting with hourly dosages and tapering off as the clinical situation improves. The use of steroids is controversial; it likely has no role in an appropriately resolving *Acanthamoeba* keratitis, but may be necessary in patients with extraocular inflammatory manifestations such as scleritis or dacryoadenitis.

Fungal infections of the cornea are more common in hot, humid environments, such as India or Florida, where fungal keratitis accounts for 40% and 16% of all cornea infections, respectively. Fungi are ubiquitous in the environment and can be broadly divided into yeast (*Candida* species) and molds (filamentous fungi, e.g., *Fusarium* and *Aspergillus*). Yeast infections are more common in temperate climates while filamentous fungi predominate in more tropical environments. However, trends in the United States show an increasing frequency of filamentous fungal keratitis over the last decade not only with *Fusarium* spp., which remains the single most common corneal pathogen, but also with drug-resistant, uncommon molds such as *Paecilomyces*, *Scedosporium*, and *Alternaria*. The epithelial barrier is the most important defense mechanism against all forms of infectious keratitis, including fungi. By far the most important risk factor for fungal keratitis is ocular trauma, especially when the

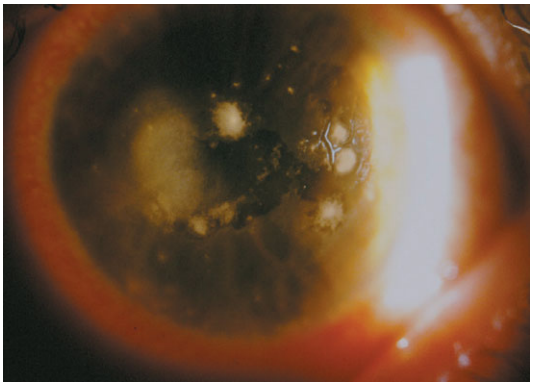


Figure 12.9 Fungal keratitis.

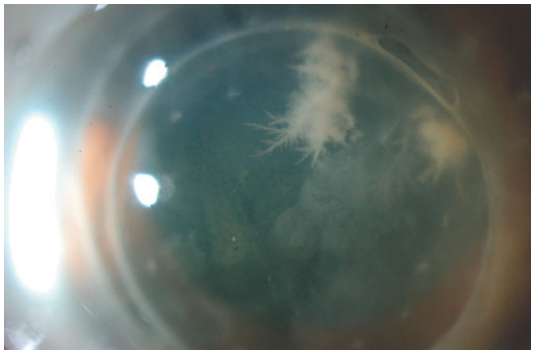


Figure 12.10 Fungal keratitis endothelial plaques.

trauma involves contact with soil or vegetable matter. Other risk factors include ocular surface disease such as neurotropic keratitis and chronic use of steroids. Patients with atopic disease, immunocompromised patients, or those hospitalized in intensive care units are also at increased risk for fungal keratitis. Although contact lens wear has not been considered a major risk factor for fungal keratitis, a cluster of *Fusarium* keratitis cases in otherwise healthy soft-contact lens wearers was noted throughout the world in 2006 (Figure 12.9). Multiple studies around the world found a strong association with the use of a contact lens cleaning solution Renu with MoistureLoc, which was withdrawn from the market in April 2006. This resulted in a substantial reduction of the number of reported cases of *Fusarium* keratitis in contact lens wearers to near the baseline incidence prior to the solution's market introduction.

Clinical signs of fungal infection include nonspecific signs of any corneal infection. Specific clinical features that should raise suspicion include infiltrates with indistinct or "feathery" edges, multifocal infiltrates, satellite lesions, immune rings, and endothelial plaques (Figure 12.10). The patient history is an important clue to the diagnosis as patients typically have a history of outdoor trauma and a waxing and waning course of symptoms and signs that have been unresponsive to empiric management. Severe pain and elevated intraocular pressure are common. Early diagnosis is critical for successful treatment because ophthalmic topical antifungals have variable penetration into the deep corneal stroma and corneal fungal pathogens have a propensity to proliferate vertically and to penetrate an intact Descemet's membrane, leading to endophthalmitis. The diagnosis of fungal keratitis is often delayed because it is uncommon, resulting in a low index of clinical suspicion, and because the organism can be difficult to recover if it has spread deep into the cornea. In vivo confocal microscopy can be a powerful tool in detecting filamentous fungal pathogens. Culture and vital staining is the gold standard of diagnosis, but is often negative.

Treatment of fungal keratitis is also challenging because currently available antifungal medications have a limited spectrum of activity and often have poor penetration into the cornea. The most widely used topical antifungal medications are the polyenes, amphotericin B, and natamycin (Pimaricin). Natamycin is the only commercially available antifungal topical medication in the United States. Earlier-generation azole compounds have been used topically (clotrimazole and miconazole) and systemically (ketoconazole, fluconazole, and itraconazole). Of the newer triazoles, voriconazole has been used extensively for both topical and systemic treatment of fungal keratitis. Unfortunately, multiple case series and a randomized trial have demonstrated its inferiority to natamycin as a primary empiric agent in this disease. Voriconazole, posaconazole, and the echinocandins (caspofungin and micafungin) remain useful as either adjunctive or secondary agents, however, in ulcers resistant to natamycin and/or amphotericin B, especially if in vitro sensitivities suggest susceptibility. Treatment of fungal keratitis is prolonged and often lasts for weeks to months. The use of a topical steroid is contraindicated because it can worsen disease and interferes with the efficacy of certain antifungal agents.

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13. Iritis

Alice Lorch and Ann-Marie Lobo

DEFINITION OF UVEITIS

The uveal tract in the eye is the darkly pigmented, vascular, "middle layer" of the eye. It sits between the inner retinal layer and outer corneal–scleral layer, and is composed of the choroid, ciliary body, and iris. Uveitis is inflammation of the uveal tract. Uveitis can be classified according to anatomic structures involved: the iris or anterior ciliary body (anterior uveitis or iritis) the posterior ciliary body or anterior vitreous (intermediate uveitis), or choroid (posterior uveitis). Posterior uveitis can also include inflammation of the retina (retinitis), retinal blood vessels (vasculitis), and optic nerve (optic neuritis.) Many of the inflammatory and infectious etiologies of uveitis can cause both anterior and posterior uveitis, known as panuveitis. Therefore, anterior uveitis can be isolated or a harbinger of posterior uveitis and all patients with uveitis should have careful evaluation of both chambers. Only anterior uveitis, or iritis, will be discussed in this chapter, as intermediate and posterior uveitis are discussed elsewhere.

Anterior uveitis is most commonly idiopathic, but can be diagnosed as either inflammatory or infectious in etiology. Anterior uveitis can also be due to reactive inflammation from mild trauma or corneal disease. Neoplasias such as retinoblastoma or lymphoma can present as anterior uveitis, with tumor cells in the anterior chamber. Finally, iritis can be drug-related: cidofovir, diethylcarbamazepine, pamidronic acid, interleukin-3 and interleukin-6, oral contraceptives, quinidine, rifabutin, streptokinase, and sulfonamides are among medications that have been implicated in the past.

Infectious causes are generally either bacterial or viral, but can be related to protozoa or worms. Again, many of these diseases present with anterior segment findings but also have posterior involvement on further examination.

CLINICAL PRESENTATION

Anterior uveitis can present with sudden onset or chronic signs and symptoms. Classic symptoms of acute iritis are eye pain, redness, photophobia, and blurred vision. Examination is significant for conjunctival injection, described as ciliary flush when at the corneal limbus, without discharge. Slit-lamp examination reveals white blood cells floating in the anterior chamber; when white cells are layered forming a visible white line, this is referred to as a hypopyon (Figure 13.1). The presence of a hypopyon should always raise concern for an infectious endophthalmitis in patients with a history of recent surgery, trauma, or possible endogenous source (i.e., fungemia.) Anterior uveitis with hypopyon is otherwise most commonly seen in patients with HLA-B27-related disease or Behçet's disease. Keratic precipitates are another common finding in anterior uveitis; these are deposits of white blood cells on the posterior cornea. Keratic precipitates can be "fine," indicating a nongranulomatous disease such as Fuch's iridocyclitis, HLA-B27-related disease, or juvenile idiopathic arthritis. In granulomatous disease, such as sarcoidosis, syphilis, tuberculosis, or

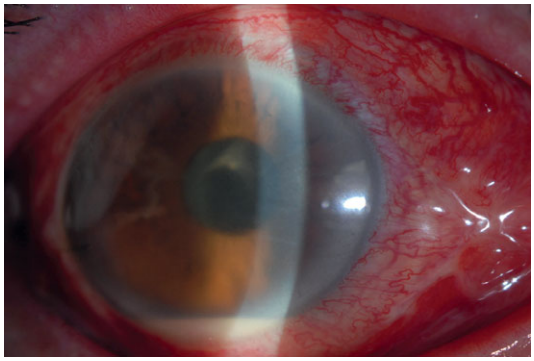

Figure 13.1 Slit-lamp photograph of a hypopyon in a patient with infectious endophthalmitis after cataract surgery.

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toxoplasmosis, keratic precipitates are large and yellowish, described as "mutton fat." White blood cells can also deposit on the iris, particularly in granulomatous uveitis; these are called Busacca nodules if in the iris stroma and Koeppe nodules if at the pupillary margin. Chronic iris inflammation can lead to adhesions between the iris and lens, known as posterior synechiae; these can lead to the appearance of a small or irregular pupil.

DIAGNOSTIC TESTS

Laboratory testing is pursued for patients with anterior uveitis that is recurrent, bilateral, or if there are concerns for a particular systemic disease. A large number of cases of anterior uveitis are classified as "idiopathic" when results of serologies are negative. These cases are thought to be due to an underlying unknown autoimmune or viral condition. Newer diagnostic modalities may help both in distinguishing between known etiologies of uveitis and in making a diagnosis in cases otherwise designated as "idiopathic."

Molecular diagnostic tests have enabled the use of small quantities of ocular fluid samples to be tested for certain infections. Anterior chamber paracentesis is a safe procedure that can be performed by an ophthalmologist at the slit lamp to obtain a small-volume sample of aqueous for testing. Aqueous samples can be tested for antibodies to determine the Goldmann–Witmer coefficient, a ratio of the total immunoglobulin in aqueous compared with that in the serum. A ratio greater than three indicates the true presence of antibodies in ocular fluid (and not just spillover from serum due to leaky inflamed blood vessels). Polymerase chain reaction (PCR), a technique used to amplify small amounts of DNA or RNA for microbial identification, can be used to identify specific viruses in intraocular fluid. Real-time PCR can quantify virus in a small volume of intraocular fluid. PCR does not have high sensitivity for all viruses and so must be used in conjunction with clinical suspicion and other diagnostic tests. Currently, PCR is used to detect herpesviruses (including herpes simplex virus [HSV] type 1 and 2, cytomegalovirus [CMV], Epstein–barr virus [EBV] and varicella-zoster virus [VZV]), toxoplasmosis, and bacterial 16S rRNA.

INFECTIOUS ETIOLOGIES (TABLE 13.1)

Table 13.1 Infectious etiologies of iritis

Endophthalmitis
Herpesviruses
Syphilis
Bartonella
Tuberculosis
Lyme disease
Brucellosis
Whipple's disease
Leprosy
Chikungunya
Leptospirosis
Toxoplasmosis
HIV

Endophthalmitis

Patients with inflammation or hypopyon in the anterior chamber after intraocular surgery or trauma should be suspected of having endophthalmitis rather than anterior uveitis. Endophthalmitis can be acute, presenting with decreased vision and pain soon after surgery; these infections are generally due to staphylococcus or streptococcus infections. Delayed-onset endophthalmitis after cataract surgery can be due to *Proprionibacterium acnes*. Classically, patients with *P. acnes* endophthalmitis have white plaques on the posterior lens capsule. Endophthalmitis can also be endogenous; this is seen in patients with indwelling catheters, intravenous drug users, or others with risk of bacterial or fungal seeding of the blood. Candidemia can lead to a panuveitis with fluffy white lesions in the retina or vitreous. Endophthalmitis, whether exogenous or endogenous, must be treated immediately by an ophthalmologist with injection of antimicrobial agents into the vitreous or vitrectomy to prevent vision loss.

Herpesviruses

Herpesviruses, including HSV-1 and HSV-2, CMV, or VZV, are the most common type of infectious anterior uveitides. HSV anterior uveitis can be seen in patients with prior or concurrent HSV keratitis; however, simultaneous keratitis is not necessary for diagnosis. Herpes zoster

ophthalmicus is caused by involvement of VZV in the ophthalmic branch of the trigeminal nerve. Diagnosis of herpetic uveitis can be made definitively by PCR of an aqueous sample, but treatment, with antiviral agents and topical steroids, is usually initiated based on clinical appearance. Characteristic findings of herpetic uveitis are unilateral disease and sectoral iris atrophy. Herpetic uveitis is one of the few uveitic processes that can be associated with increased intraocular pressure (others include sarcoidosis and toxoplasmosis.) Like the HSV virus, CMV can also cause anterior uveitis associated with high intraocular pressure and iris atrophy.

The herpesviruses can cause devastating vision loss if there is posterior involvement. Acute retinal necrosis (ARN) is a rapidly progressive necrotizing retinitis that can lead to retinal ischemia and retinal breaks and requires immediate and aggressive therapy. ARN is most commonly seen in immunocompetent patients, although it also can be seen in the immunocompromised. The initial presentation of ARN can be anterior uveitis and so it is essential that all patients with anterior uveitis receive a dilated fundus examination. Progressive outer retinal necrosis (PORN) is a retinitis similar to ARN that develops primarily in immunocompromised patients and is most commonly associated with VZV. As described above, PCR of ocular fluids can be used to identify herpetic viruses. Treatment of both ARN and PORN is with intravenous antiviral medications (acyclovir, ganciclovir) and potentially intravitreal antiviral medications (ganciclovir, foscarnet).

Syphilis

Syphilis usually produces a granulomatous uveitis (although nongranulomatous presentations have been reported) that can involve all parts of the eye. Congenital syphilis presents with interstitial keratitis accompanied by anterior uveitis that presents in teenage years with "salt-and-pepper" fundus changes. In acquired syphilis, the onset of ocular involvement is in secondary or tertiary disease, and is most commonly iritis. Other common presentations of ocular syphilis include posterior placoid chorioretinitis, retinal vasculitis, vitritis, and papillitis and so a dilated fundus exam is essential for complete diagnosis.

Patients with suspected ocular syphilis should have indirect (rapid plasmin reagent [RPR] or Venereal Disease Research Laboratory [VDRL]) and direct serum testing (fluorescent treponemal antibody [FTA-ABS]). Patients with positive serum tests should undergo lumbar puncture for diagnosis of neurosyphilis. Screening for HIV also should be performed. Ocular syphilis is treated the same as neurosyphilis, with intravenous penicillin G. Topical steroids and mydriatics can be used as an adjunct to systemic treatment. Systemic steroids can be used to prevent a Jarisch–Herxheimer reaction at the time of treatment.

Bartonella species (cat scratch disease)

Bartonella (including *Bartonella henselae* and *Bartonella quintana*) is spread via contact with a contaminated cat. Patients can present with Parinaud's oculoglandular syndrome, which is a constellation of granulomatous conjunctivitis and regional lymphadenopathy. *Bartonella* can also cause a neuroretinitis that clinically presents with optic nerve edema and a "star'-like pattern of exudates in the macula (referred to as a macular star). Anterior uveitis alone is rare, but patients can present with a panuveitis with neuroretinitis. Diagnosis is confirmed by serologies as other infections can also present with neuroretinitis. Treatment with antimicrobial agents, including doxycycline and rifampin, is based on the severity of disease.

Tuberculosis

The diagnosis of ocular tuberculosis (TB) can be very difficult since many patients may have no history of systemic TB. Recent exposure to TB or a positive tuberculin skin test in a patient with chronic granulomatous uveitis should raise suspicion. The recently introduced interferon-gamma release assay (Quantiferon-Gold) can distinguish between exposure to *Mycobacterium tuberculosis* and to atypical mycobacteria or the bacille Calmette–Guérin vaccine; however, this test cannot distinguish between latent and active TB. Aqueous and vitreous cultures are often falsely negative and PCR testing is unreliable. The most characteristic eye findings are granulomatous anterior uveitis with multifocal choroiditis and occasionally choroidal tubercles. Treatment is with an antituberculous multidrug regimen (isoniazid, rifampin, pyrazinamide, ethambutol) and systemic steroids.

Lyme disease

Lyme disease results from tick-borne transmission of *Borrelia burgdorferi* and ophthalmic symptoms can vary and include unilateral or bilateral

anterior uveitis, intermediate uveitis, oculomotor palsies, and scleritis. Patients generally present in Stage 2 disease, and may have systemic symptoms of headaches, arthritis, meningitis, or peripheral neuropathies. Presenting ocular complaints can include blurred vision, photophobia, eye pain, or diplopia. Patients should be screened in high-prevalence areas of the Northeastern and Midwestern United States, in the habitat of the bacteria's vector, the *Ixodes* tick. Serologic testing is performed using screening ELISA followed by a confirmatory Western blot. Treatment for ocular involvement is equivalent to that for neurologic involvement in Lyme disease, most commonly with intravenous ceftriaxone. Topical steroids and mydriatics can be used as an adjunct to systemic treatment.

Rare diseases

Brucella is a rare cause of uveitis; this bacterium is harbored in the genitourinary tract of sheep and cows and transmitted via direct contact or airborne spread from contaminated animals, meat, or dairy products. *Brucella* produces a granulomatous uveitis and is treated with topical steroids and mydriatics. Traditional systemic therapy includes doxycycline with either rifampin or streptomycin.

Whipple's disease, primarily a disease of malabsorption of the gastrointestinal tract, is caused by *Tropheryma whipplei*. Patients generally present with a chronic nongranulomatous anterior uveitis but can also have vitritis and sheathing of the retinal vessels. Definitive diagnosis is made by jejunal biopsy. Treatment includes an initial course of either IV ceftriaxone or IV streptomycin with penicillin G followed by a prolonged course of trimethoprim–sulfamethoxazole for systemic disease; periocular or systemic steroids can often make the uveitis worse.

The majority of patients with ocular leprosy present with bilateral, chronic and relapsing iridocyclitis. Examination can reveal prominent corneal nerves with a "beaded" appearance. Iris "pearls," or aggregations of bacilli, are pathognomonic for the disease; these are white spots along the pupil margin that can coalesce and become pedunculated, falling into the anterior chamber and leaving an atrophic appearance to the iris. Involvement of the posterior segment is rare but there have been reports of white lesions in the peripheral fundus, also resembling "pearls." Treatment is for systemic disease, with dapsone and rifampin for paucibacillary disease and the addition of clofazimine for multibacillary disease.

Chikungunya is a viral disease spread by *Aedes* mosquitoes, initially discovered in Africa but with outbreaks in Asia and India. The disease is characterized by persistent fever, arthritis, and skin rash. The most common ocular manifestations are iridocyclitis and retinitis. Treatment is with systemic and topical anti-inflammatory medications.

Leptospirosis is transmitted via bacteria in the urine of infected animals; it is active as long as it is moist and so outbreaks commonly occur in tropical environments. Patients can present with a nongranulomatous hypopyon anterior uveitis or panuveitis with vitritis and retinal vasculitis. Leptospirosis is treated with systemic antibiotics, although evidence for their efficacy has not been conclusive. IV penicillin G is generally used in severe cases, although doxycycline and third-generation cephalosporins have also been tried.

Of note, toxoplasmosis is the most common infectious uveitis in the world and can present with anterior chamber inflammation, but findings are predominantly posterior uveitis and as such it is not discussed in detail in this chapter.

Human immunodeficiency virus

HIV can cause a nongranulomatous uveitis as part of seroconversion or in association with a high viral load. Patients with HIV anterior uveitis often have fine keratic precipitates and no retinal findings. The inflammation does not respond to topical steroids but does respond well to highly active antiretroviral therapy. The association between HIV and anterior uveitis is more frequently due to the increased susceptibility of HIV patients to infections such as syphilis or CMV.

SUMMARY

Anterior uveitis can be caused by a variety of infectious or inflammatory diseases. Diagnosis of a particular infection is made based on clinical history as well as ocular and systemic exam findings. All patients with anterior uveitis should also have a thorough examination of the posterior segment for signs of intermediate or posterior uveitis. Ocular inflammation after surgery or in the setting of disseminated infection should always raise the concern for infectious endophthalmitis, which must be treated emergently by an ophthalmologist. Emerging diagnostic techniques might

enable more rapid diagnosis of known infectious causes or the discovery of novel infectious etiologies of uveitis in the future.

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14. Retinitis

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CYTOMEGALOVIRUS RETINITIS

Cytomegalovirus (CMV) retinitis is the most common and clinically significant opportunistic ocular infection seen in immunocompromised patients, including those with acquired immunodeficiency syndrome (AIDS). With the extensive use of highly active antiretroviral therapy (HAART) in human immunodeficiency virus (HIV)-positive patients, there has been a marked decrease in the incidence of CMV retinitis in these patients (23 per 10 000 HIV/AIDS cases in the pre-HAART era to 8 per 10 000 HIV/AIDS cases in the post-HAART era).

The presentation of CMV retinitis may be unilateral or bilateral. The onset is insidious, and symptoms may include blurred vision, floaters, visual field defects, or other nonspecific visual complaints. Clinically, the various types of active chorioretinal lesions include (1) hemorrhagic pattern showing confluent area of full-thickness retinal necrosis with a yellow-white granular appearance and associated retinal hemorrhages; this has been referred to as a "pizza-pie" appearance (Figure 14.1); (2) "brush fire" pattern showing a rapidly spreading zone of retinal necrosis with yellow-white margin; and (3) a granular pattern showing areas of retinal atrophy amid white granular punctate lesions. In all of these clinical patterns vitreous inflammation is minimal or absent. Visual loss may be severe if the macula or optic nerve is involved. Without treatment, CMV retinitis will become bilateral in 80% of cases and eventually will result in blindness from retinal atrophy, retinal detachment, or optic nerve involvement.

In patients known to have HIV or to be immunosuppressed, the diagnosis of CMV retinitis is based on the clinical examination and confirmed by positive blood cultures for CMV. In individuals not known to be HIV positive, the diagnosis is suspected based on the clinical appearance, and prompt investigation of immune status is essential.

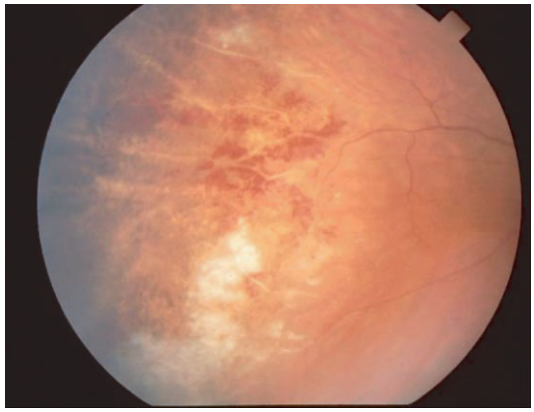

Figure 14.1 Photo of the peripheral fundus showing a yellow-white granular appearing area of retinal necrosis associated with retinal hemorrhages ("pizza-pie appearance"), representing an active chorioretinal lesion due to CMV retinitis.

In an effort to halt its progression and improve visual outcome, CMV retinitis requires treatment with one of five currently available virostatic agents: ganciclovir, valganciclovir, foscarnet, cidofovir, and fomivirsen (Table 14.1). The choice of the antiviral agent and its route of delivery should be based on the location and extent of the infection, potential side effects, and the effectiveness of prior treatments.

Ganciclovir, an inhibitor of CMV DNA polymerase, may be administered intravenously, orally, or intravitreally. Intravenous (IV) ganciclovir should be used as induction therapy for 14 to 21 days, followed by maintenance therapy by either an IV or oral route. Because ganciclovir is virostatic, maintenance therapy is required indefinitely. In patients with impaired renal function, the full dosage of ganciclovir cannot be tolerated and requires reduction. The most common side effect of ganciclovir is neutropenia, which arises in 20% to 40% of patients and is reversible on discontinuation of the drug. Ganciclovir and zidovudine may both result in granulocytopenia;

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Table 14.1 Therapy for retinitis

	Agent	Regimen	Side effects
CMV retinitis	Ganciclovir	Induction of 5 mg/kg IV q12h for 14 to 21 days, then 5 mg/kg/d IV 7 d/wk or 6 mg/kg 5 d/wk 1000 mg PO three times daily as maintenance therapy	Granulocytopenia Thrombocytopenia Anemia
	Valaganciclovir	Induction dose of 900 mg twice daily PO for 14 to 21 days and maintenance dose of 900 mg once daily PO	Granulocytopenia Anemia
	Foscarnet	Induction of 60 mg/kg IV q8h for 14 to 21 days, then 90 to 120 mg/kg/d IV	Nephrotoxicity Electrolyte imbalance Seizures/headache
	Cidofovir	Induction of 3 to 5 mg/kg IV once per week for 2 weeks, then 3 mg/kg IV every 2 weeks as maintenance	Nephrotoxicity Neutropenia Uveitis
	Fomivirsen	Induction of 330-μg intravitreal injection weekly for 2 weeks, then 330-μg intravitreal injection every 4 weeks as maintenance	Uveitis Rise of intraocular pressure Visual field disturbance Retinal pigment epitheliopathy Bull's eye maculopathy
Ocular toxoplasmosis	Pyrimethamine	75 mg PO, then 25 mg PO daily for 4 to 6 weeks	Anemia Thrombocytopenia Leukopenia
	Sulfadiazine	2 g PO, then 1 g PO four times daily for 4 to 6 weeks	Stevens–Johnson syndrome Hypersensitivity reaction Crystalluria
	Clindamycin	300 mg PO four times daily for 4 to 6 weeks	Diarrhea Pseudomembranous colitis
Acute retinal necrosis	Acyclovir	500 mg/m^2 IV q8h for 7 to 10 days, then 800 mg PO five times daily for 6 to 12 weeks	Localized phlebitis Elevated serum creatinine
Progressive outer retinal necrosis	Ganciclovir	Combination of intravenous and intravitreal in combination with intravenous and intravitreal foscarnet. No established dosing regimen	Granulocytopenia Thrombocytopenia Anemia
	Foscarnet	Combination of intravenous and intravitreal in combination with intravenous and intravitreal ganciclovir. No established dosing regimen	Nephrotoxicity Electrolyte imbalance Seizures/headache

Abbreviations: CMV = cytomegalovirus; IV = intravenously; PO = orally.

the concomitant use of these two agents may result in pronounced bone marrow suppression.

The use of a sustained-release ganciclovir implant placed directly into the vitreous cavity of the eye protects against reactivation of CMV retinitis for up to 7 months. The intravitreal implant reduces intraocular recurrence of CMV retinitis and systemic side effects of ganciclovir, but it is not protective against involvement of the fellow eye or systemic CMV infection. Adverse effects associated with the ganciclovir implant include decreased vision in the postoperative period and an increased risk of retinal detachment.

Valganciclovir is a prodrug of ganciclovir and has good penetration into the vitreous cavity after oral administration. A positive response equivalent to ganciclovir given intravenously has been demonstrated with the use of oral induction therapy with valganciclovir. The adverse effects of the two drugs are similar.

Foscarnet, an inhibitor of DNA polymerase and reverse transcriptase, is administered intravenously for 14 to 21 days as induction therapy,

followed by maintenance therapy indefinitely. The most common side effect of foscarnet is nephrotoxicity, which occurs in 25% of patients and is reversible with early cessation of the drug. Because foscarnet undergoes renal elimination and is nephrotoxic, careful monitoring of renal function is necessary. However, it is effective in the treatment of ganciclovir-resistant retinitis.

Cidofovir acts by inhibiting CMV DNA polymerase. It does not require virus-dependent phosphorylation for activation. The advantage of cidofovir over ganciclovir and foscarnet is that it requires less frequent IV administration: once weekly as induction for 2 weeks and once every 2 weeks for maintenance therapy thereafter. Nephrotoxicity is the most common dose-limiting side effect, which may be reduced with the concurrent administration of oral probenecid and IV hydration.

Fomivirsen, the newest agent available for the treatment of CMV retinitis, acts by interfering with CMV mRNA encoding. The mode of administration is intravitreal injection, and it is being used for CMV retinitis that is resistant to other antiviral agents. The various ocular toxic effects include uveitis, retinal pigment epitheliopathy, and bull's eye maculopathy.

The initial response to any antiviral therapies usually occurs 1 to 2 weeks after the initiation of the induction regimen and is evidenced by termination of the extension of the retinal lesions and gradual atrophy of the involved retina. Ophthalmologists should examine patients' fundi every 2 to 3 weeks to monitor the effectiveness of the antiviral therapy. Recurrence of CMV retinitis occurs in 30% to 50% of patients receiving maintenance doses of systemic antiviral therapy. The treatment of recurring CMV retinitis is reinduction for 2 weeks followed by indefinite maintenance therapy. In the era of HAART therapy, HIV-positive patients with CMV retinitis having a sustained CD4+ T-cell count greater than 100 cells/mm^3 for 3 to 6 months can terminate maintenance therapy. However, maintenance therapy needs to be restarted if the immune status is compromised (CD4+ T-cell count 50–100 cells/mm^3). Furthermore, these patients should undergo ophthalmic screening at 3- to 6-month intervals, depending on the immune status.

The various surgical treatments that have been used in the management of CMV retinitis include laser photocoagulation and vitrectomy. Prophylactic laser photocoagulation surrounding areas of retinal necrosis has been shown to reduce the rate of retinal detachments. When retinal detachments develop, the standard approach for repair is vitrectomy surgery with silicone oil instillation.

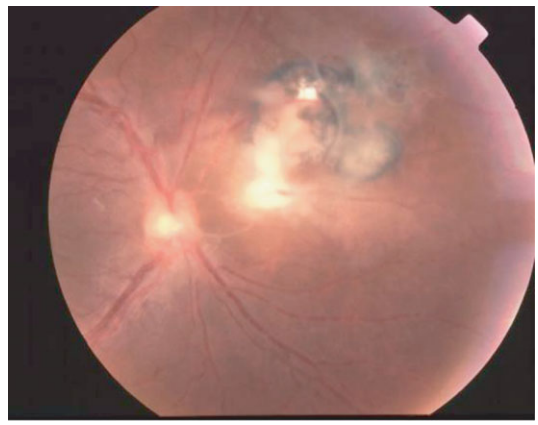

Figure 14.2 Fundus photo of the posterior pole showing an excavated atrophic chorioretinal scar and overlying epiretinal membrane in the macula consistent with resolved focal necrotizing chorioretinitis secondary to toxoplasmosis.

OCULAR TOXOPLASMOSIS

Ocular toxoplasmosis, which accounts for 30% to 50% of all cases of posterior uveitis, is caused by the obligate intracellular parasite *Toxoplasma gondii*. Infection may be congenital through transplacental transmission or acquired through contact with cat excreta or by ingestion of oocysts from undercooked meat. Most cases of ocular toxoplasmosis occur as a result of reactivation of congenital ocular lesions.

Symptoms of active infection include blurred vision and vitreous floaters. Most commonly, ocular toxoplasmosis presents as a white-yellow area of focal necrotizing retinitis adjacent to an old atrophic chorioretinal scar (Figure 14.2). Vitreous inflammation typically is present over the area of active retinitis, and granulomatous iridocyclitis or optic nerve swelling may be present. The various complications associated with larger lesions include rhegmatogenous or exudative retinal detachment, macular edema, retinal vessel occlusions, subretinal neovascularization, and epiretinal membranes.

Not all active retinal lesions require treatment when present in immunocompetent individuals. Small peripheral lesions, which often are self-limited and not visually threatening, can be observed. Without treatment, active lesions generally heal in 2 to 4 months. Medical therapy is

indicated when the toxoplasma lesions involve or threaten the macula or optic nerve or when visually disabling vitreous inflammation is present.

The goal of treatment for ocular toxoplasmosis is to halt the infectious process and reduce scarring of the retina and vitreous. Traditional therapy consists of the concurrent use of two folate antagonists: sulfadiazine and pyrimethamine. Sulfadiazine is administered as a loading dose of 2 g orally, followed by 1 g four times daily for 4 to 6 weeks. Pyrimethamine is given as a loading dose of 75 mg followed by 25 mg orally per day for a similar duration. Pyrimethamine requires weekly complete blood counts and may be administered with leucovorin calcium, 5 mg orally twice weekly, to reduce the incidence of bone marrow suppression. Clindamycin, 300 mg orally four times daily for 4 to 6 weeks, has been suggested in combination with sulfadiazine and pyrimethamine for severe ocular toxoplasmosis infections. Systemic corticosteroids should be administered when inflammation from the active toxoplasmosis lesions threaten the macula or optic nerve and when severe vitreous inflammation is present. Corticosteroids should never be used in the treatment of ocular toxoplasmosis without the concurrent use of antibiotic agents. Prednisone at a dosage of 60 to 80 mg/day is administered during the first week of treatment and rapidly tapered based on clinical response and patient tolerance.

The various regimens widely used for treatment of toxoplasmosis are as follows: (1) triple therapy consisting of pyrimethamine, sulfadiazine, and prednisone and (2) quadruple therapy consisting of pyrimethamine, sulfadiazine, clindamycin, and prednisone. A maintenance therapy with pyrimethamine–sulfadiazine is useful in severely immunocompromised patients.

ACUTE RETINAL NECROSIS SYNDROME

Acute retinal necrosis (ARN) is a necrotizing retinitis associated with infection by the varicella-zoster virus (VZV) or, less commonly, the herpes simplex virus (HSV) types 1 and 2. Although initially described only in immunocompetent patients, recent cases have been reported in immunosuppressed individuals, including those with AIDS.

Clinically, ARN presents as patchy or confluent areas of white retinal necrosis in the far periphery (Figure 14.3), which may spread to the posterior pole rapidly within days. The onset of

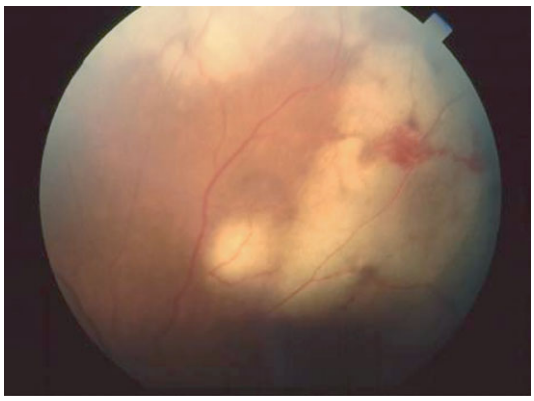

Figure 14.3 Photo of the peripheral fundus showing confluent white areas of retinal necrosis with occlusive retinal vasculitis and retinal hemorrhages, suggestive of acute retinal necrosis.

ARN typically is unilateral, although bilateral involvement may occur in up to 30% of patients within several weeks of onset. In addition, moderate to severe vitritis and occlusive retinal vasculitis (arteritis and phlebitis) are seen. Anterior uveitis, ischemic vasculopathy involving the optic nerve, and macular edema may be associated findings. The active phase of inflammation generally lasts several weeks and is followed by a convalescent phase. As many as 52% of patients with ARN may develop retinal breaks and subsequent rhegmatogenous retinal detachments. Retinal detachments may occur from 9 days to 5 months after the onset of retinitis.

The current standard of care for ARN includes IV acyclovir (1500 mg/m^2) administered in three divided doses daily for 7 to 10 days followed by oral acyclovir 800 mg five times daily for 4 to 6 weeks. The antiviral therapy is useful to suppress unilateral disease and reduce the risk of involvement of the fellow eye. The oral prodrugs valacyclovir and famciclovir, which have higher bioavailability than oral acyclovir, may also be considered. Systemic and periocular corticosteroids may be administered to reduce the tissue damage caused by the necrotizing intraocular inflammation but must be concomitant with antiviral therapy. A thorough search for retinal breaks is essential in the first 6 months, and prophylactic laser barrier photocoagulation should be performed within 3 weeks of onset of symptoms or at the earliest time possible. The barrier laser treatment consists of the application of confluent rows of argon laser burns posterior to the area of retinal necrosis and around retinal breaks.

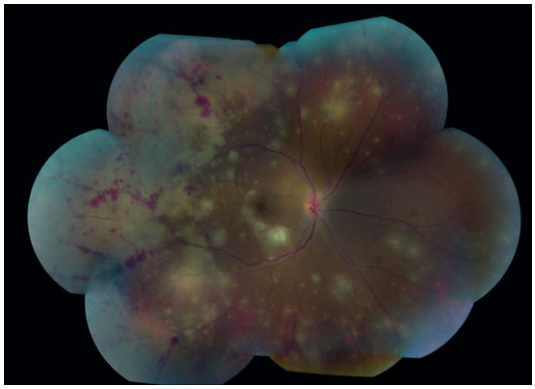

Figure 14.4 Fundus photo of the posterior pole showing white and confluent areas of retinal necrosis and hemorrhage in an AIDS patient, suggestive of progressive outer retinal necrosis. (Photo courtesy of James Eadie, MD at the University of Wisconsin and Lisa Faia, MD at Associated Retinal Consultants in Royal Oak, MI.)

PROGRESSIVE OUTER RETINAL NECROSIS SYNDROME

Progressive outer retinal necrosis (PORN) is a necrotizing retinitis associated with infection by VZV. Although seen almost exclusively in AIDS patients, this condition has been described in patients with other mechanisms of immunosuppression (chemotherapy) as well.

PORN is characterized by patchy or confluent deep outer retinal lesions involving the peripheral retina with or without macular involvement (Figure 14.4). The inner retina and the retinal vasculature are spared in the early stages of the disease. The condition often starts in one eye and the other eye becomes involved in weeks to months. The condition progresses rapidly with two-thirds of patients having no light perception (NLP) after 4 weeks. Loss of vision occurs secondary to retinal necrosis and retinal detachment. In contrast to ARN vascular inflammation is absent and there is minimal to no vitreous inflammation.

Recent studies have demonstrated that combination of IV and intravitreal antiviral therapy may achieve a better final vision than the traditional treatment with IV acyclovir only. The suggested combination includes a regimen of intravitreal ganciclovir and foscarnet plus IV foscarnet and IV ganciclovir or oral valganciclovir. Prophylactic laser demarcation may be beneficial in preventing retinal detachment.

ACKNOWLEDGMENT

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15. Endophthalmitis

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INTRODUCTION

Endophthalmitis is a vision-threatening inflammation of the inner eye fluids and tissues. Infectious endophthalmitis results from either exogenous or endogenous entry of microbes into the eye. In reported clinical series, exogenous endophthalmitis is much more common than endogenous (or metastatic) endophthalmitis. By far, the most common cause of exogenous infection is intraocular procedures. Until recently, cataract surgery was the most frequently performed type of intraocular procedure, accounting for the greatest number of exogenous endophthalmitis cases. Intravitreal injection has now surpassed cataract surgery as the most frequently performed intraocular procedure and consequently is a significant contributor to the total number of exogenous endophthalmitis cases reported. Exogenous endophthalmitis can also occur after other types of intraocular surgery, including secondary lens implantation, glaucoma filtering surgery, vitrectomy surgery, and corneal transplantation. Organisms may also enter the eye during penetrating trauma, intraocular injection of medication, and contiguous spread into the eye from an infected corneal ulcer. Gram-positive bacteria are the most common cause of exogenous endophthalmitis.

INCIDENCE

Postoperative endophthalmitis cases from the University of Miami (Bascom Palmer Eye Institute) over an 8-year period (2002 to 2009) demonstrated the incidence of nosocomial endophthalmitis after cataract surgery to be 0.025%. Endophthalmitis occurs after open-globe injuries in 3% to 30% of patients depending on the nature of the injury. The rate of development of *Candida* endogenous endophthalmitis in patients with documented candidemia has been reported to range from 2.8% to 45%.

CLINICAL FEATURES

Most cases of acute-onset endophthalmitis post-cataract surgery present within 2 weeks of intraocular surgery (Figure 15.1). Symptoms may start as early as 12 hours after the surgery. The classic symptoms include marked visual loss and ocular pain in 75% of cases. The loss of vision is typically profound and vision is reduced out of proportion to the usual postoperative course. The presenting signs often include lid edema, conjunctival injection and swelling, conjunctival discharge, corneal edema, anterior chamber inflammation, fibrin formation, and vitreous inflammatory response. In most cases, a layer of inflammatory cells (hypopyon) can be visualized in the inferior portion of the anterior chamber (Figure 15.2). Redness and purulent discharge from the conjunctiva and lid margins are also commonly seen. A severe intraocular inflammatory response will often obscure a view of the posterior pole and may cause loss of the red reflex. In these cases echographic exam of the eye may be useful in ruling out posterior segment complications, such as retinal detachment and retained lens fragments.

In the Endophthalmitis Vitrectomy Study (EVS), the coagulase-negative staphylococci were the most commonly cultured organisms (68%) among patients with confirmed growth. Other gram-positive organisms were cultured in 22% of patients and included *Streptococcus* and *Staphylococcus aureus*. Gram-negative organisms were isolated in 6% of the cases in the EVS and more than one species was confirmed in 4% of the cases. Fortunately, the coagulase-negative staphylococci are one of the least virulent causes of acute-onset postoperative endophthalmitis. *S. aureus*, *Streptococcus* species, and the gram-negative organisms usually produce a more rapidly progressive and fulminant inflammation often leading to severe visual loss.

Another subgroup of post-cataract surgery endophthalmitis is the delayed-onset category

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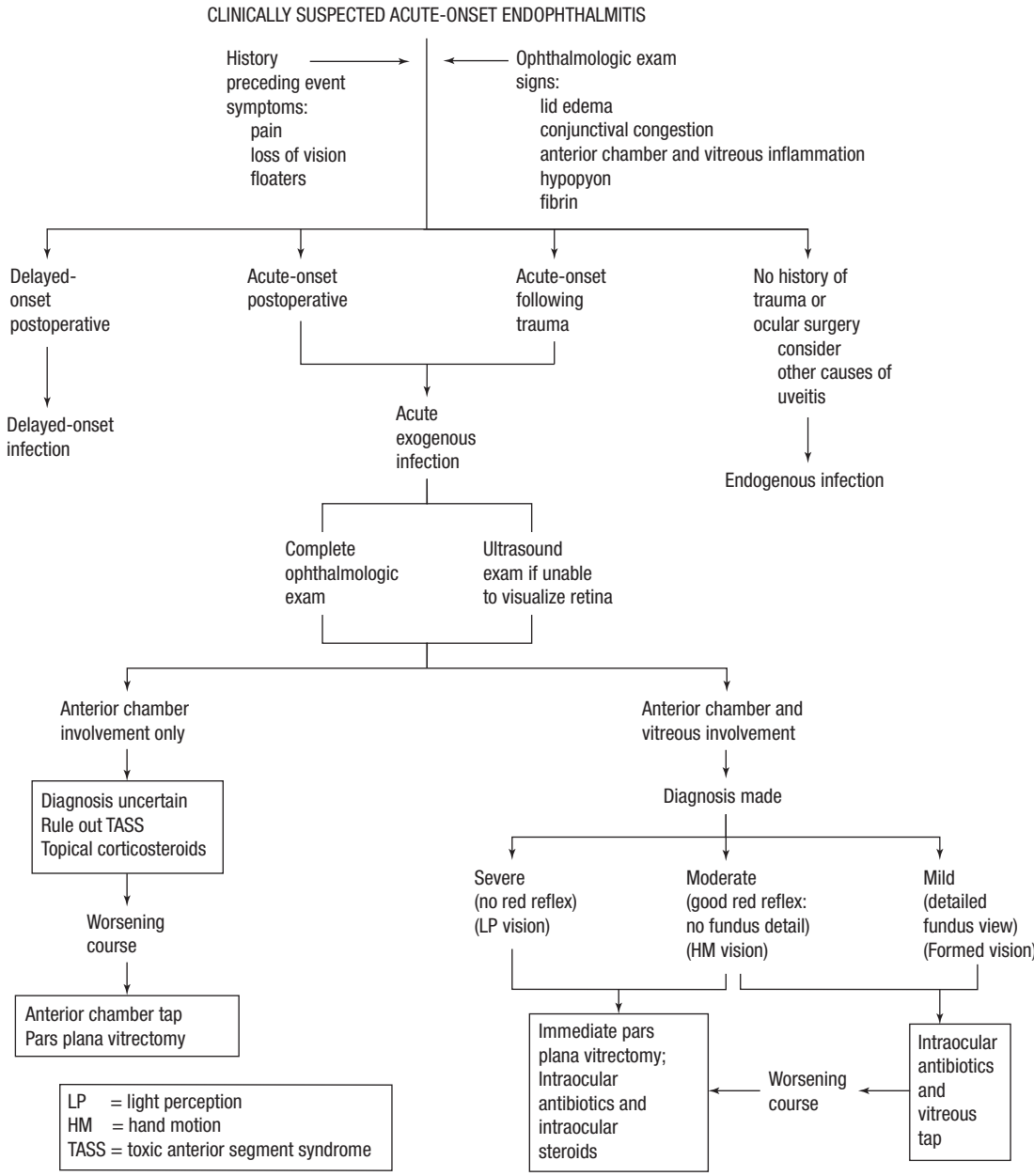

Figure 15.1 Algorithm for management of acute-onset endophthalmitis.

(Figure 15.3). These patients present 6 weeks or more after cataract surgery with a slowly progressive, often milder, inflammatory response. The inflammation can be isolated to the anterior segment or involve both the anterior segment and vitreous. The intraocular inflammation may respond initially to topical steroid therapy but usually recurs as the topical steroids are tapered. A common cause of delayed-onset postoperative endophthalmitis is *Propionibacterium acnes*. This is a ubiquitous, gram-positive, non-spore-forming pleomorphic bacillus. Clinical features of intraocular infections caused by this organism include granulomatous inflammation with large keratitic precipitates (clumps of inflammatory cells) on the corneal endothelium. A characteristic diagnostic feature is the presence of white intracapsular plaque, which has been shown to be composed

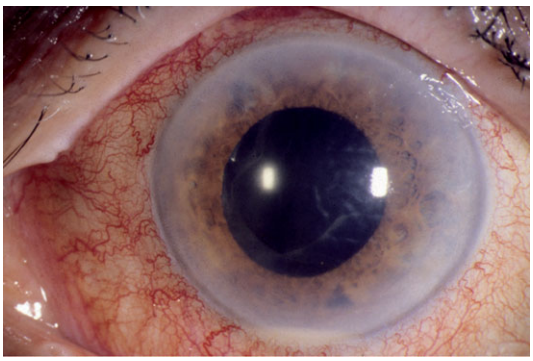

Figure 15.2 Hypopyon (layering of white blood cells in the anterior chamber) in an eye with acute-onset post-cataract surgery endophthalmitis.

of organisms mixed with residual lens cortex (Figure 15.4). Because *P. acnes* is a slow-growing anaerobic organism, it is important for the microbiology laboratory to be instructed to keep these anaerobic cultures for at least 2 weeks. Other organisms responsible for delayed-onset postoperative endophthalmitis include *Candida*, *Staphylococcus epidermidis*, and *Corynebacterium* species.

Delayed-onset endophthalmitis associated with conjunctival filtering blebs may present months or even years after glaucoma filtering surgery. The organisms enter the eye directly through the thin wall of the conjunctival bleb, which may develop purulent material initially

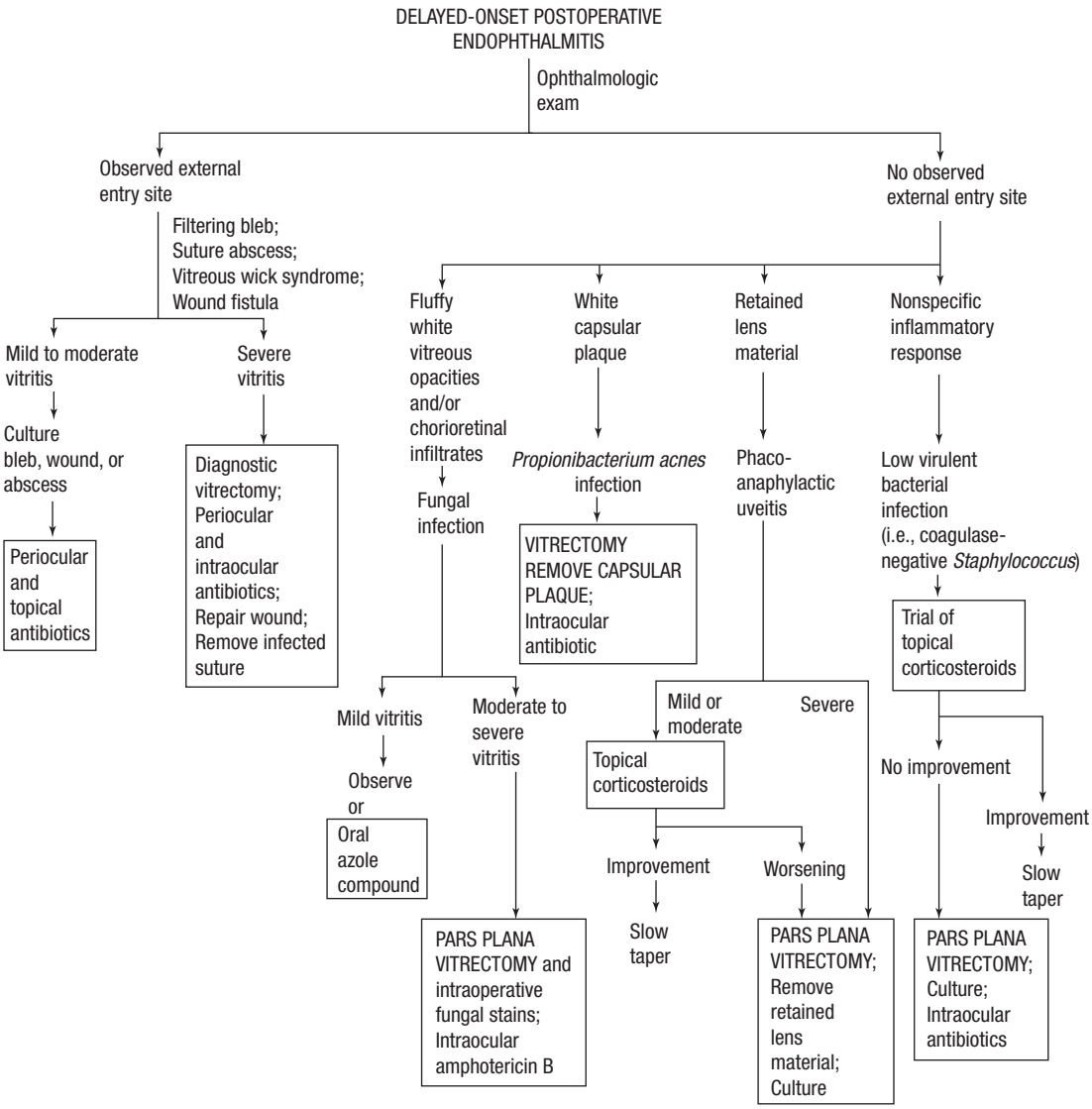

Figure 15.3 Algorithm for management of delayed-onset endophthalmitis.

Figure 15.4 White capsular plaque in a patient with *Propionibacterium acnes* endophthalmitis.

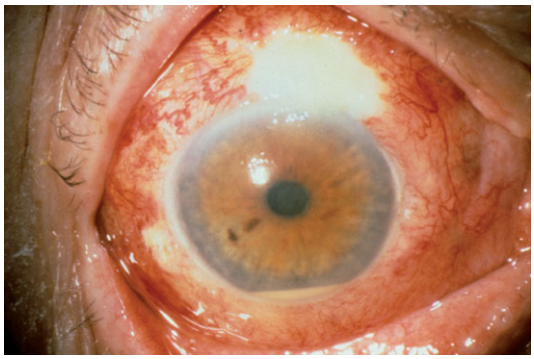

Figure 15.5 Purulent material in a filtering bleb in an eye with endophthalmitis 6 months following glaucoma filtering surgery.

(Figure 15.5). The presenting symptoms and signs are similar to acute-onset postoperative endophthalmitis. Streptococcal species are the most common organisms isolated. *Haemophilus influenzae* is also a common cause of this category of endophthalmitis. Because these organisms are more virulent than those causing acute-onset postoperative endophthalmitis, the visual outcomes are generally worse. Optic nerve damage from the pre-existing glaucoma may also be a factor in poor visual outcomes. Less than half of the eyes achieve 20/400 or better vision. The treatment is similar to that for acute-onset postoperative endophthalmitis.

Endophthalmitis after open-globe trauma should be suspected whenever a greater than expected inflammatory response is observed. Because the organisms (e.g., *Bacillus* species and *Streptococcus* species) causing open globe-related endophthalmitis are, in general, more virulent than organisms causing postoperative endophthalmitis, the final visual outcome is often poor. The associated trauma to the eye and the

Table 15.1 Exogenous endophthalmitis categories

Acute-onset postoperative
Delayed-onset postoperative
Conjunctival filtering bleb associated
Open globe-associated
Associated with microbial keratitis
Associated with intravitreal injections

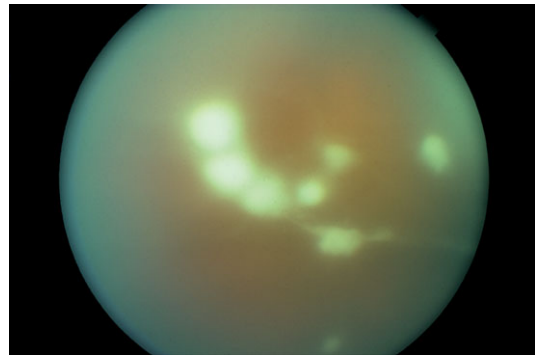

Figure 15.6 White inflammatory vitreous opacities in a "string of pearls" configuration in a patient with endogenous *Candida* endophthalmitis.

frequent delay in diagnosis also contribute to a poor visual prognosis. A high index of suspicion and early diagnosis are important, because even traumatized eyes infected with virulent organisms can sometimes be salvaged when treatment is promptly initiated. Prophylactic antibiotic treatment from high-risk injuries (rural setting, injuries involving vegetable matter or soil, contaminated eating utensils, retained foreign bodies) should be administered. The management of open globe-related endophthalmitis is similar to other endophthalmitis categories and often includes vitrectomy and intravitreal, subconjunctival, and topical antibiotics and steroids.

Endogenous endophthalmitis results from hematogenous spread of organisms to the eye (Table 15.1). Fungi are a more common cause than bacteria and *Candida albicans* is the most common fungus isolated. The classic ocular finding is white vitreous opacities attached to each other by inflammatory vitreous bands in a configuration termed "string of pearls" (Figure 15.6). The second most frequently encountered fungus is *Aspergillus* species. *Streptococcus* species, *S. aureus*, and *Bacillus* species are the most common cause of endogenous bacterial endophthalmitis. These patients are frequently debilitated or

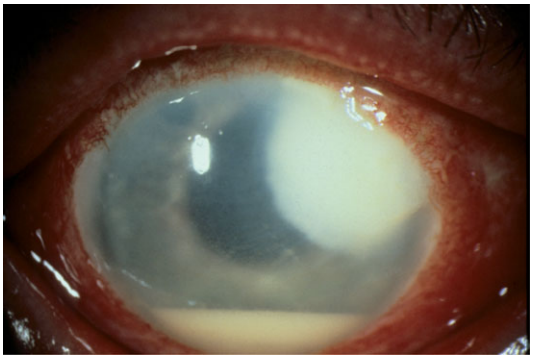

Figure 15.7 Infectious corneal ulcer associated with endophthalmitis.

immunocompromised with indwelling catheters, although endogenous endophthalmitis can occur in drug abusers and rarely in otherwise healthy patients after dental procedures or childbirth. The infection may be caused by a transient bacteremia or fungemia in which case blood cultures may be negative. Sepsis with deep organ involvement may also be present. When the source of infection is not apparent, a systemic workup is indicated.

Endophthalmitis can occur from direct spread of organisms into the eye from an infected corneal ulcer (Figure 15.7). Factors predisposing to the development of endophthalmitis associated with microbial keratitis include corticosteroid use, systemic immune dysfunction, as well as local ocular factors such as prolonged wear of contact lenses or contaminated lens solutions. Visual outcomes are poor due to the unusual and virulent nature of the infecting organisms.

Endophthalmitis may also occur following intravitreal injection of medications. The greater utilization of this route of therapy to treat various retinal diseases has increased the prevalence of this subgroup of endophthalmitis. Despite the growing number of intravitreal injections administered, endophthalmitis remains an uncommon complication. It has been reported after intravitreal injection of most medications, including vascular endothelial growth factor (VEGF) inhibitors and triamcinolone acetonide (IVTA). The incidence of endophthalmitis resulting from intravitreal injections ranges from 0.02% to 0.1% of injections. Since many patients receive multiple injections to treat a chronic retinal disease an individual patient's risk approaches 1%. The clinical findings in intravitreal injection-related endophthalmitis may be similar to other forms of infectious endophthalmitis and include iritis, vitritis, hypopyon, pain, red eye, and decreased vision. The median time to presentation is earlier in post-intravitreal injection cases (3 days) compared with postoperative cases in which it is approximately 11 days. This may in part be related to the preponderance of more virulent organisms (streptococcal species) in the post-injection cases compared with postoperative cases. Hypopyon occurs less frequently in post-intravitreal injection cases (20%) compared with postoperative cases (64%). A sterile inflammatory uveitis may also occur after intravitreal drug injections and must be distinguished from true infection. The noninfectious cases usually present earlier following the injection (median 1.5 days) and the external inflammatory signs such as redness and purulent discharge are usually less apparent. In addition, pain is much less common in noninfectious cases. Characteristics that may increase the risk of infection include immunosuppression, decreased ocular barrier function (presence of filtering bleb), contamination during compounding the drug, and poor sterile techniques.

DIAGNOSIS

Two important factors in the diagnosis of endophthalmitis include the clinical recognition and microbiologic confirmation. Endophthalmitis should be suspected in any eye that has a marked inflammatory response out of proportion to that usually seen in the typical clinical course. Because of the potential for significant visual loss, diagnostic tests are usually performed concurrently with treatment.

The clinical diagnosis is confirmed by obtaining aqueous fluid and vitreous specimens. Although vitreous specimens are more likely to yield a positive culture than simultaneously acquired aqueous specimens, both are important because either one can be positive without the other. Aqueous cultures are obtained by needle aspiration. Vitreous cultures can be obtained using needle aspiration or using an automated vitrectomy instrument, which simultaneously cuts and aspirates the vitreous. Vitreous obtained by needle aspiration can be directly inoculated onto appropriate culture media including chocolate agar, 5% blood sheep agar, thioglycollate broth, or Sabouraud agar. A specimen obtained during vitrectomy can be concentrated by filtration though a 0.45-μm filter, and is then placed on culture media. An alternative method for processing the vitrectomy specimen involves inoculating approximately 10 mL of the diluted

vitrectomy specimen into standard blood culture bottles. The culture technique has been shown to yield a similar rate of culture positivity when compared with the traditional membrane filter technique. Gram stains are usually performed on aqueous and vitreous samples. In suspected fungal cases, cultures should be held at least 2 weeks and additional information may be obtained using the Giemsa, Gomori's methenamine silver, and periodic acid–Schiff stains.

TREATMENT

Endophthalmitis can lead to rapid intraocular tissue destruction and irreparable damage. The mainstay of treatment for bacterial endophthalmitis is intraocular antibiotic therapy. The unique properties of the eye, including the fact that it is an enclosed cavity, as well as the presence of a blood–ocular barrier, make intraocular injection of antibiotic an ideal way of achieving rapid and high antibiotic concentrations within the eye (Table 15.2).

Systemic antibiotics have traditionally been used to supplement intravitreal antibiotic injections in the management of endophthalmitis. The EVS randomized patients received ceftazidime and amikacin versus no systemic antibiotic therapy, but all patients received intravitreal antibiotics. The results of that study demonstrated there was no beneficial effect on final visual outcome or media clarity when these systemic antibiotics were used.

Table 15.2 Treatment for acute-onset presumed bacterial postoperative endophthalmitis

Route	Drug	Dose
Intravitreal	1. Vancomycin	1.0 mg/0.1 mL
	2. Ceftazidime	2.25 mg/0.1 mL
	or amikacin	0.4 mg/0.1 mL
	3. Dexamethasone	0.4 mg/0.1 mL
Subconjunctival (optional)	1. Vancomycin	25 mg/0.5 mL
	2. Ceftazidime	100 mg/0.5 mL
	3. Dexamethasone	10 to 24 mg/1.0 mL
Topical (optional)	1. Vancomycin	50 mg/mL
	2. Ceftazidime	100 mg/mL
	3. Steroids and cycloplegics	
Systemic (optional)	1. Vancomycin	1.0 g IV q12h
	2. Ceftazidime	1.0 g IV q12h
	(or fourth-generation fluoroquinolone for appropriate organism)	

In addition to intravitreal antibiotics as the recommended treatment for suspected endophthalmitis, intravitreal dexamethasone (0.4 mg/0.1 mL) may also be used. Although both animal studies and small retrospective clinical trials have shown improved endophthalmitis treatment results when intravitreal steroids were combined with intravitreal antibiotic injection, definitive proof of the value of intravitreal steroids is not available. The EVS protocol did not utilize intravitreal steroids, but EVS patients were placed on oral prednisone (60 mg daily) for 5 to 10 days. In addition to intravitreal dexamethasone, we also consider a 10 to 24 mg subconjunctival injection of dexamethasone at the time of initial treatment.

Vitrectomy surgery (Figures 15.1, 15.3, and 15.8) has traditionally been recommended for more severe cases of endophthalmitis (e.g., initial visual acuity of light perception only and rapid onset within 2 days of surgery, more severe intraocular inflammation). Theoretical advantages of vitrectomy include the rapid removal of infecting organisms, intraocular toxins, removal of vitreous opacities and membranes that may lead to traction retinal detachment, and more rapid clearing of the vitreous cavity. Vitrectomy also allows for collection of a greater volume of material for culture and the potential for enhanced distribution of intravitreal antibiotics.

The management of endogenous fungal endophthalmitis depends on the specific fungus isolated and the severity of infection (Figure 15.8). When a diagnosis of endogenous fungal endophthalmitis is suspected, a workup to look for other organ involvement is recommended. This should usually be done in conjunction with an internist or infectious disease subspecialist. The use and type of systemic antifungal therapy depends on the presence or absence of systemic fungal infection. When the infection is limited to the choroid and retina, systemic therapy alone may be adequate. Fluconazole or voriconazole may be used instead of amphotericin B as the systemic drug of choice for treating *Candida* endophthalmitis not associated with significant systemic involvement. Both fluconazole and voriconazole are systemically less toxic than amphotericin B and have better intraocular penetration. When moderate to severe vitreous involvement is present, a pars plana vitrectomy and intravitreal injection of amphotericin B (5–10 μg) or voriconazole (100 μg) is usually recommended. Eyes with minimal vitreous involvement may be treated with an intravitreal antifungal agent without vitrectomy.

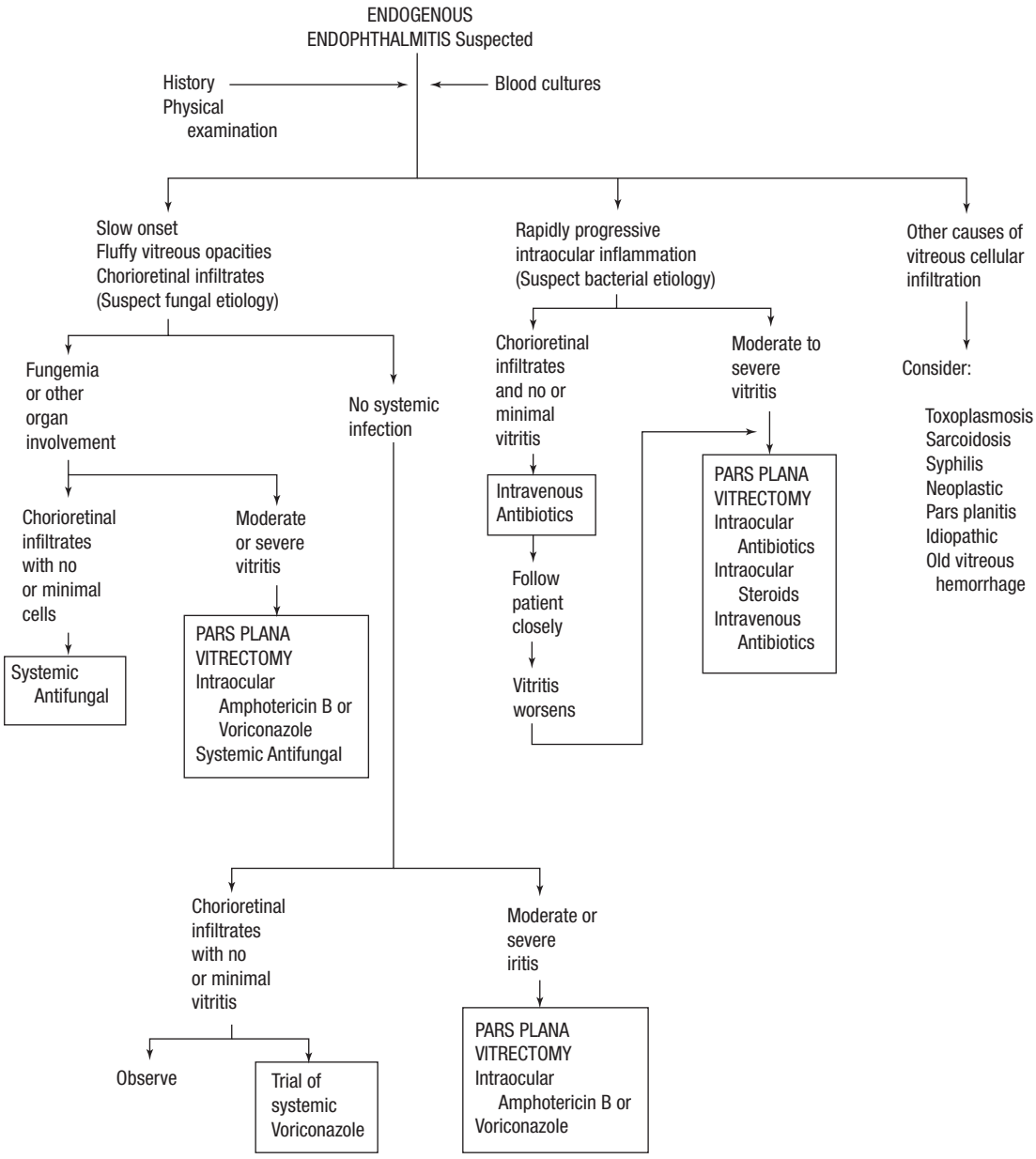

Figure 15.8 Algorithm for management of endogenous endophthalmitis.

Endogenous *Aspergillus* endophthalmitis more often occurs in immunocompromised patients, patients with *Aspergillus* endocarditis or pulmonary disease, or patients with a history of intravenous drug abuse. This organism has a propensity to involve the macular area, resulting in macular abscess and a layering of white blood cells under the retina or internal limiting membrane (Figure 15.9). A combination of local ocular therapy and systemic antifungal therapy (amphotericin B or voriconazole) is often recommended for treatment of this virulent organism.

PREVENTION

Because the ocular surface and adnexa are the primary sources of bacteria in exogenous endophthalmitis cases, the rate of postoperative

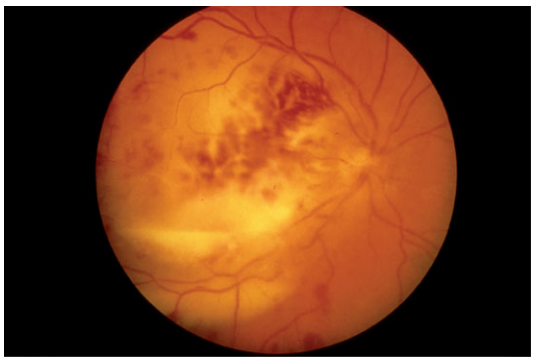

Figure 15.9 Macular abscess with a pseudohypopyon caused by endogenous *Aspergillus* infection.

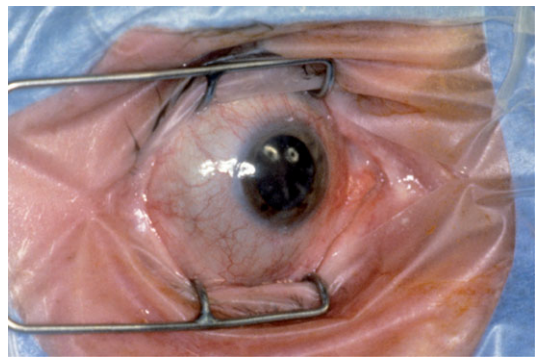

Figure 15.10 Eye undergoing surgery, demonstrating plastic drape covering eyelid margin.

endophthalmitis could theoretically be reduced by minimizing the ocular surface flora. The administration of topical 5% povidone-iodine solution to the conjunctival surface significantly reduces the conjunctival bacterial colony count. Reduction of conjunctival organisms may also be enhanced with the addition of 3 days of topically applied, broad-spectrum antibiotics. Additional preventive measures include covering the eyelashes completely with a sterile plastic drape (Figure 15.10), meticulous surgical technique, including careful wound closure, and aseptic technique. Minimizing excessive pooling of fluid around the wound may also be helpful.

The role of prophylactic antibiotics added to the irrigating solution during the surgery is controversial. A multicentered European study demonstrated a significant reduction in the risk of developing endophthalmitis after cataract surgery when intracameral cefuroxime was administered at the time of surgery. In the EVS, 10 enrolled patients with endophthalmitis had a history of receiving intraocular antibiotics in the irrigating fluid during the cataract surgery. In addition, the potential for intraocular toxicity and development of resistant organisms limit the potential value of this method of prophylaxis. Postoperative topical antibiotics are commonly used, but again are unproven in reducing the incidence of postoperative endophthalmitis.

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16. Periocular infections

Marlene L. Durand

Periocular infections are infections of the soft tissues surrounding the globe of the eye. These include infections of the eyelids, lacrimal system, and orbit.

EYELID INFECTIONS

Each eyelid contains a fibrous tarsal plate that gives structure to the lid. Within each tarsal plate are 20 to 25 vertical meibomian glands that secrete sebum at the lid margins. Glands of Zeis, smaller sebaceous glands adjacent to the lid-margin hair follicles, also secrete sebum. Sebum prevents ocular surface drying by slowing the rate of tear film evaporation.

Hordeolum

An internal hordeolum is an acute infection of a meibomian gland and presents as a tender, swollen nodule within the lid, pointing either to the skin or conjunctival surface. An external hordeolum (stye) is an acute infection of a gland of Zeis and points to the lid margin. Both are usually caused by *Staphylococcus aureus* and respond to frequent warm compresses and topical bacitracin or erythromycin ointment.

Chalazion

A chalazion is a nontender nodule within the lid that points to the conjunctival surface and is due to a sterile granulomatous reaction to inspissated sebum within a meibomian gland. Most chalazia resolve spontaneously within 1 month, but intralesional triamcinolone or incision and curettage may be used if conservative measures fail. Recurrences are common in patients with chronic blepharitis. Persistent or recurrent chalazia should be biopsied to exclude squamous cell carcinoma.

Marginal blepharitis

Marginal blepharitis is a diffuse inflammation of the lid margins and is usually due to hypersecretion of meibomian glands, although superinfection with *S. aureus* may play a role. Recurrent blepharitis is often associated with seborrheic dermatitis or rosacea. It may be treated with gentle lid scrubs and topical bacitracin; oral tetracycline may be helpful if there is associated rosacea. Unusual causes of blepharitis have included *Pseudomonas*, *Capnocytophaga*, herpes simplex virus, crab lice, and *Demodex* mites. *Demodex* infestations, characterized by cylindrical dandruff around the lashes, cause chronic blepharitis and may be treated by lid scrubs with tea tree oil.

INFECTIONS OF THE LACRIMAL SYSTEM

Tears are mainly produced by the lacrimal gland, which is located beneath the upper outer rim of the orbit. Tears flow medially across the eye, collect via the puncta, canaliculi, lacrimal sac, and lacrimal duct and drain into the nose beneath the inferior nasal turbinate.

Dacryocystitis, or infection of the lacrimal sac, is the most common infection of the lacrimal system and results from obstruction of the lacrimal duct. Patients often give a history of chronic unilateral tearing (epiphora). Acute dacryocystitis presents as a painful, red swelling near the nasal corner of the eye (Figure 16.1). The most common bacteria involved are *S. aureus* and streptococci, although gram-negatives such as *Escherichia coli* may be present in up to 25% of cases. Treatment requires systemic antibiotics and often incision and drainage of the lacrimal sac abscess. A dacryocystorhinostomy is often performed to treat the underlying chronic duct obstruction once the acute infection has subsided.

Dacryoadenitis, or infection of the lacrimal gland, is uncommon. Patients present with swelling in the lateral portion of the upper lid. Acute

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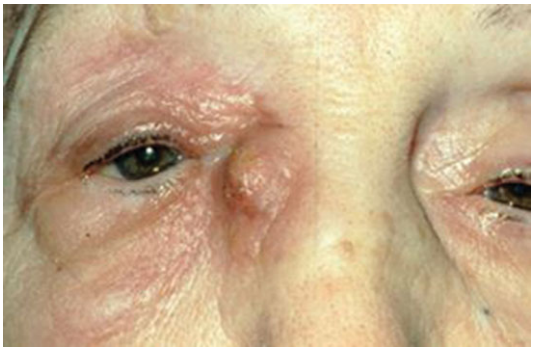

Figure 16.1. Acute dacryocystitis. Note swelling below the nasal corner of the right eye.

infection is most often due to *S. aureus* or streptococci, but Epstein–Barr virus may cause acute dacryoadenitis in mononucleosis. Chronic dacryoadenitis is usually seen as part of Sjogren's syndrome, sarcoidosis, or other inflammatory conditions, although *Mycobacterium tuberculosis* may rarely cause chronic dacryoadenitis. Tumors cause 25% of cases of chronic lacrimal gland enlargement.

Canaliculitis is usually a chronic infection of the canaliculi due to *Actinomyces israelii*, which forms concretions ("sulfur granules"). Staphylococci and streptococci are other etiologies. Treatment is usually office curettage of the concretions, and/or topical antibiotic eyedrops. See also Chapter 9, Infection of the salivary and lacrimal glands.

PERIORBITAL INFECTIONS

The term *periorbital cellulitis* is commonly used but is imprecise, as it does not distinguish between preseptal cellulitis and orbital cellulitis. The term *orbital cellulitis* is often used to include subperiosteal and orbital abscesses as well as orbital cellulitis. The barrier between the preseptal and orbital soft tissues is the orbital septum, a fibrous membrane that arises from the periosteum of the orbital rim and extends to the tarsal plates of the lids. The distinction between preseptal and orbital infections is important, as preseptal infections are not vision threatening and almost never extend into the orbit, whereas orbital infections may rapidly cause vision loss. Patients with either preseptal cellulitis or orbital cellulitis present with swollen, red lids (Figure 16.2). The lids may be swollen shut, but it is essential to open them and examine the eye in order to determine if there are any "orbital signs." Orbital signs are: decreased vision, proptosis, and limitation

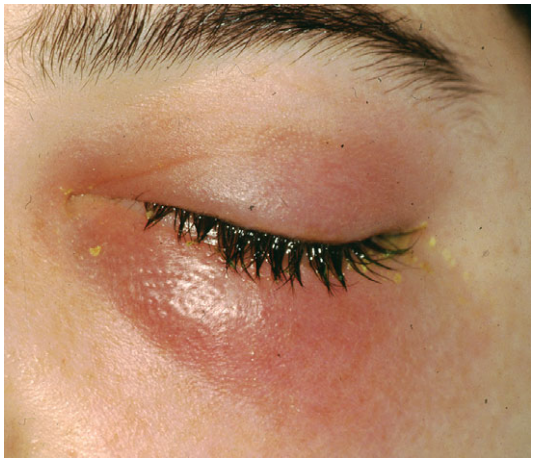

Figure 16.2. Lid swelling and erythema, shown here, are features of both preseptal and orbital cellulitis; opening the eyelids is necessary in order to distinguish these entities.

in extraocular movement. Patients with orbital infections have at least one of these three features, while patients with preseptal cellulitis have none. Both preseptal and orbital cellulitis occur more often in children than in adults. Sinusitis is the etiology of 80% to 90% of these infections in any age group. The ethmoid sinus is the source of most infections, as it is separated from the orbit by the "paper-thin" bone, the lamina papyracea. However, frontal sinusitis may also lead to orbital infections, often from acute bacterial superinfection of a previously undiagnosed mucocele that has eroded the frontal sinus floor (orbital roof) by chronic pressure (Figure 16.3A, B).

Preseptal cellulitis is similar to facial cellulitis, and is an infection of the superficial lid skin and preseptal soft tissues. It presents as unilateral redness and swelling of the eyelids, but with normal vision and extraocular movements. There is no proptosis. The etiology is ethmoid sinusitis in most cases. The bacterial etiology of the cellulitis is unknown but presumed to reflect the common causes of acute sinusitis, *Streptococcus pneumoniae* and *Haemophilus influenzae*, in addition to *S. aureus*. Some cases of preseptal cellulitis are due to superinfection of a break in the lid skin (e.g., insect bite, rash, and abrasion), and these cases are usually caused by *S. aureus* or group A streptococci. Methicillin-resistant *S. aureus* should also be considered in areas where this organism is prevelant. A third etiology of preseptal cellulitis is bacteremic seeding. This is now very rare, although it was more common in the pre-Hib vaccine era when most cases were due to

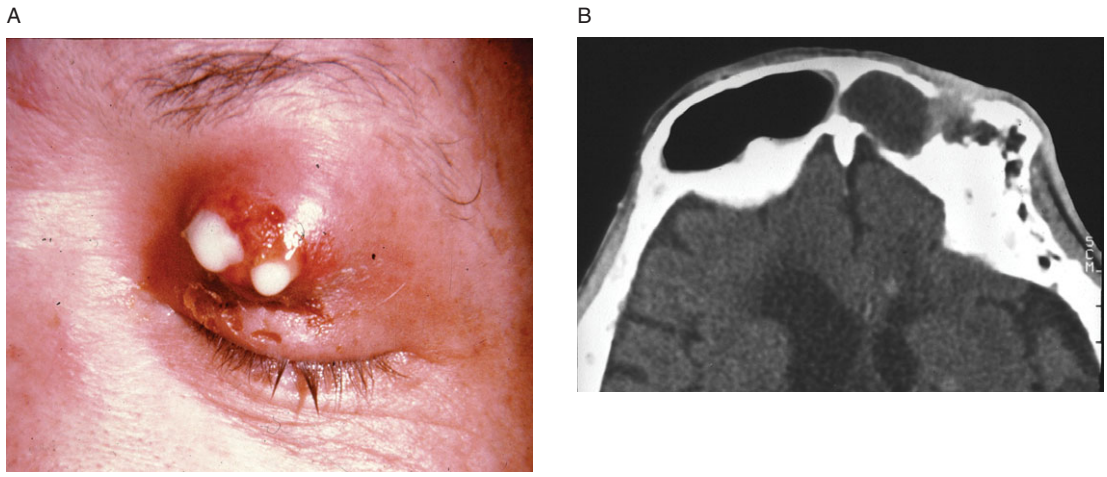

Figure 16.3 (A) Purulent drainage in upper lid from frontal sinusitis (superinfection of chronic frontal sinus mucocele). (B) CT of patient shown in A. Chronic frontal sinus infection had led to erosion of the floor of the frontal sinus, which is also the roof of the orbit.

H. influenzae bacteremia. The entity is usually seen only in young children (e.g., under age 3), and is now caused by *S. pneumoniae*, group A streptococci, other streptococci, or occasionally nontypeable *H. influenzae*. These children should be hospitalized for treatment with intravenous antibiotics directed against the cause of the bacteremia. Preseptal or orbital cellulitis has been described as a rare manifestation of bacteremia due to *S. pneumoniae* in adults with lupus erythematosis or hematologic disorders. *Pseudomonas* bacteremia has also caused preseptal or orbital cellulitis in neutropenic cancer patients.

Orbital cellulitis is an infection of the soft tissues of the orbit. Patients present with unilateral eyelid swelling and erythema, eye pain, and some degree of ophthalmoplegia or proptosis or both. There is often pain with eye movement. The proptosis may not be obvious and should be measured with a Hertel's exophthalmometer. A difference of 2 mm or more between the eyes signifies proptosis. Vision may be decreased, and there may be an afferent pupillary defect. Fever and leukocytosis are usually present in pediatric cases but may be absent in adults. Nearly all cases of orbital cellulitis in children and most in adults are caused by sinusitis, and many patients give a history of recent sinusitis symptoms. Occasional cases in adults are caused by extension of infection from acute dacryoadenitis, dacryocystitis, endophthalmitis, peribulbar anesthesia, or penetrating orbital trauma. As noted above, pneumococcal and *Pseudomonas* bacteremia may rarely cause preseptal or orbital cellulitis in the patients with certain risk factors. Diagnosis of orbital cellulitis is by physical examination and computed tomography (CT) scan of the orbit. The CT scan shows inflammation in the orbital soft tissues (e.g., fat "stranding") but no abscess. Treatment is with intravenous broad-spectrum antibiotics directed against *S. aureus*, streptococci, anaerobes, and *H. influenzae*. Sinus drainage surgery is occasionally necessary as well.

Orbital subperiosteal abscess presents like orbital cellulitis, although symptoms are usually more severe. Because the ethmoid sinus is the source of infection in nearly all cases, the purulent collection is usually beneath the medial orbital periosteum. The periosteum bulges into the orbit, limiting medial rectus movement and causing the eye to look "down and out." Orbital CT scan demonstrates the collection. Nearly all cases in older children and adults require immediate surgical drainage of the abscess in addition to intravenous antibiotics. The need for immediate drainage surgery in children younger than 9 with normal vision is controversial, and some authors argue that they may be observed initially on intravenous antibiotics alone. Broad-spectrum antibiotics (e.g., vancomycin, metronidazole, and ceftriaxone) are needed initially in all cases until culture results are available. Most cases are caused by a mixture of anaerobes and aerobes, with aerobes including one or more of the following: *S. aureus*, *Streptococcus anginosus (milleri)* group, group A streptococci, *H. influenzae*, *Moraxella catarrhalis*.

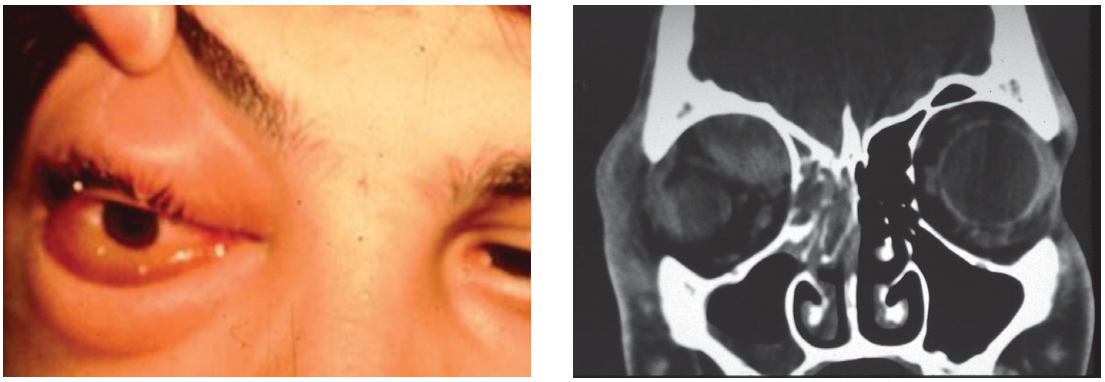

Figure 16.4 (A) Orbital abscess causing eye to look "down and out." (B) CT of patient in A. Note abscess in superomedial right orbit.

Orbital abscess has clinical and microbiologic features identical to those of orbital subperiosteal abscess. The abscess is usually medial or superomedial in the orbit, so the eye typically looks in the "down and out" direction, as in subperiosteal abscess (Figure 16.4A). An orbital CT scan reveals the collection (Figure 16.4B). Treatment is immediate surgical drainage and broad-spectrum intravenous antibiotics. Delay in drainage of the abscess may lead to permanent loss of vision.

Cavernous sinus thrombophlebitis (CST) is a very rare complication of orbital infections or of other infections in the midface "danger triangle." The two cavernous sinuses are venous plexuses that are connected by intercavernous sinuses; involvement of one sinus can rapidly spread to the opposite side. Cranial nerves III, IV, V1, V2, and VI run through the cavernous sinus. Patients with CST typically present with headache, unilateral orbital cellulitis and hypesthesia in the distribution of V1 and V2 (forehead and cheek). They sometimes then develop similar findings in the opposite eye. Diagnosis is by clinical findings supported by magnetic resonance imaging (MRI) and MR venography (MRV). The most common bacterial etiology is *S. aureus*, but streptococci, anaerobes, and gram-negative bacilli may be present depending on the origin of infection. Treatment is with broad-spectrum intravenous antibiotics. The value of anticoagulation is unknown (see also Chapter 77, Intracranial suppuration).

Invasive fungal sinusitis usually presents with orbital cellulitis, and at presentation, there may be hypesthesia of cranial nerve V divisions V1 and V2 due to orbital apex or cavenous sinus involvement. Mucormycosis should be suspected in any patient with appropriate risk factors who presents with symptoms and signs of orbital cellulitis. Risk factors include diabetes (70% of cases), hematologic malignancies, immunosuppression (e.g., organ transplant and chronic corticosteroid use), or deferoxamine therapy. Clinical findings include ophthalmoplegia, proptosis, and lid edema (Figure 16.5), and in contrast with bacterial orbital cellulitis, lid erythema may be faint rather than "hot" looking. While patients with bacterial orbital cellulitis complain of pain in their involved eye and orbit, patients with mucormycosis may complain that the most prominent pain is in the temple and forehead. Hypesthesia of the cheek and forehead is often present, and the periorbital skin, including the forehead, may be indurated. *Aspergillus* infections of the orbit and cavernous sinus usually arise from invasive sphenoid sinus aspergillosis. Patients may present subacutely, with gradual onset of proptosis, ophthalmoplegia, and visual

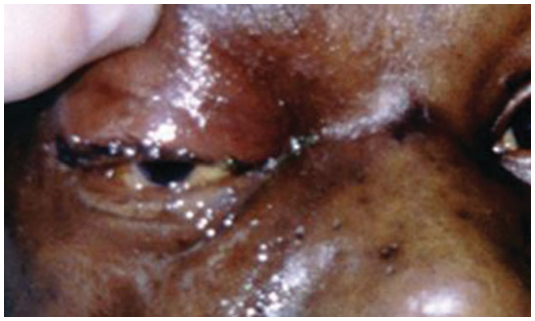

Figure 16.5 Rhinocerebral mucormycosis in a diabetic patient. The lids are swollen but less erythematous than they would be in typical acute bacterial orbital cellulitis.

loss over days to weeks. There may be minimal lid swelling and erythema. The orbital apex may be involved first, leading to an orbital apex syndrome. The optic nerve and cranial nerves III, IV, VI, and V1 run through the orbital apex, so patients with this syndrome usually present with unilateral blindness, ptosis, proptosis, a fixed dilated pupil, and ophthalmoplegia.

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PART IV

Clinical syndromes: skin and lymph nodes

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17. Fever and rash

John W. Sensakovic and Leon G. Smith

Fever and rash is one of the common symptom complexes presenting in medical practice. Because of the wide range of diseases that can present with this complex, the patient presenting with fever and rash is also one of the most challenging clinical syndromes.

Although both infectious and noninfectious disease processes can present with fever and rash, infectious causes are considered here. Nevertheless, noninfectious causes such as drug reactions, systemic vasculitis, serum sickness, erythema multiforme, toxic epidermal necrolysis, and Sweet's syndrome are often in the differential diagnosis.

The approach to the patient with infectious fever and rash should begin with the appreciation that causes include common infections that are often benign, serious emergent infections that can be rapidly fatal, and unusual infections that can pose a diagnostic challenge. Key features in the history and physical can be particularly important. These include childhood diseases and immunization history, seasonal diseases, travel history and geography, exposure, sexual history, and medication usage, as well as prodromal and accompanying symptoms. Physical examination, with particular attention to the characteristics of the rash, can be key, along with vital signs to assess severity of the illness, and particular attention to meningeal signs, lymph nodes, mucous membranes, conjunctiva, and joint examination. Features of the rash to consider include characteristics and distribution of the lesions, timing of onset of rash in relation to fever, and changes in morphology of the lesions.

When faced with the patient with fever and rash, the physician must be acutely aware of those several very serious infections that are commonly fulminant and that can be rapidly fatal. Thus, the physician must quickly address a series of important issues simultaneously (Table 17.1). These include the question of contagious potential to the medical staff, the need for rapid resuscitation in those patients who can present in shock, the rapid recognition of and therapeutic intervention for those infections that tend to be fulminant, and the need for a thorough evaluation and workup for the extensive list of diagnostic possibilities that can present with fever and rash.

Table 17.1 Major issues in patients with fever and rash

Contagious potential
Resuscitation
Rapid therapy
Diagnostic evaluation
Clinical setting
Severity of illness
Nature of rash
Petechial
Cellulitic
Vesiculobullous
Maculopapular

EMERGENT CONDITIONS PRESENTING WITH FEVER AND RASH

Rapid recognition and therapeutic intervention are essential in certain diseases presenting with fever and rash to minimize as much as possible the associated morbidity and mortality. The major conditions involved include meningococcemia, Rocky Mountain spotted fever, staphylococcal toxic shock syndrome, streptococcal toxic shock-like syndrome, bacteremia or endocarditis with septic emboli, and the rapidly spreading cellulitis (Tables 17.2 and 17.3). All of these conditions can present with fever and rash in a fulminant, rapidly progressive form, requiring expedient therapeutic intervention, often on an empiric basis, before confirmation of the diagnosis, if the associated mortality rates are to be minimized.

Generally, the most serious and rapidly progressive of these are associated with a petechial rash. These 1- to 2-mm purple lesions do not

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Table 17.2 Approach to seriously ill patients with fever and rash

Clues	Disease	Diagnosis
Multiple purpuric lesions Earliest lesions small of back Rapid progression over hours	Meningococcemia	Gram stain of pustules Blood cultures
Tick exposure, headache, fever, rash 2nd–6th days Wrists, ankles, progressing to palms, soles, trunk	Rocky Mountain spotted fever	DFA of skin biopsy Serology (CF)
Fever, rash, hypotension, menstruating female using tampons Surgical wound or skin infection	Toxic shock syndrome	Isolation of phage group I staphylococci
Fever, rash, hypotension, rapid onset of organ dysfunction	Group A streptococcal toxic shock-like syndrome	Evidence of group A streptococcal infection
Elderly or immunocompromised patient Several lesions, macular to necrotic pustules	Bacteremia with septic emboli	Gram stain of pustules Blood cultures Gram stain of buffy coat
Painful spreading lesions Local trauma	Rapidly spreading cellulitis	Clinical

Abbreviations: DFA = direct fluorescent antibody; CF = complement fixation.

Table 17.3 Characteristics of serious rashes

Onset with or after fever
Petechial lesions
Rapid spread
Purpuric lesions
Palmar/plantar involvement

blanch with pressure, often coalesce to form larger ecchymotic areas, and usually are in the presence of leukocytosis and thrombocytopenia. Meningococcemia, Rocky Mountain spotted fever, and bacteremia/endocarditis with septic emboli are perhaps the most notable. However, other causes include gonococcemia, typhus, and rat-bite fever; viral infection, including dengue, hepatitis B, rubella, and Epstein–Barr virus (EBV); and noninfectious causes, including thrombotic thrombocytopenia purpura, Henoch–Schönlein purpura, vasculitis, and scurvy.

Rapidly progressive diseases with erythematous rash include staphylococcal toxic shock syndrome and streptococcal toxic shock-like syndrome, as well as the rapidly progressive cellulitis, which often have a vesicobullous component. In these conditions, as well as with necrotizing fasciitis, the patient often looks toxic out of proportion to the extent of the rash.

MENINGOCOCCEMIA

Of all the diseases presenting with fever and rash, meningococcemia is the one most likely to be rapidly fatal without early recognition and treatment. The ominous palpable purpura in an acutely ill, febrile patient characteristically suggests this disease. Other features that may be helpful in earlier diagnosis include sore throat, fever, muscle tenderness, and headache in the presence of significant leukocytosis and thrombocytopenia. The illness tends to occur in late winter and early spring and is well known to occur under crowded living conditions. The initial rash may be maculopapular, with the earliest petechial lesions occurring over pressure points such as the small of the back, and can easily be overlooked. The rash can progress rapidly over a few hours to the more classic, petechial form with peripheral acrocyanosis. Management requires immediate recognition, vigorous fluid replacement, and rapid therapy with aqueous penicillin or a third-generation cephalosporin, 12 to 24 million units daily intravenously (IV). Patients presenting with signs of adrenal insufficiency also require steroid replacement. The use of gamma globulin is controversial for patients with meningitis. Dexamethasone for 2 days started just before or with the first dose of antibiotics is indicated.

ROCKY MOUNTAIN SPOTTED FEVER

Rocky Mountain spotted fever can also present with fever and petechial rash in an acutely ill patient, yet is different from meningococcemia in several respects. The illness begins with fever and severe headache, occurs between May and

September in temperate-zone states, and there is a history of tick exposure in 75% of the cases. The rash appears several days into the illness, begins as a maculopapular rash on wrists and ankles, and progresses to a petechial form and spreads to palms, soles, and trunk. A leukocytosis with thrombocytopenia is commonly present. Therapy is doxycycline, 100 mg every 12 hours, and must be instituted early on a presumptive basis, before serologic confirmation, if mortality is to be significantly reduced. Alternative therapy is with chloramphenicol, 50 mg/kg/day IV. In institutions where available, immunofluorescence staining of a skin biopsy specimen of the rash can yield a rapid diagnosis. A review from Duke University Medical Center cited 10 cases of illness without rash or with fleeting atypical skin eruptions, emphasizing the need for a high index of suspicion in acutely ill patients with endemic tick exposure.

TOXIC SHOCK SYNDROME

Toxic shock syndrome caused by the pyrogenic exotoxin of phage group 1 *Staphylococcus aureus* classically presented in a young menstruating female using a tampon. Causive strains produce staphyloccal exotoxin TSST-1. However, recently cases more commonly occur as a result of nonvaginal foci of staphylococcal infection, including surgical wound infections, infectious endocarditis nasal packing, and infected catheters. The rash tends to be diffuse and scarlatiniform in character, with associated conjunctival hyperemia and a "strawberry tongue." The rash is associated with fever, hypotension, and evidence of multisystem derangement. Therapy requires vigorous fluid replacement, removal of the infected tampon or other foreign body, or drainage of an identified infected focus, and nafcillin or oxacillin at 8 to 12 g/day. Some experts also recommend vaginal lavage with a betadine solution as a local antibacterial agent as well as for removal of any nonabsorbed exotoxin.

Staphylococcal scalded skin syndrome can be seen in young children infected with a staphylococcal strain producing epidermolysin A or B. The result is a superficial sloughing of the skin with a painful erythema. Nikolsky's sign, "onion skin" peeling of the skin with gentle pressure, is seen.

A somewhat similar noninfectious entity, toxic epidermal necrolysis, is seen in adults. This typically is drug induced, and the sloughing of the skin occurs deeper, at the dermal–epidermal junction.

GROUP A STREPTOCOCCAL TOXIC SHOCK-LIKE SYNDROME

The changing epidemiology of group A streptococcal infections has been recognized as a resurgence in rheumatic fever and an increase in the frequency of invasive infections and bacteremia. In addition, the group A streptococcal toxic shock-like syndrome has been recently defined by its characteristic early onset of shock and multiorgan failure in the presence of group A streptococcal infection, often with a generalized erythematous rash that may desquamate. Most of the isolates produce pyrogenic exotoxin A, and some cases have been associated with necrotic soft-tissue infections. In group A streptococcal toxic shock-like syndrome, mortality up to 30% has been described compared to 3% with staphylococcal toxic shock syndrome.

Septic emboli

The diagnosis of septic emboli associated with bacterial bloodstream infection must be considered in any seriously ill patient with fever and rash. Such infections most commonly present in elderly or immunocompromised patients. Solitary or widely scattered purplish lesions, nonblanching and often with necrotic centers, suggest the diagnosis. The lesions often involve the digits. Ecthyma gangrenosum is one such lesion seen with *Pseudomonas aeruginosa* bacteremia. Such lesions are also seen most often in *S. aureus* bacteremia, *Candida albicans* fungemia, and infectious endocarditis. Gram stain of aspirates from the skin lesions and of the buffy coat of the blood can be rapidly diagnostic; blood cultures are confirmatory. Presumptive therapy should cover methicillin-resistant *S. aureus* as a problem; a regimen of vancomycin, 1 g IV every 12 hours, and gram-negative coverage is recommended pending culture identification.

Rapidly spreading cellulitis

The various types of rapidly spreading cellulitis associated with fever and rash are not difficult to recognize in most instances because of the painful spreading inflammatory lesion on the skin. The diagnostic difficulty involves differentiating the various types of rapidly spreading cellulitis based on probable causative organism or organisms and whether infection is confined to the surface or extends to deeper structures, including fascia and muscle. With deep extension, case adequate

surgical debridement is essential, along with appropriate antibiotic therapy. "Flesh-eating" necrotizing fasciitis from group A streptococcus can be difficult to diagnose, and it is increasing in frequency.

COMMON INFECTIONS PRESENTING WITH FEVER AND RASH

The most common infections presenting with fever and rash also fortunately include conditions that are generally benign.

Many of these febrile exanthems are due to viral illnesses of children or inadequately immunized adults. Such illnesses as measles, varicella, rubella, erythema infectiosum due to parvovirus B19, and roseola infantum due to human herpesvirus type 6 (HHV-6) are typical. Kawasaki syndrome and streptococcal scarlet fever should also be considered in this age group.

In older children presenting with fever, rash, sore throat, and adenopathy, EBV infection is common. In young adults presenting in such fashion where EBV and group A *Streptococcus* have been ruled out, pharyngitis with fever and rash due to a recently described organism, *Arcanobacterium*, should be considered. This gram-positive bacillus is usually very sensitive to erythromycin.

Enteroviral infections due to Coxsackieviruses and echoviruses frequently present with febrile exanthem and should especially be considered during summer months and when accompanied with gastrointestinal symptoms.

UNUSUAL INFECTIONS THAT CAN POSE A DIAGNOSTIC CHALLENGE

A wide variety of less common infections that can present with fever and rash should also be considered, especially if associated with geographic or seasonal exposure (Table 17.4).

Lyme borreliosis can present with fever and a characteristic erythema migrans rash, resulting from geographic tick exposure. Diagnosis can be difficult early in the infection when serology can be negative and the rash can be atypical or missed. Follow-up serology may be diagnostic.

The recently recognized syndromes of West Nile virus infection, including West Nile fever, encephalitis, and facial paralysis, can present with fever and rash. The disease has a summer–fall prevalence and is associated most often with exposure to infected household mosquitoes. Other uncommon infections to be considered, also with geographic and seasonal occurrence, include ehrlichiosis, dengue fever, tularemia, plague, leptospirosis, and typhoid fever.

Although a wide variety of diagnostic tests and procedures can be helpful in the workup of the patient presenting with fever and rash, none of these is as important as a careful history and physical examination.

Table 17.4 Rare causes of fever and rash

Infectious		
Viral		
Parvovirus	Hand-foot-mouth	West Nile
EBV	Herpes simplex	RSV
CMV	Herpes zoster	HHV-6
Coxsackie	HIV	Smallpox
Enterovirus (echo)	Hepatitis B and C	Vaccina
Dengue	Monkeypox	
Ebola	Rubella	
Bacteria		
Rat-bite fever	Leptospirosis	Neisseria
Mycoplasma pneumoniae	Lyme	Gonorrhea
BCG	Bartonella	Salmonella
Mycobacteria	Borrelia	
Fungal		
Candida	Coccidiomycosis	Histoplasmosis
Sporotrichosis		
Noninfectious		
Erythema multiforme	Vasculitis's	Porphyria
Kawasaki	Sweet's syndrome	Drug reaction
Graft vs. host	Pyoderma gangrenosum	

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18. Staphylococcal and streptococcal toxic shock and Kawasaki syndromes

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TOXIC SHOCK SYNDROME

Staphylococcal and streptococcal toxic shock syndromes (TSS) are acute-onset multiorgan illnesses defined by criteria listed in Tables 18.1 and 18.2. Staphylococcal TSS is caused by *Staphylococcus aureus* strains that produce pyrogenic toxin superantigens (SAgs). Human coagulase-negative staphylococci do not produce the causative toxins, though coagulase-negative strains from animals occasionally do produce SAgs. Streptococcal TSS is caused primarily by *Streptococcus pyogenes* (group A) strains but occasionally by groups B, C, and G strains. Several subsets of staphylococcal TSS exist, with two major categories being menstrual and nonmenstrual.

Menstrual TSS (Figure 18.1), which occurs within a day or two of or during menstruation, primarily has been associated with use of certain tampons, notably those of high absorbency, and is associated with production of TSS toxin-1 (TSST-1) by the causative bacterium. When initially described, menstrual TSS occurred primarily in women of ages 15 to 25. Presently, menstrual TSS occurs more often in younger females, particularly ages 12 to 15; the reason for this shift in menstrual TSS to the younger age group is unclear. There are two major mechanisms that explain the association of tampons with menstrual TSS: (1) tampons introduce oxygen, which is absolutely required for production of TSST-1, into the otherwise anaerobic vagina; and (2) Pluronic L-92, a surfactant present in the TSS-associated Rely tampon from the 1980s and no longer used in tampons, amplifies TSST-1 production.

Nonmenstrual TSS occurs in both males and females, adults and children, and is associated with *S. aureus* strains that produce TSST-1 or staphylococcal enterotoxins, notably enterotoxin serotypes B and C. These three SAgs are produced in amounts nearly 10^5 times higher than most other SAgs. Nonmenstrual TSS occurs in association with nearly any kind of staphylococcal infection, but major forms have been identified: postsurgical, upper respiratory virus (influenza)-associated, RED syndrome (see below), enterocolitis-associated, and occasionally with use of contraceptive diaphragms. Postsurgical TSS is often associated with

Table 18.1 Diagnostic criteria for staphylococcal toxic shock syndrome

1. Temperature greater than 38.8°C
2. Systolic blood pressure ≤90 mm Hg for adults, less than the 5th percentile for children, or greater than 15 mm Hg orthostatic drop in diastolic blood pressure or orthostatic dizziness/syncope
3. Diffuse macular rash with subsequent desquamation
4. Three of the following organ systems involved:
   - Liver: bilirubin, AST, ALT more than twice the upper normal limit
   - Blood: platelets <100 000/mm^3
   - Renal: BUN or creatinine more than twice the upper normal limit or pyuria without urinary tract infection
   - Mucous membranes: hyperemia of the vagina, oropharynx, or conjunctivae
   - Gastrointestinal: diarrhea or vomiting
   - Muscular: myalgias or CPK more than twice the normal upper limit
   - Central nervous system: disorientation or lowered level of consciousness in the absence of hypotension, fever, or focal neurologic deficits
5. Negative serologies for measles, leptospirosis, and Rocky Mountain spotted fever; blood or CSF cultures negative for organisms other than *Staphylococcus aureus*

Abbreviations: AST = aspartate transaminase; ALT = alanine aminotransferase; BUN = blood urea nitrogen; CPK = creatine phosphokinase; CSF = cerebrospinal fluid.

Table 18.2 Diagnostic criteria for streptococcal toxic shock syndrome

1. Isolation of group A streptococci:
   From a sterile site for a *definite* case
   From a nonsterile site for a *probable* case
2. Clinical criteria:
   Hypotension *and* two of the following:

Renal dysfunction	Coagulopathy
Liver involvement	ARDS
Erythematous macular rash	Soft-tissue necrosis

Abbreviations: ARDS = adult respiratory distress syndrome.

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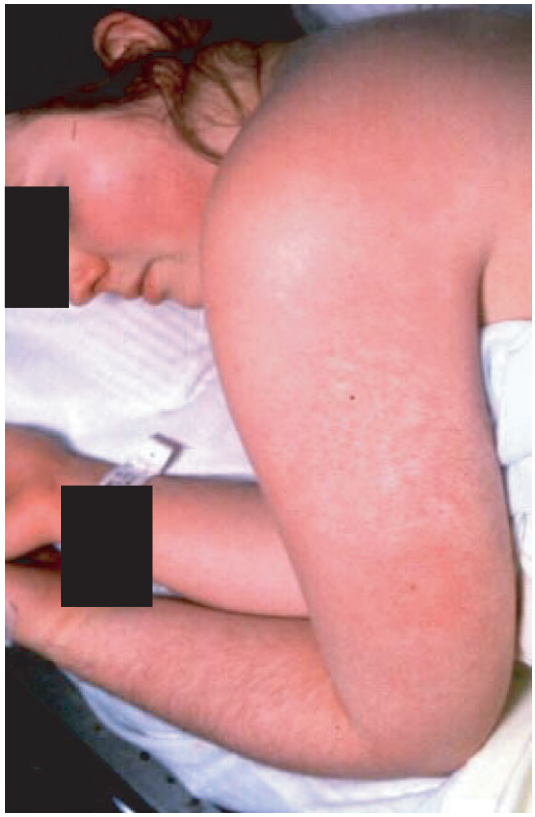

Figure 18.1 Menstrual toxic shock syndrome (vaginal colonization): diffuse blanching erythema. (Courtesy of David Schlossberg, MD.)

S. aureus infections that do not result in pyogenic responses, and thus the infection source may be difficult to find. Influenza TSS may occur as a consequence of influenza or parainfluenza damage to the respiratory tract epithelium and superinfection with SAg-producing *S. aureus* (Figures 18.2 and 18.3). This illness is highly fatal in children. RED syndrome is a recalcitrant erythematous desquamating disorder in patients with acquired immunodeficiency syndrome (AIDS) that may last 70 or more days until the patient succumbs. Recently, staphylococcal TSS has been associated with enterocolitis. Until enterocolitis became highly associated with *Clostridium difficile* infection, staphylococcal enterotoxins were associated with the illness. Although sometimes forgotten, staphylococcal SAgs should be considered as causes of enterocolitis with TSS symptoms when *C. difficile* cannot be isolated from patients. Finally, nonmenstrual TSS associated with use of diaphragms may be similar to menstrual TSS.

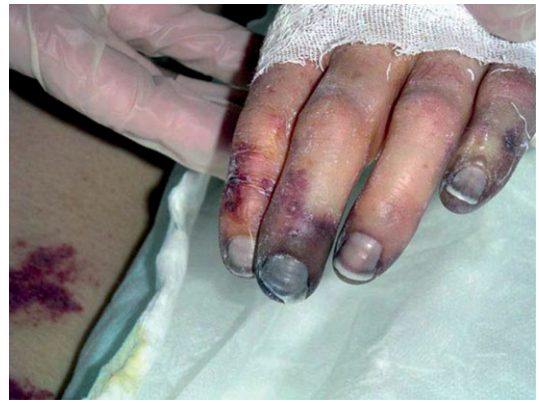

Figure 18.2 Gangrenous fingers and skin peeling with nonmenstrual staphylococcal toxic shock syndrome (pulmonary infection). (Courtesy of Gary R. Kravitz, MD, St. Paul Infectious Disease Associates, St. Paul, MN.)

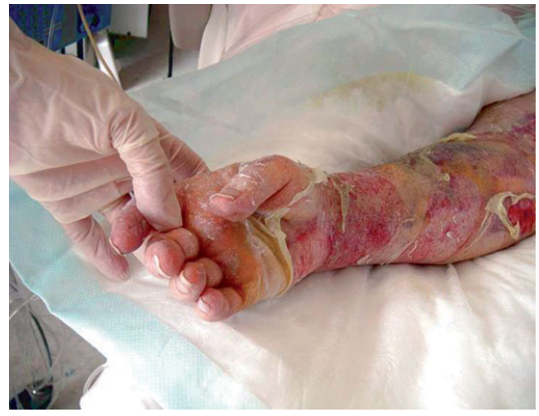

Figure 18.3 Same patient as in Figure 18.2, demonstrating extensive peeling and tissue damage. (Courtesy of Gary R. Kravitz, MD, St. Paul Infectious Disease Associates, St. Paul, MN.)

Streptococcal TSS is primarily associated with group A streptococcal infections, particularly M serotypes 1, 3, and 18. The illness may or may not be associated with necrotizing fasciitis or myositis (Figure 18.4). The case:fatality rate is higher in cases with necrotizing myositis than when this condition is absent. Occasionally, streptococcal TSS is caused by other groups of streptococci, primarily groups B, C, and G.

Group A streptococcal strains that cause TSS produce streptococcal pyrogenic exotoxin SAgs. The major associations have been with serotypes A and C, but other family members contribute significantly. Nongroup A streptococcal strains associated with TSS also produce streptococcal pyrogenic exotoxin SAgs that are related or identical to the group A streptococcal SAgs.

Major risk factors for development of streptococcal TSS include chickenpox in children, penetrating and nonpenetrating wounds, use of nonsteroidal anti-inflammatory agents, and pregnancy.

KAWASAKI SYNDROME

Kawasaki syndrome is an acute multisystem vasculitis that occurs primarily in children younger than 4 years of age (Table 18.3). Kawasaki syndrome shares many features with streptococcal scarlet fever and TSS, except that hypotension is absent. Kawasaki syndrome is a leading cause of acquired heart disease in this age group. Coronary artery abnormalities, including aneurysms, develop in 15% to 25% of patients.

The causative agent of KS remains unclear, but studies suggest that staphylococcal and streptococcal SAgs may have important causal roles in many cases.

Table 18.3 Clinical criteria for Kawasaki syndrome[a]

1. Fever, usually of at least 5 days' duration
2. Four of five of the following: Extremity changes, induration, edema, erythema Oropharyngeal and lip changes, strawberry tongue, cracked lips Cervical lymphadenopathy: at least one node >1.5 cm Injected conjunctivae Rash, erythematous and polymorphous
3. Other diseases excluded

[a] Strict fulfillment is not always necessary; see Suggested reading.

EVALUATION AND TREATMENT OF TOXIC SHOCK SYNDROMES

Differential diagnosis of toxic shock syndrome

- Viral disease, including measles, rubella, parvovirus B19
- Spotted fever group rickettsiae
- Leptospirosis
- Drug reactions, including Stevens–Johnson syndrome
- Collagen vascular diseases, including systemic lupus erythematosus and Still's disease

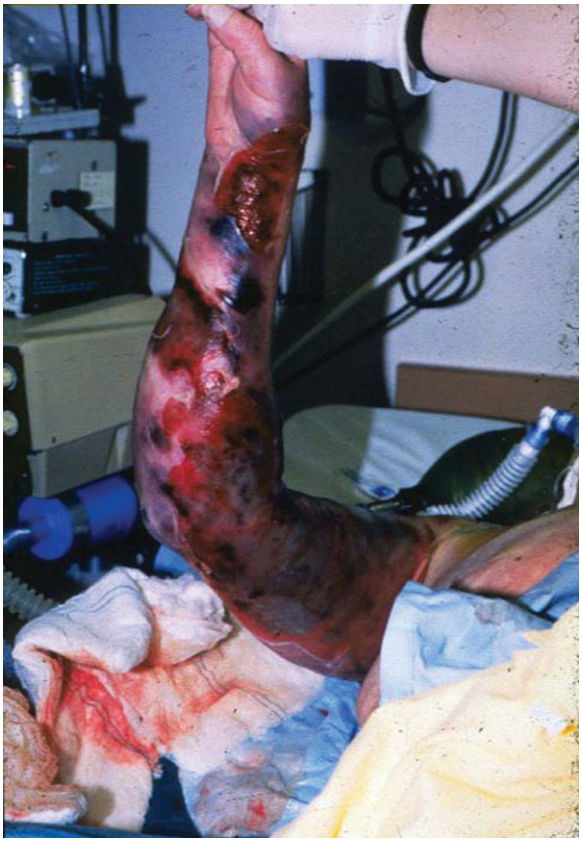

Figure 18.4 Necrotizing fasciitis: note the extensive necrosis in this patient's arm. At the time, this patient was hypotensive with multiple organ failure and severe pain at the site of infection.

- Scarlet and rheumatic fever
- Syphilis
- Typhoid fever.

The physician should consider myositis or necrotizing fasciitis in any patient who presents with severe local pain, especially in an extremity, and other nonspecific influenza-like or gastrointestinal symptoms. Fever, erythema, and edema are usually absent. Early intervention is lifesaving for patients with necrotizing soft-tissue infections, so it is important to maintain a very high index of suspicion. An elevated creatinine, elevated creatine kinase (CK), or significant bandemia may suggest the diagnosis.

Initial evaluation

Possible sources of infection or foreign bodies must be identified. The physician should perform a vaginal examination, remove any tampon, and culture for *S. aureus*. Any wounds should be unpacked and inspected. A thorough examination of the skin and soft tissues should be undertaken, paying special attention to any painful areas, even if typical signs of inflammation are absent. Cultures of blood and other sites, as appropriate, should be obtained. Early surgical intervention is extremely important. MRI may be used to identify deep soft-tissue necrosis and guide surgical intervention.

Supportive care

Supportive care is of primary importance. Patients often require large amounts of intravenous fluids, vasopressors, and management of associated comorbidities, such as acute renal failure, adult respiratory distress syndrome, disseminated intravascular coagulation, or myocardial suppression.

Antibiotics

Antistaphylococcal therapy decreases the risk of recurrence of staphylococcal TSS and will treat any active infection with *S. aureus* or β-hemolytic streptococci. Nafcillin (adults: 2 g IV every 4 hours; children: 150 mg/kg/day IV divided every 6 hours) or cefazolin (adults: 1–2 g IV every 8 hours; children: 50–100 mg/kg/day IV divided every 8 hours) can be used. However, for critically ill patients, suspected methicillin-resistant *S. aureus*, or patients with an anaphylactic penicillin or cephalosporin allergy, vancomycin (adults: 1 g IV every 12 hours; children 40 mg/kg/day IV divided every 6 hours), daptomycin (adults: 4–6 mg/kg IV every 24 hours; children 4–10 mg IV every 24 hours, varies with age), or linezolid (adults: 600 mg IV every 12 hours; children 10 mg/kg every 8 hours up to age 12) can be used. Clindamycin, a protein synthesis inhibitor (adults: 900 mg IV every 8 hours; children: 40 mg/kg/day IV divided every 6–8 hours), should be given in addition (unless linezolid is used) as experimental data suggest that it inhibits exotoxin and M protein production. Dosage adjustments for renal failure may be required.

Once a microbiologic diagnosis has been established, the spectrum of therapy can be narrowed, if appropriate, using penicillin (adults: 4 million units IV every 4 hours; children: 250 000 U/kg/day IV divided every 4 hours), ampicillin (adults: 2 g IV every 6 hours; children 50 mg/kg/day divided every 6 hours), ceftriaxone (adults: 2 g IV every 24 hours; children: 50–75 mg/kg/day IV divided every 12–24 hours), or clindamycin alone, as appropriate. Therapy should be given for approximately 10 to 14 days unless a diagnosis, such as osteomyelitis, is made that requires extended therapy.

Intravenous immunoglobulin

Lack of neutralizing antibodies seems to be a risk factor for staphylococcal and streptococcal TSS. Human and animal studies appear to support the use of intravenous immunoglobulin (IVIG) in these diseases. Preparations of IVIG may vary not only by manufacturer but also by batch in their ability to neutralize superantigenic toxins. Therefore, retreatment with a different preparation may be warranted in a patient who has not responded to initial therapy. Various IV doses have been used as follows: 1 g/kg on day 1 followed by 0.5 g/kg each day on days 2 and 3, 0.4 g/kg IV once daily for 5 days, or a single dose of 2 g/kg with a repeat dose at 48 hours if the patient remains unstable.

Steroids

The clinician should not miss the patient with absolute or relative adrenal insufficiency. However, steroids are not routinely given to patients with TSS.

Surgical intervention

Any obvious source of infection should be drained. There should be a low threshold to

explore other sites as expected signs of inflammation may be absent, especially in streptococcal myositis. Radionuclide white blood cell scanning has been used to identify undrained foci of necrotizing fasciitis in a nonresponding patient.

Prevention

Up to 30% recurrence has been suggested. Elimination of staphylococcal colonization can be attempted. Avoidance of further tampon use is prudent after menstrual TSS. Close contacts of an index case of streptococcal TSS may be colonized with toxin-producing streptococci.

TREATMENT OF KAWASAKI SYNDROME

Differential diagnosis of Kawasaki syndrome

- Acute adenoviral infection
- Other viral exanthemata, especially measles
- Scarlet fever
- Drug reactions, Stevens–Johnson syndrome, erythema multiforme
- Spotted fever group rickettsiosis
- TSS
- Staphyloccocal scalded skin syndrome
- Juvenile rheumatoid arthritis
- Leptospirosis
- Mercury poisoning

Differential diagnosis

Irritability and gastrointestinal symptoms are common. Adenoviral infection may present the most common diagnostic dilemma. Incomplete Kawasaki syndrome, more common in children less than 12 months of age, may be diagnosed when the patient has 5 or more days of fever and two or more criteria for diagnosis. The risk of coronary artery aneurysms increases significantly in patients not treated within 10 days.

Supportive care

Cardiorespiratory monitoring, close clinical observation, and attention to fluid balance are required.

Aspirin

The physician should give high doses of aspirin (80–100 mg/kg/day in four divided doses, maximum of 4 g/day) until 48 hours after the fever is gone and then maintain low doses (3–5 mg/kg/day in single dose) for 6 to 8 weeks or until the platelet count and sedimentation rate are normal. Consider monitoring of serum salicylate levels in nonresponders. Some prefer high doses until day 14. Aspirin therapy should be continued indefinitely in any patient with coronary artery abnormalities. Influenza or varicella exposure may prompt discontinuation of aspirin therapy for up to 14 days because of the risk of Reye's syndrome. Dipyridamole (4–9 mg/kg/d divided BID or TID) may substitute during this time in high-risk patients. Give influenza vaccination yearly while on aspirin.

Intravenous immunoglobulin

The recommended dose is 2 g/kg IV given over 12 hours. Retreatment may be necessary in those whose fever persists or recurs. Measles, mumps, and rubella vaccines should be delayed for 11 months after IVIG unless there is high risk. If so, give the vaccination on schedule and repeat 11 months later.

Steroids

Intravenous methylprednisolone will hasten the resolution of fever and improve laboratory markers of inflammation when given in 1–3 pulse doses of 30 mg/kg. This should be considered especially for patients who fail treatment with IVIG but is not routinely recommended.

Monitoring for cardiac complications

Inpatient and outpatient serial exams are important. Obtain electrocardiogram and cardiac echo early and repeat at 6 and 8 weeks. Pediatric cardiology consultation should be obtained. Stress testing and coronary angiography have value in specific clinical situations. The patient with coronary artery lesion (CAL) requires more intensive monitoring.

Evaluation of therapy

Ten percent of patients may not respond. If fever or signs of inflammation persist or recur, consider retreatments with IVIG (1–2 g/kg over 10–12 hours). Pulsed doses of corticosteroids have been used in nonresponders with success despite initial reports that corticosteroids may increase the risk for CALs.

Long-term management

Restrict physical activity for 6 to 8 weeks. Determine frequency of follow-up on an individual basis. It is possible to identify a group of low-risk patients that may not require intensive follow-up. Complicated management issues, such as use of warfarin, calcium channel blockers, and angiography, are beyond the scope of this text. The reader is referred to the excellent reviews of Kawasaki syndrome found in the suggested reading section.

Other issues

Antibiotics are not routinely used. Pentoxifylline has been tried experimentally but is of no proven benefit.

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19. Classic viral exanthems

Lisa M. Chirch, Kevin D. Dieckhaus, and Jane M. Grant-Kels

During the early 1900s, six common childhood exanthematous infections were defined by the numbers 1 through 6. The etiologic agents of these infections were unknown. Over the next century, the etiologies of these exanthems were defined, and four of the six were demonstrated to be caused by viruses (Table 19.1). The first exanthem was caused by the measles virus, the third by the rubella virus, the second and fourth by bacterial toxins, the fifth by parvovirus, and the sixth by human herpesvirus 6 (HHV-6). This chapter will address the epidemiology, clinical manifestations, and diagnosis of the classic childhood viral exanthems: measles (rubeola), German measles (rubella), and exanthem subitum (roseola). Parvovirus infection, scarlet fever, and fourth disease are discussed elsewhere in the text.

Table 19.1 Classic exanthems of childhood

Order	Exanthems	Agent
First	Rubeola or measles	Measles virus
Second	Scarlet fever	Streptococcal toxin
Third	Rubella or German measles	Rubella virus
Fourth	Filatov–Dukes' disease	Unknown, possibly strep. or staph. toxin
Fifth	Erythema infectiosum	Parvovirus
Sixth	Exanthem subitum or roseola	Human herpesvirus 6

RUBEOLA (MEASLES)

Epidemiology and virology

Global measles-related deaths have declined markedly. However, despite impressive improvements in our understanding of infectious diseases such as rubeola (measles) and the widespread availability of effective vaccine, vaccination is far from universal and outbreaks have been reported in recent years from the developing world to the suburbs of US cities. In addition, seroprevalence in newly arrived refugee children to the United States is relatively low, with only 82% having protective antibody to measles in a recent analysis, raising the possibility of transmission of wild-type virus within these populations. Investigations of recent outbreaks found that the majority of measles cases occurred in unvaccinated people, highlighting gaps in vaccine coverage as an important risk factor. Given recent outbreaks of rubeola in the United States, a high degree of vigilance and early recognition of clinical presentations is of ongoing importance among providers.

Rubeola is caused by an RNA virus with one serotype and is classified in the genus *Morbillivirus* in the Paramyxoviridae family. Most cases of measles occur in the late winter or spring. Humans are the only natural hosts and transmission occurs by exposure to infectious droplets. Rubeola is one of the most highly contagious of the infectious agents. Appropriate isolation of cases in hospital settings is critical to limit nosocomial transmission. A patient hospitalized with measles requires airborne precautions for 4 days after the onset of rash. However, if the patient with measles is immunosuppressed, airborne precautions are required until the illness completely resolves. The measles virus is labile and survives only a short time on fomites. The highest rates of transmission occur in the home, day-care centers, nursery schools, primary and secondary schools, colleges, and universities. School outbreaks can occur despite greater than 95% immunity among students.

Clinical and laboratory diagnosis

Clinical measles demonstrates a fairly characteristic clinical presentation. However, given a dramatically lower incidence of illness in recent years, many contemporary providers have not seen a classic measles infection, so diagnosis

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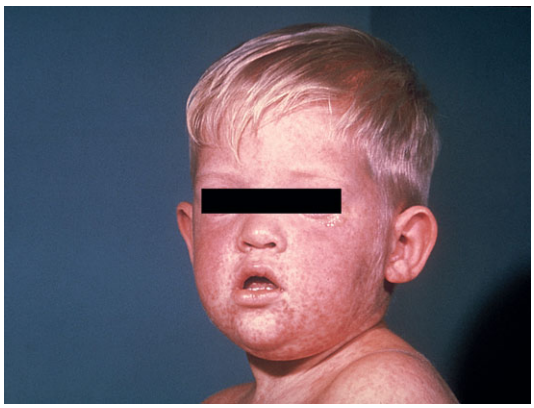

Figure 19.1 Measles in a 9-year-old child presenting as morbilliform lesions on the face, trunk, and palms.

may not be straightforward. In addition, presentation may be atypical in immunocompromised patients.

The incubation period is 10 to 12 days. There is a prodrome of low-grade fever, malaise, and headache. This is followed or accompanied by cough, coryza, and conjunctivitis. During the prodrome, an enanthem appears on the buccal mucosa, and may spread to the hard or soft palate. The typical enanthem of measles (Koplik spots) consists of punctate white or gray lesions described as grains of sand on erythematous bases. As the infection evolves, the number of Koplik spots increases and lesions coalesce. These resolve with the onset of the rash. After about 4 days of increasing prodromal symptoms, the patient develops high fever and rash. The rash (Figure 19.1) begins as erythematous macules and papules at the hairline, on the forehead, behind the ears, and on the upper neck. This characteristic morbilliform rash occurs in the large majority of normal individuals. The rash spreads centrifugally to the trunk and extremities over the next 3 days. This erythematous rash blanches on pressure and may coalesce, and when it resolves, it may leave brownish hyperpigmentation that results from capillary hemorrhage. The rash may not occur at all, or could be severe in patients who are immunosuppressed. When present, the high fever and rash persist for 2 to 4 days. As the rash fades, the coryza and conjunctivitis clear, but the cough may persist for another 5 days. Immunocompetent patients are contagious from the onset of the prodrome until approximately 4 days after the onset of the rash.

The most common complications of measles are secondary bacterial infections, including pneumonia and otitis media. Diarrhea may also occur as a complication. The risk of complications is highest for infants younger than 1 year of age. Postinfectious encephalomyelitis occurs in approximately 1 per 1000 measles cases within a few days of rash onset. Most patients recover but many have persistent developmental sequelae. Acute disseminated encephalomyelitis (ADEM) is a demyelinating disease that occurs later, within 2 weeks of recovery. Also called postinfectious or postvaccine encephalomyelitis, ADEM may be related to an autoimmune response and carries a 10% to 20% mortality, with survivors commonly suffering neurologic sequelae. In contrast, subacute sclerosing panencephalitis (SSPE) occurs several years (classically 7–10) after natural infection, and carries a very high mortality. This complication has become exceedingly rare with the dramatic decrease in measles cases over the past few decades due to immunization.

Measles can be confirmed by viral cultures of the nasopharynx, conjunctiva, blood, or urine. However, culture is technically difficult and not readily available. Sera may be obtained for measles antibody determinations both at the onset of the rash and 2 to 4 weeks later. A significant increase of measles immunoglobulin (Ig)G antibody (acute and convalescent) is diagnostic. A measles-specific IgM antibody test is also available. This IgM antibody is detectable from about 3 to 30 days after the onset of the rash. Finally, isolation of measles virus RNA by polymerase chain reaction (PCR) from clinical specimens such as those listed above is diagnostic, but may only be available at state public health laboratories. Immunity after measles infection is lifelong, and a second attack is very rare.

Treatment and prevention

Treatment of measles is usually symptomatic; acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID) is used for pain and fever. Oral vitamin A supplementation lessens morbidity and mortality in malnourished patients. For reasons that are not well defined, malnourished patients may suffer acute vitamin A deficiency when infected with measles. Vitamin A is necessary for the maintenance of epithelial integrity and for normal immune function. The World Health Organization (WHO) now recommends treatment with vitamin A supplementation once a day for 2 days for all children with acute measles; specific doses vary with age (200 000 IU for children 12 months and older; 100 000 IU for infants 6 to 11 months; 50 000 IU for infants under

6 months). Because measles may be complicated by secondary bacterial infection, prophylactic antibiotics are sometimes prescribed, although not generally recommended. The most common bacterial complication is pneumonia caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Staphylococcus aureus*. Measles virus is susceptible in vitro to the antiviral agent ribavirin. However, ribavirin is not approved by the US Food and Drug Administration (FDA) for this indication. There are anecdotal reports of successful use of intravenous and/or aerosolized ribavirin to treat severely ill, immunosuppressed patients with measles.

Measles vaccine is routinely recommended at ages 12 to 15 months. This vaccine is a live attenuated strain grown in chick embryo cells. In infants, the efficacy of this vaccine is hindered by passive maternal antibody, which is no longer present by 12 months. If the mother is immune via natural infection, not immunization, then maternal antibody can persist in the infant until 15 months. A second measles vaccine dose is recommended at 5 to 12 years of age. In areas of high measles prevalence, vaccine is given at less than 1 year of age to protect this particularly vulnerable population. However, due to possible interference from maternal antibody, vaccine doses administered at younger than 1 year of age should not be counted towards vaccine requirements. Unimmunized children and adults should be given two measles doses at least 1 month apart. Following one measles vaccine dose, approximately 95% of patients will show a positive measles antibody response. This response rate increases to >99% following two doses.

Patients who are exposed to measles and have not been immunized may benefit from a measles vaccine if given within 72 hours of exposure. In addition, unimmunized patients susceptible to infection via close or household contact may receive immune globulin (IG; 0.25 mg/kg intramuscularly) within 6 days of exposure to prevent or minimize disease. Because measles inoculation is a live vaccine, it is not recommended for immunosuppressed patients (see Table 19.2 for contraindications). An exception to this rule is that vaccine should be administered to patients with well-controlled, stable human immunodeficiency virus (HIV) infection (with CD4 counts > 200 cells/mm^3) because of the potentially devastating outcome of measles in this group. Severe immunocompromise or a low CD4% (<15%) would, however, be a contraindication of the live vaccine. Ensuring immunization of close contacts may confer additional protection for these patients by decreasing their chances of exposure.

Table 19.2 Contraindications for measles vaccine

Pregnancy
Immunodeficiency except for well-controlled human immunodeficiency virus infection
History of anaphylaxis to eggs
History of anaphylaxis to neomycin

International travelers should be evaluated for measles immune status and risk. Infants traveling to developing countries where measles is endemic may receive the measles vaccine as early as 6 months of age. Adults born after 1957 who have inadequate or undocumented vaccine status may opt to have antibody testing to determine vaccination needs for travel.

RUBELLA (GERMAN MEASLES)

Epidemiology and virology

Rubella virus is an enveloped togavirus with a single strand of RNA at its core. Before the widespread availability of the rubella vaccine, the major danger posed by rubella virus was the specter of infection during pregnancy, which could cause congenital rubella syndrome in the newborn. With universal vaccination of children, the incidence of rubella in the United States has decreased by more than 99%. Since 2003, fewer than 15 cases have been reported per year. Rubella is no longer endemic in the United States; however, approximately 10% of US-born individuals remain susceptible despite vaccination. Women born outside the United States are less likely to have received immunization; therefore the risk of congenital rubella in the United States is the highest in infants born to those women.

Clinical and laboratory diagnosis

Rubella infection in infants and children is usually mild, and up to 50% of infections in children are asymptomatic. A prodrome characterized by tender posterior auricular, posterior cervical, and suboccipital adenopathy with malaise is common among adolescents and adults with rubella. The adenopathy may persist for weeks. The rubella exanthem begins on the face, neck, and scalp and spreads centrifugally to the trunk

and extremities. The rash may be associated with fever, headache, myalgias, and arthralgias. The rash consists of pink macules and papules that range in diameter from 1 to 4 mm. The exanthem fades as it spreads; thus it may be absent on the face when it is prominent on the trunk. The enanthem, Forchheimer's sign, occurs in 20% of patients and is characterized as petechiae or red spots on the soft palate. It occurs during the prodrome or at the onset of the exanthem. Rubella is most commonly seen during late winter and early spring.

Rubella is spread by small droplets from the respiratory mucosa. Patients are most contagious from a few days before until up to 7 days after the onset of rash. Viral shedding can occur for up to 14 days after the onset of rash. Prolonged exposure usually is necessary for transmission of rubella. The incubation period is 14 to 23 days.

Complications of rubella are unusual. The most common complication is arthritis, which occurs almost exclusively in females and has an increasing incidence with older age groups. Rare complications include thrombocytopenia and encephalitis. The most devastating complication is congenital rubella syndrome. The frequency of congenital rubella is 50% if rubella infection occurs during the first 12 weeks of pregnancy. This incidence diminishes to 25% for infections occurring from 13 to 24 weeks. Congenital rubella syndrome is rare if maternal infection occurs after 24 weeks' gestation. Congenital rubella syndrome is commonly characterized by deafness, congenital cataracts, and patent ductus arteriosus. Severe involvement is often fatal, and infection involves many organs, including the skin (described as a blueberry muffin because of bluish areas of extramedullary hematopoiesis).

Rubella can be diagnosed by the typical exanthem and associated posterior auricular adenopathy. Rubella virus can be isolated from nasal secretions, but most laboratories do not have the proper reagents needed for isolation. Acute and convalescent (2 to 4 weeks after rash) serology should show a 4-fold or greater rise in IgG antibodies. A rubella-specific IgM antibody test is also available, and is indicative of recent infection. The IgM antibody persists for several months after acute infection. False-positive IgM titers are associated with rheumatoid arthritis, parvovirus infection, and heterophile antibodies. Molecular diagnosis and typing using reverse transcriptase PCR may be useful in epidemic settings.

Table 19.3 Contraindications for rubella vaccine

Pregnancy
Immunodeficiency except well-controlled human immunodeficiency virus infection
Immunoglobulin in the last 3 months

Treatment and prevention

Typical rubella infection is mild and requires no therapy. The occasional patient with severe arthralgias or arthritis should respond to therapy with NSAIDs. Arthralgias and arthritis are much more common in females. The routine administration of IG after exposure is not recommended. However, the administration of intramuscular IG may be considered if a pregnant woman is exposed in early pregnancy.

Rubella vaccine should be given with measles and mumps vaccine (MMR) in the same two-dose schedule: the first dose at 12 to 15 months and the second at 5 to 12 years of age. Contraindications for rubella vaccine are listed in Table 19.3. Because rubella is a live vaccine and can potentially infect the fetus, it should not be given during pregnancy, although the risk of fetal infection is low. In a study of 226 susceptible women who were inadvertently immunized with rubella vaccine during the first trimester, there were no congenital abnormalities in the offspring and two offspring showed asymptomatic infection. This benign outcome may reflect the fact that this is an attenuated viral vaccine. Although immunocompromising states are relative contraindications to receipt of MMR vaccine, immunization should be considered in susceptible patients with well-controlled HIV infection (see Rubeola).

ROSEOLA (EXANTHEM SUBITUM)

Epidemiology and virology

Roseola is caused by human herpesvirus (HHV)-6. This is a double-stranded DNA herpesvirus, and as with others in this family, after initial infection, the virus becomes latent. Primary HHV-7 infection may also present as typical roseola, although many infections are asymptomatic.

At birth, passively acquired HHV-6 antibody usually is present in the newborn. This protects the infant until about 6 months of age. From 6 to 24 months of age, about 80% of infants become infected with HHV-6, and almost all children are seropositive by 4 years. Cases of roseola occur

throughout the year. The mode of transmission is unknown. It is unusual to demonstrate roseola spreading from one infant to another. After acute infection, HHV-6 can often be isolated from saliva. Saliva transmission from an asymptomatic contact to a susceptible infant may be the most common route of transmission. HHV-6 can also be isolated from both peripheral blood lymphocytes and cerebrospinal fluid.

First isolated in 1986, HHV-6 is a herpesvirus distinct from herpes simplex 1 and 2, varicella-zoster virus, cytomegalovirus, and Epstein–Barr virus. This was followed by the isolation of HHV-7 in 1990. HHV-6 may be divided into two major groups, variants A and B. Primary infection is almost always caused by variant B strains. In addition to causing roseola, HHV-6 causes a febrile illness without rash, a febrile illness with lymphadenopathy, gastroenteritis, upper respiratory infection, and inflamed ear drums; see Chapter 188, Human herpesvirus 6, 7, 8. Reactivation of HHV-6 infection in immunocompromised patients has myriad manifestations, including but not limited to rash, hepatitis, pneumonia, bone marrow involvement, and encephalitis.

Clinical and laboratory diagnosis

The incubation period of roseola is 9 to 10 days, and the disease has no prodrome. Clinical illness begins with a high fever (102°F to 105°F). Febrile seizures occur in a significant number of infected children. Roseola or other HHV-6-related illnesses account for at least 10% of visits to the emergency room for infants younger than 2. In addition, roseola accounts for 33% of febrile and recurrent febrile seizures seen in emergency rooms. The fever typically lasts 3 days. When the fever resolves, the exanthem usually appears, but it may also begin before the fever resolves. The exanthem is characterized by discrete, pale pink macules, varying in size from 1 to 5 mm in diameter. Around each lesion is a pale areola. The rash commonly begins on the trunk, on the neck, and behind the ears and spreads to the proximal extremities, and rarely involves the face or distal extremities. The rash may become confluent and usually lasts for 2 to 48 hours. Before the rash appears, an enanthem of erythematous macules may be present on the soft palate. Vertical transmission of HHV-6 occurs in 1% to 2% of births. The significance of vertical transmission of HHV-6 is unknown.

Acute HHV-6 infection may be diagnosed by seroconversion from HHV-6 antibody negative to HHV-6 positive. A specific IgM antibody peaks 7 to 14 days after the onset of illness and usually becomes undetectable in several weeks. However, HHV-6 IgM antibody may persist in some patients and, thus, may be present without acute infection. Specific IgG antibody develops 2 to 4 weeks after the onset of illness and remains detectable indefinitely. Also, the IgG antibody may intermittently rise and fall, especially in association with cytomegalovirus or Epstein–Barr virus infections. HHV-6 can be cultured from saliva and from mononuclear cells and viral DNA can be detected in blood and cerebrospinal fluid by PCR.

Treatment and prevention

At present, no treatment or prevention strategies are available for HHV-6 infection in normal children and adults. In immunosuppressed patients possible therapies include ganciclovir, foscarnet, and cidofovir (see Chapter 89, Infections in transplant recipients). Finally, as the mechanism of spread is not definitively known, only standard precautions are recommended for hospitalized patients.

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20. Skin ulcer and pyoderma

Joanne T. Maffei

Skin lesions are important clues to systemic diseases and, conversely, host factors make patients susceptible to skin infections caused by certain organisms. The skin has a limited response to insults from the microbial world, forming vesicles and pustules that eventually rupture and leave exposed dermis. Accurate diagnosis and appropriate treatment depend on a detailed history that includes systemic complaints, history of exposure and travel, and the initial appearance of the skin lesions. Sound diagnosis of difficult cases also depends on appropriate cultures and histopathology. When possible, cultures should be obtained by aspirating pus or blister fluid from under intact skin; cultures from ulcerated skin are less reliable because of colonization by nonpathogenic skin flora. A Gram stain and routine culture should be done first; if the ulcer persists despite a course of antibiotics, a skin biopsy with histopathology and cultures for routine agents, acid-fast organisms, and fungal pathogens is appropriate. If the lesion has multiple thin-walled vesicles with interspersed shallow ulcers and crusts or is on a mucous membrane, a direct fluorescent antibody (DFA) test for herpes and viral culture should be considered.

Most superficial skin infections and ulcers can be treated empirically according to the typical clinical presentation of the lesions. A workup is required for lesions that do not respond to routine therapy, that are rapidly progressive, or that occur in an immunocompromised host.

SKIN ULCERS

Skin ulcers are superficial defects in the tissues of the epidermis and dermis, with surrounding inflammation. Infection, collagen vascular diseases, and malignancy can cause cutaneous ulcerations. Information on host factors, exposure history, and the clinical course of the lesions is critical to narrowing the differential diagnosis. The lesion's anatomic location also may offer clues to the cause. Facial ulcers may be caused by syphilis, herpes, or blastomycosis, whereas ulcers of the arms or hands may be caused by sporotrichosis, nocardia, atypical mycobacteria, herpetic whitlow, or cutaneous anthrax. Ulcers on the chest wall from underlying pulmonary involvement, or associated with intravenous catheters may be caused by aspergillosis. Ulcers in the groin or perineum may result from sexually transmitted diseases such as syphilis, chancroid, and herpes, as well as from Behçet's disease or fixed drug eruption.

Ulcers on the lower extremities result from venous insufficiency in 70% to 90% of cases and occur below the knee but never on the bottom of the foot. The patient with venous stasis ulcers has good peripheral pulses and no peripheral neuropathy. Ulcers in patients with poor peripheral pulses, an ankle/brachial pressure index less than 0.9, or sensory loss must be investigated further because venous stasis is not the cause. Any ulcer on the leg that does not respond to treatment for venous stasis ulcers should be further investigated by biopsy and culture, as should any ulcer that is rapidly progressive or appears on an immunocompromised host. Figure 20.1 outlines the steps in evaluating and treating leg ulcers.

A history of unusual occupation, hobby, or exposure can suggest causes of skin ulcers such as tularemia in rabbit hunters, *Mycobacterium marinum* in aquarium enthusiasts, and leishmaniasis in travelers to endemic areas of the Middle East, North Africa, and Central and South America. Host factors also may predispose individuals to any of several types of ulcers. Patients with malignancies can be at risk for ecthyma gangrenosum caused by *Pseudomonas aeruginosa*, or dense neutrophilic infiltration of the dermis that is noninfectious but responds to steroids (Sweet's syndrome, discussed later). Ecthyma gangrenosum caused by *P. aeruginosa* is a rapidly progressive (12 to 24 hours), necrotic ulceration with hemorrhagic bullae and skin sloughing in the setting of gram-negative

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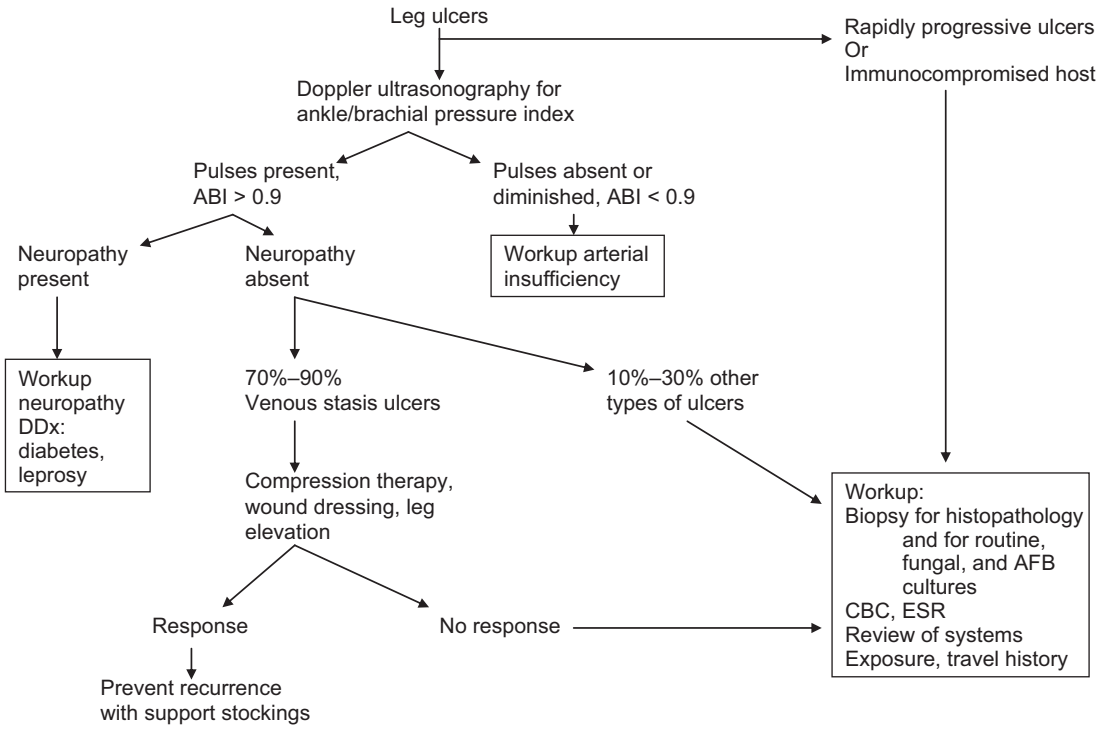

Figure 20.1 Algorithm for the evaluation of leg ulcers. ABI, ankle/brachial index; DDx, differential diagnosis; CBC, complete blood count; ESR, erythrocyte sedimentation rate; AFB, acid-fast bacilli.

sepsis and neutropenia. Empiric agents for ecthyma gangrenosum should include tobramycin plus piperacillin, ceftazidime, or imipenem.

Treatment of skin ulcers depends on the cause of the lesion. For venous stasis ulcers, local care with occlusive dressings on the wounds and compression bandages to aid venous return is necessary. If cellulitis or folliculitis is present, antibiotics to cover *Staphylococcus aureus* (including methicillin-resistant *S. aureus* [MRSA]), streptococci, and gram-negatives should be administered empirically pending cultures. After the ulcer has healed, compression stockings should be worn to prevent new ulcers. Therapy for other types of ulcers should address their cause; Table 20.1 outlines the clinical presentation and epidemiology of infectious ulcers.

Noninfectious ulcers

Noninfectious causes of cutaneous ulcers include drug reactions, collagen vascular diseases, and malignancy. Drugs reported to cause ulcerations include methotrexate, etretinate, and warfarin. Wegener's granulomatosis, a systemic disease with involvement of the respiratory tract and kidneys, can form necrotizing ulcerations of the skin. Biopsy of these lesions may be positive for leukocytoclastic vasculitis, granuloma, and inflammatory infiltrates. Serology for immunoglobulin G (IgG) antibodies against neutrophilic cytoplasmic components (c-ANCA) is highly specific for Wegener's granulomatosis. Treatment includes corticosteroids and cyclophosphamide. Behçet's disease is another systemic condition that involves recurrent oral and genital aphthous ulcerations, arthritis, and uveitis; in some cases it attacks the central nervous system. Treatment includes corticosteroids alone or in combination with colchicine, interferon-α, or azathioprine. Malignancy should always be considered as a possible cause of ulcers that have not responded to antimicrobial therapy because basal cell carcinoma, hematologic malignancies, and metastatic cancers may form skin ulcers.

PYODERMA

Pyoderma is a general term used to describe superficial disruption of the skin with pus formation in response to a bacterial infection. Generally caused by a single organism, pyoderma can be primary

Table 20.1 Clinical presentation of skin ulcers caused by infectious agents

Cause	Laboratory workup	Epidemiology	Clinical clues to diagnosis
Bacterial	Routine culture and Gram stain		
Bacillus anthracis (anthrax)	Gram (+) rod, biopsy for immunohistochemistry and PCR	Wool handler; Western Asia, West Africa, Eastern Europe; injection drug users (heroin); potential bioweapon	Lesions on face and arms; painless papule develops into vesicle that dries, forming black eschar that then separates from the base to form an ulcer with marked surrounding gelatinous edema; LN common; injectional anthrax – higher mortality and shock, significant edema
Corynebacterium diphtheriae (diphtheria)	Gram (+) rod	Tropical climates; rare in the United States	Ulcer with sharp margins and clean base; pre-existing skin lesions may become infected
Francisella tularensis (tularemia)	Gram (–) coccobacillus, serology	Rabbits, muskrats, beavers; North America, Japan, Europe, former Soviet Union; potential bioweapon	Systemic febrile illness; tender ulcer with painful LN
Nocardia spp.	Branching, beaded gram (+) rod, modified AFB (+)	Immunocompromised patients, soil exposure	Ulcer with purulent drainage, nodular lymphangitis
Pseudomonas aeruginosa (ecthyma gangrenosum)	Gram (–) rod, may have associated bacteremia	Neutropenic or immunocompromised patients	Rapidly progressive eruption from papules to hemorrhagic vesicles or bullae that undergo central necrosis and ulceration
Polymicrobial	Mixed gram (+), gram (–), and anaerobes	Debilitated, immunocompromised, diabetic patients	Pressure sores, decubitus ulcers, foot ulcers
Yersinia pestis (plague)	Gram (–) coccobacillus, bipolar-staining "safety pin" morphology, serology	Rodent zoonosis transmitted to humans via fleas; Far East, India, Africa, Central and South America, potential bioweapon	Bubonic plague with classic inguinal painful LN; may have skin lesions on lower extremities; pustule, papule, vesicle, or eschar may occur at inoculation site
Spirochetes			
Treponema pallidum (syphilis)	Serology	Sexually transmitted disease	Tertiary syphilis; nodular, ulceronodular, gummas; punched-out ulcer with gummy discharge
Fungal	Fungal smear, culture		
Aspergillus spp.	Septate hyphae; serum galactomannan assay in high risk patients	Immunocompromised, HIV positive	Ulcers, plaques, nodules, pustules; may be associated with trauma, intravenous catheter sites, secondary colonization of existing wounds, or direct extension from lung to chest wall
Blastomyces dermatitidis	Broad-based budding yeast, dimorphic fungus	Sugar cane worker, HIV positive, immunocompromised; North America, Africa	Subcutaneous nodule that enlarges and ulcerates, forming a crusted, verrucous plaque; may resemble squamous cell carcinoma
Coccidioides immitis	Dimorphic fungus, serology	Soil exposure, HIV positive; Southwestern United States, Northern Mexico, Central and South America	Usually single nodule or plaque; may form pustules, subcutaneous nodules, or abscesses
Cryptococcus neoformans	India ink, encapsulated yeast, mucicarmine (+) capsule, cryptococcal antigen (serum and CSF)	Exposure to pigeons, soil exposure, HIV positive, immunocompromised	Papule with crust resembling molluscum contagiosum; also forms ulcers on skin, mouth, and genitalia; may have lung or CNS involvement
Histoplasma capsulatum	Dimorphic fungus, histoplasma antigen (urine and serum)	Bats, birds, and soil exposure; HIV positive, immunocompromised; Eastern and Central United States in Ohio/Mississippi river valleys, Central	Papule with crust resembling molluscum contagiosum; ulcerative plaques and oral ulcerations

Table 20.1 *(continued)*

Cause	Laboratory workup	Epidemiology	Clinical clues to diagnosis
		and South America, West Indies, Africa, Madagascar	
Sporothrix schenckii	Dimorphic fungus	Rose gardening, soil exposure	Papule or pustule at inoculation site develops into subcutaneous nodules or ragged-edged ulcer with proximal nodular lymphangitis; usually on upper extremities
Mycobacterial	AFB smear, culture		
Mycobacterium marinum	AFB (+), growth at 30–32°C	Water, aquarium enthusiasts	Ulcer with thin seropurulent drainage, nodular lymphangitis
Mycobacterium ulcerans (Buruli ulcer)	AFB (+), PCR for the insertion sequence IS*2404* and IS*2606* in swabs or tissue samples	Africa, Australia, South East Asia, South America, North America (Mexico); 2- to 3-month incubation period, usually associated with trauma	Subcutaneous nodule that ulcerates with extensive scarring and contracture formation; edematous lesion rapidly progresses to extensive ulceration, may have osteomyelitis contiguous to ulcer
Mycobacterium avium complex	AFB (+)	HIV positive, immunocompromised; soil, water	Multiple subcutaneous nodules or ulcers; may be associated with cervical lymphadenitis drainage to skin, or direct inoculation
Mycobacterium haemophilum	AFB (+), requires iron-supplemented culture medium and incubation at 30–32°C	Australia, United States, Canada, France, Germany, Singapore; HIV positive, transplantation	Papules develop into pustules which form deep ulcers, usually on extremities overlying joints; may have septic arthritis +/– osteomyelitis, may have LN
Mycobacterium tuberculosis	AFB (+), PPD or interferon-γ release assay helpful if positive	Worldwide	Nodules or ulcers especially in HIV-positive patients, scrofuloderma, plaques
Viral			
Herpes simplex	DFA, viral culture	Sexually transmitted disease	Oral, perineal, genital ulcers; whitlow on hands; lesions with thin-walled vesicles; shallow painful ulcers
Parasitic			
Leishmaniasis	Punch biopsy, aspirates, or scrapings of skin for culture, histopathology and touch prep using Wright's and Giemsa stains looking for amastigotes at base of lesion; serology; PCR of tissue aspirates or peripheral blood	Sandfly bites, travel to endemic area (military or civilian); incubation period weeks to months	Papule at the site of insect bite enlarges to form a nodule, which then develops into a punched-out ulcer; may have associated LN; rarely nodules form without ulceration; may involve nasal or oral mucosa
Old World *L. major* *L. tropica* *L. (L.) aethiopica*		Mediterranean, Middle East, Africa, Southern Asia, India	
New World *L. mexicana* complex *Viannia* subgenus: *L. (V.) braziliensis* *L. (V.) panamensis* *L. (V.) guanensis* *L. (V.) peruviana*		Latin America, Central and South America	

Abbreviations: LN = lymphadenopathy; Gram (+) = gram-positive; Gram (–) = gram-negative; AFB = acid-fast bacilli; CNS = central nervous system; DFA = direct fluorescent antibodies; PCR = polymerase chain reaction; PPD = purified protein derivative; CSF = cerebrospinal fluid.

or secondary. Similar lesions can be produced by neutrophilic dermatoses such as pyoderma gangrenosum and Sweet's syndrome. Table 20.2 outlines the clinical presentation of pyoderma and suggested treatment.

Primary pyoderma

Primary pyoderma is an infection of previously healthy skin, usually caused by *S. aureus* or *Streptococcus pyogenes*.

IMPETIGO

Impetigo is a superficial infection of the skin involving only the epidermis (see Figure 20.2). Impetigo is highly contagious and usually occurs in young children following minor skin trauma. Nonbullous impetigo, the classic honey-colored crusts on the face or extremities, is caused by *S. pyogenes* or *S. aureus*; toxin-producing strains of *S. aureus* cause bullous impetigo (varnish-like crust). Treatment of bullous and nonbullous impetigo requires coverage of methicillin-sensitive *S. aureus* (MSSA): dicloxacillin 500 mg orally every 6 hours, or first-generation cephalosporins such as cephalexin 500 mg orally every 6 hours for 7 days; (note – the oral cephalosporins cefixime, and ceftibuten have no activity against MSSA). For penicillin-allergic patients, clindamycin 300 to 450 mg orally every 6 hours or clarithromycin 500 mg orally every 12 hours is appropriate. Because most areas have seen the emergence of community-acquired MRSA, empiric therapy targeting MRSA with trimethoprim–sulfamethoxazole, one to two double-strength tablets orally every 12 hours, or minocycline 100 mg orally every 12 hours is warranted. Topical mupirocin ointment 2% applied to the lesion three times daily for 7 to 12 days is an equally effective alternative to systemic therapy. Topical retapamulin ointment 1% applied to the lesion twice a day for 5 days is an option for MSSA lesions (not for MRSA).

ECTHYMA

Ecthyma (Figure 20.3) is impetigo that extends through the epidermis, forming shallow ulcers with crusts. It occurs in immunocompromised patients and is caused by *S. pyogenes* or *S. aureus*. Gram stain and culture of the lesion must be performed to rule out MRSA or ecthyma gangrenosum, which is caused by *P. aeruginosa* sepsis. Treatment of ecthyma due to streptococci or staphylococci is the same as that for impetigo, but duration of therapy may be longer. Unlike impetigo, ecthyma may heal with scarring.

FOLLICULITIS

Folliculitis is an inflammation of the hair follicles, usually caused by *S. aureus*. Topical therapy with mupirocin three times daily for 7 days is usually adequate. If the infection does not respond, oral therapy with agents used for impetigo should be adequate. Lesions that do not respond to antistaphylococcal antibiotics should be cultured because they may be caused by MRSA or other pathogens. Therapy should be tailored to antimicrobial sensitivities. On rare occasions, gram-negative organisms cause folliculitis, typically in association with either superinfection in patients taking long-term antibiotics for acne vulgaris or hot-tub bathing. Gram-negative folliculitis in acne patients is caused by *Klebsiella, Enterobacter,* and *Proteus* species and usually occurs on the face. Treatment depends on susceptibilities, but ampicillin–clavulanate or trimethoprim–sulfamethoxazole may be used empirically. Hot-tub folliculitis caused by *P. aeruginosa* is usually self-limiting in a normal host, and no action is necessary beyond decontaminating the water and ensuring proper chlorination.

FURUNCLES AND CARBUNCLES

Furuncles are skin abscesses caused by *S. aureus*; they may begin as folliculitis that extends into the surrounding dermis and subcutaneous tissue. Carbuncles comprise several furuncles that coalesce to form loculated abscesses with draining pus. If the patient is afebrile and the abscess is less than 5 cm in diameter, incision and drainage and warm compresses without oral antimicrobials should suffice. If the patient is febrile, or if the lesion is greater than 5 cm, oral antistaphylococcal antibiotics targeting MRSA should be prescribed in addition to careful incision and drainage of the abscess. In either case, cultures of the abscess should be obtained to guide therapy in the event there is no response to the initial treatment. Some patients with recurrent furuncles and carbuncles may require elimination of nasal *S. aureus* carriage with nasal applications of mupirocin, bathing with chlorhexidine, and either oral rifampin plus doxycycline, or rifampin plus trimethoprim–sulfamethoxazole.

Neutrophilic dermatoses

Pyoderma caused by neutrophilic infiltrates usually is associated with underlying disease such as cancer or inflammatory bowel disease (IBD). The main entities are pyoderma gangrenosum and Sweet's syndrome.

Table 20.2 Clinical presentation and therapy of pyoderma

Type of disease	Distinguishing features	Causative organism	Treatment
Primary pyoderma			
Impetigo Nonbullous impetigo Bullous impetigo	Superficial honey-colored crusts Thin vesicles and bullae, when ruptured produce varnish-like crust	*Streptococcus pyogenes, Staphylococcus aureus* Toxin-producing strains of *S. aureus* (rare *Streptococcus pyogenes*)	For MSSA: Ampicillin–clavulanate 875 mg PO q12h or Dicloxacillin 500 mg PO q6h or Cephalexin 500 mg PO q6h *(Not cefixime)* or Clindamycin 300–450 mg PO q6h or Clarithromycin 500 mg PO BID or Mupirocin ointment 2% topically TID or Retapamulin ointment 1% topically BID (note - for MSSA lesions only, not MRSA) For MRSA: Mupirocin ointment 2% topically TID or Minocycline 100 mg PO BID or Trimethoprim–sulfamethoxazole (TMP–SMX) 1–2 double-strength tablets (TMP 160 mg) PO BID or Clindamycin 300–450 mg PO q6h
Ecthyma	Ulcer with crust	*Streptococcus pyogenes*, *S. aureus*	Treat as impetigo with oral agents, may need longer duration of therapy
Folliculitis	Hair follicle with pustules, erythema	*S. aureus*	*Topical*: Clindamycin or Erythromycin or Mupirocin or Benzoyl peroxide lotion *Unresponsive:* Treat as impetigo
Gram-negative folliculitis	Usually on face in patients with acne vulgaris on chronic suppressive antibiotic therapy	*Klebsiella, Enterobacter, Proteus* species	Ampicillin–clavulanate 875 mg PO q12h or TMP–SMX one double-strength tablet (TMP 160 mg) PO BID
Hot-tub folliculitis	Pustules and vesicles on an erythematous base in bathing-suit distribution	*Pseudomonas aeruginosa*	Self-limited in normal hosts; decontaminate and chlorinate hot tub
Furuncle/carbuncle	Abscess formation in dermis, subcutaneous tissue that may coalesce and drain; if cellulitis or sepsis associated, needs intravenous antibiotics; patients may have recurrences; suggest culture to rule out MRSA or gram-negative organisms	*S. aureus* both MSSA and MRSA, now many community-acquired strains are MRSA	Careful incision and drainage, and warm compresses; for lesions over 5 cm and patients with fever, add antistaphylococcal antibiotics targeting MRSA including: TMP–SMX 1–2 double-strength (TMP 160 mg) PO BID +/– Rifampin 300 mg PO BID or Minocycline 100 mg PO BID If associated with cellulitis or sepsis:

Type of disease	Distinguishing features	Causative organism	Treatment
			Vancomycin 1 g IV q12h or Daptomycin 4 mg/kg IV q24h (dosed for skin/soft tissue only, not bacteremia) If recurrent, eradicate nasal carriage of *S. aureus* by: Chlorhexidine 2% daily wash with mupirocin (topical 2%) intranasally BID × 7 days Along with either: Rifampin 300 mg PO BID plus doxycycline 100 mg PO BID × 7 days or Rifampin 300 mg PO BID plus TMP–SMX 1 tab PO BID × 7 days
Neutrophilic dermatoses			
Pyoderma gangrenosum	Rapidly progressive painful ulcers, ragged violaceous edges with necrotic centers, usually on lower legs; Underlying IBD, malignancy, arthritis, monoclonal gammopathy *Biopsy:* PMN, lymphocytic infiltration, +/– vasculitis	No organisms seen, culture negative	Methylprednisolone 0.5–1 mg/kg/d (+/– cyclosporine) or Cyclosporine 5 mg/kg/day (+/– methylprednisolone) For PG associated with Crohn's disease: Infliximab Other agents used include: mycophenolate mofetil, clofazimine, azathioprine, methotrexate, tacrolimus, thalidomide, dapsone (contraindicated in G6PD-deficient patients) Localized PG: topical or intralesional corticosteroids, or tacrolimus ointment
Sweet's syndrome	Fever, neutrophilia, prompt response to steroids, painful erythematous plaques, may form bullae and ulcerate; located on head, neck, arms; 20% have associated malignancy, usually AML, elevated sedimentation rate *Biposy*: dense PMN infiltration of the dermis, no vasculitis	No organisms seen, culture negative	Prednisone 1 mg/kg/d, slow taper over 4–6 wk; dramatic response or Potassium iodide or Colchicine If steroids contraindicated, may use indomethacin, clofazimine, cyclosporine, dapsone
Secondary pyoderma	Pre-existing lesions of dermatitis such as eczema, psoriasis, or surgical/traumatic wounds		Based on culture data. Note increasing rates of community-acquired MRSA

Abbreviations: AML = acute myelogenous leukemia; G6PD = glucose-6-phosphate dehydrogenase; IBD = inflammatory bowel disease; MSSA = methicillin-sensitive *S. aureus*; MRSA = methicillin-resistant *S. aureus*; PG = pyoderma gangrenosum; PMN = polymorphonuclear leukocytes.

PYODERMA GANGRENOSUM

The diagnosis of pyoderma gangrenosum is clinical. The lesion begins as a small erythematous papule, rapidly progressing to tender pustules that undergo central necrosis and ulceration. The border of the ulcers is ragged, violaceous, and surrounded by erythema. Distinguishing characteristics include severe pain at the ulcer site, lesions at the site of minor trauma, parchment scarring, and an associated systemic disease such as IBD, rheumatologic disease, or malignancy. Biopsy of the lesions is done to exclude infection, vasculitis, malignancy, and vascular occlusive disease because histopathologic findings are nonspecific. Central necrosis and lymphocytic and neutrophilic infiltrates with or without vasculitic changes are seen on histopathology of pyoderma gangrenosum lesions;

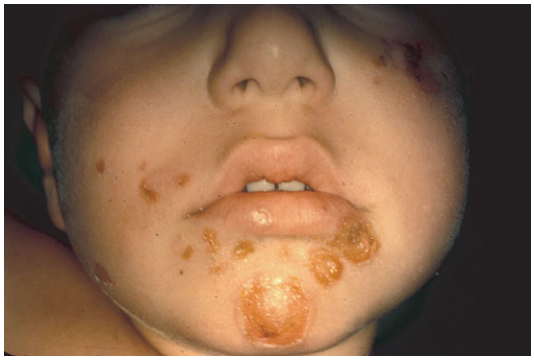

Figure 20.2 Impetigo. This is a superficial streptococcal or staphylococcal infection that occurs just beneath the stratum corneum. It generally occurs in the paranasal or perioral area in young people. Note typical honey-colored crusts, which heal without scarring. (Reproduced with permission from Sanders CV, Nesbitt LT, eds. *The Skin and Infection: A Color Atlas and Text*. Baltimore: Williams & Wilkins; 1995: page 35.)

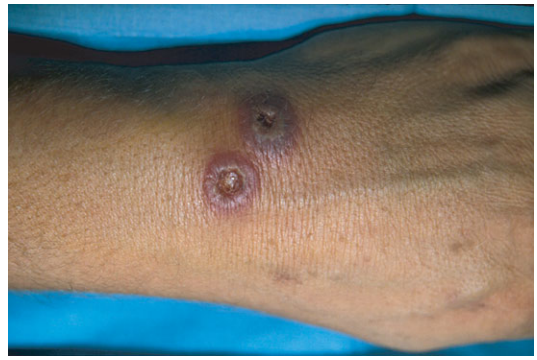

Figure 20.3 Ecthyma. This is a more serious form of impetigo in which the infection penetrates to the dermis. Scarring is common. (Reproduced with permission from Dr. Charles V. Sanders from Sanders CV, Nesbitt LT, eds. *The Skin and Infection: A Color Atlas and Text*. Baltimore: Williams & Wilkins; 1995: page 35.)

lymphocytes and plasma cells around vessels are common findings. Pyoderma gangrenosum usually occurs on the lower extremities over bony prominences, where repeated trauma aggravates the condition (pathergy); its cause is unknown. Treatment for disseminated pyoderma gangrenosum includes methylprednisolone 0.5–1 mg/kg by mouth daily or cyclosporine 5 mg/kg/day given separately or together. For pyoderma gangrenosum associated with Crohn's disease, the tumor necrosis factor-α inhibitor infliximab is recommended as first-line therapy. Mycophenolate mofetil, clofazimine, azathioprine, methotrexate, tacrolimus, thalidomide, dapsone, and many other drugs and modalities have been used to treat pyoderma gangrenosum; response to therapy varies.

SWEET'S SYNDROME

Sweet's syndrome is an acute febrile neutrophilic dermatosis that may be associated with a malignancy, infection (upper respiratory or gastrointestinal), inflammatory bowel disease, pregnancy, medications, or vaccinations (BCG and influenza), or is idiopathic. Lesions are painful erythematous plaques usually on the upper extremities, head, and neck. These lesions are classically associated with fever and neutrophilia, but some patients have myalgia, arthralgia, proteinuria, and conjunctivitis. Nearly all patients with Sweet's syndrome have an elevated erythrocyte sedimentation rate. Dense neutrophilic infiltration of the dermis without vasculitis is the classic finding on biopsy, and it is important to exclude bacteria, mycobacteria, and fungi, because steroids are the appropriate therapy for Sweet's syndrome. The response to prednisone 1 mg/kg/day is dramatic; constitutional symptoms improve within hours, and skin lesions improve over 1 to 2 days. Steroids should be tapered slowly over 4 to 6 weeks. Other first-line agents used to treat Sweet's syndrome include potassium iodide or colchicine. If steroids are contraindicated, alternative treatments include clofazimine, indomethacin, cyclosporine, and dapsone.

Secondary pyoderma

Secondary pyoderma is a bacterial superinfection of skin previously disrupted by trauma, surgery, or chronic skin conditions such as eczema or psoriasis. The usual organism is *S. aureus,* which can be methicillin-resistant whether community acquired or healthcare associated. Empiric treatment for serious wound infections is intravenous vancomycin pending culture results. Mild to moderate infections can be treated with oral trimethoprim–sulfamethoxazole (+/− rifampin) or minocycline. Secondary pyoderma caused by pressure sores and diabetic foot ulcers is usually polymicrobial and requires broad-spectrum therapy with piperacillin–tazobactam, imipenem, or a combination of ciprofloxacin and clindamycin. Table 20.2 summarizes suggested therapy for pyoderma.

Herpetic whitlow

Herpetic whitlow, a herpes simplex infection of the pulp of the finger, may occur in anyone who has mucocutaneous herpes or who comes in contact with herpetic lesions (i.e., healthcare workers). The initial lesion is a tender vesicle filled with turbid fluid. Lesions may be multiple and may ulcerate and become secondarily infected, developing purulent drainage. Axillary and epitrochlear lymphadenopathy with erythema of the proximal forearm also may occur. Diagnosis can be made by aspirating a vesicle and sending the fluid for viral culture, or performing a DFA test on the blister fluid. Treatment includes acyclovir, and surgery should be avoided.

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21. Cellulitis and erysipelas

Alok Vij and Kenneth J. Tomecki

Skin and soft-tissue infections (SSTIs) are routinely encountered by physicians in the outpatient and inpatient settings and vary in clinical presentation and severity. Erysipelas is a superficial SSTI involving the upper dermis and superficial lymphatics; cellulitis is a deeper infection of the deep dermis and subcutaneous tissues.

ERYSIPELAS

Clinical manifestations

Erysipelas is a superficial SSTI with a distinct clinical presentation. The legs are the most commonly affected sites, but erysipelas can occur anywhere on the body. Young, elderly, and immunocompromised patients are particularly susceptible to erysipelas, especially in the setting of venous insufficiency, lymphedema, obesity, or any epidermal defect that impairs barrier function (e.g., ulcers, operative or traumatic wounds, fissures). Erysipelas is more common in older women and young men.

Erysipelas classically presents as a tender, sharply demarcated, bright-red edematous plaque with a raised, indurated advancing border (Figure 21.1). Abrupt onset of fever, chills, and malaise may precede skin disease by a few hours to a day. Some patients have associated regional lymphadenopathy with or without lymphatic streaking, in addition to edema with possible bullae formation.

Because erysipelas can produce lymphatic obstruction, it tends to recur in areas of earlier infection. Such recurrences are the most common complication, occurring in approximately 30% of cases. Other complications, including progression to cellulitis or sepsis, are uncommon and are usually restricted to patients with significant comorbid conditions.

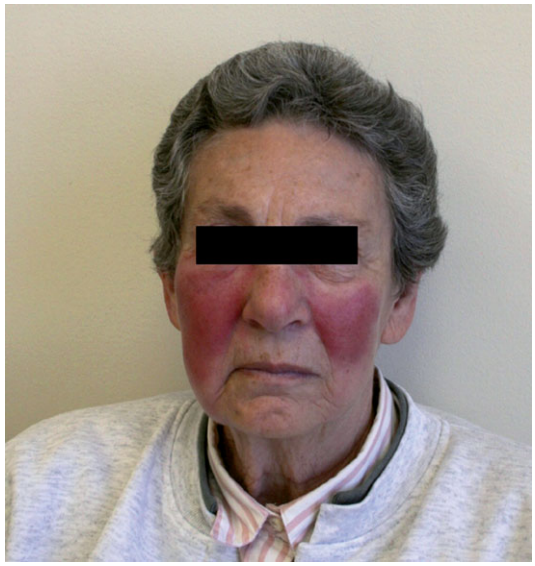

Figure 21.1 Bilateral facial erysipelas. Note discrete, raised edge of erythema.

Microbiology

Most cases of erysipelas are caused by β-hemolytic group A streptococci (GAS), including *Streptococcus pyogenes*. Less often, groups C, D, and G streptococci are the causative organisms in adults. Group B streptococcus is often the cause of erysipelas in newborns and postpartum women. Bullae formation may indicate primary or secondary infection with *Staphylococcus aureus*, including strains of methicillin-resistant *S. aureus* (MRSA). Infrequent causative agents include *Pneumococcus* species, *Klebsiella pneumoniae*, *Yersinia enterocolitica*, and nontypeable *Haemophilus influenzae*.

Diagnosis and differential diagnosis

Characteristic skin disease usually suggests the diagnosis. Swabs for Gram stain and culture from a suspected portal of entry may be helpful but are usually not necessary. Skin biopsy for tissue culture and the injection-reaspiration method of tissue fluid collection both yield poor results and

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have little diagnostic value. Blood cultures are positive in only 5% of patients. Routine lab tests are usually unrevealing, but some patients will have leukocytosis.

Differential diagnosis, especially for patients with facial erysipelas, includes allergic or photosensitive contact dermatitis, but fever, pain, and leukocytosis do not occur. Autoimmune diseases, including systemic lupus erythematosus and dermatomyositis, often exhibit facial rash and fever, but they evolve slowly, have other clinical findings, and are typically bilateral, less sharply demarcated, and lack intense erythema. Other diagnostic considerations include erythema infectiosum, Sweet's syndrome, angioedema, and erysipeloid.

CELLULITIS

Clinical manifestations

Cellulitis is an infectious inflammation of the deep dermis with variable extension into the subcutaneous tissues. Clinically, cellulitis typically presents as an ill-defined, erythematous firm plaque occurring in conjunction with the four cardinal signs of inflammation: rubor, calor, dolor, and tumor (Figure 21.2). Affected patients often have associated fever, chills, and malaise. Severe disease and signs of clinical toxicity mandate a search for systemic infection.

In healthy patients, antecedent trauma often produces a defect in the skin barrier leading to cellulitis, in contrast to a bloodborne route in immunocompromised patients. If the leg is affected, interdigital tinea pedis is often the portal of entry. Other predisposing factors include peripheral vascular disease, alcoholism, intravenous drug abuse, malignancy, diabetes, or a concomitant skin disease such as stasis dermatitis or ulceration of any type.

Fever, lymphangitis, regional lymphadenopathy, focal abscess formation, and bullae may accompany cellulitis. In addition, necrosis of the skin and subcutaneous tissues may be a complication. Sepsis is a more common complication in children or immunocompromised adults. If the causative organism is GAS, cellulitis may lead to acute glomerulonephritis and a streptococcal toxic shock-like syndrome.

Microbiology

Streptococcus pyogenes and *S. aureus*, including MRSA, are the most frequent causes of cellulitis.

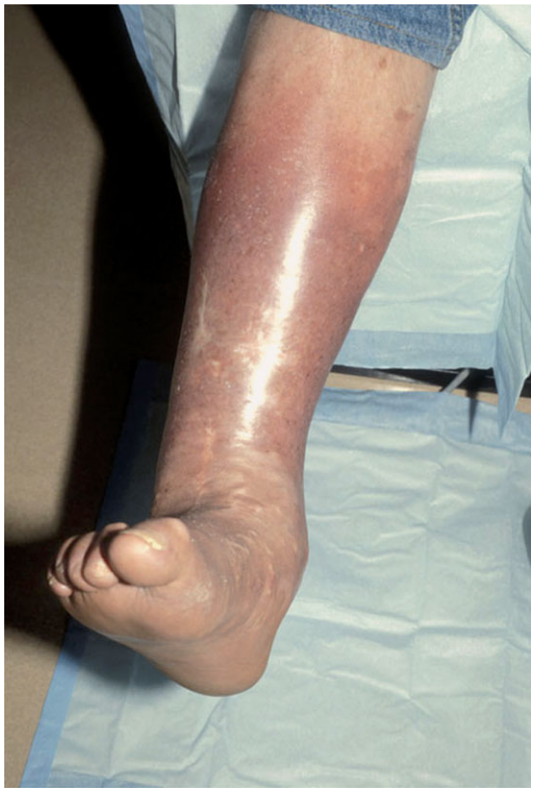

Figure 21.2 Right leg cellulitis. Note irregular margin.

Infection with MRSA typically presents with purulence, either primary or secondary. Other specific causes of cellulitis should be considered in particular clinical situations or because of certain patient exposures; these are listed in Table 21.1.

Diagnosis and differential diagnosis

Clinical presentation should suggest the diagnosis, but a positive culture is confirmatory and serves to guide therapy. Swabs from exudate, erosions, ulcerations, abscesses, and surgical wounds, as well as tissue biopsy for culture, have a high yield, more so than aspirate or blood cultures. Additional laboratory studies, including complete blood count, anti-DNase antibody, antistreptolysin titer, and blood cultures, can be performed but are neither sensitive nor specific.

Imaging studies may be helpful. Conventional radiography can delineate pockets of gas in anaerobic, especially clostridial, cellulitis. Magnetic resonance imaging (MRI) can also aid in the diagnosis of SSTI. T2-weighted images best

Table 21.1 Likely causes of cellulitis related to specific clinical situations or exposures

Type/scenario	Likely organism
Postsurgical cellulitis	*Staphylococcus aureus*
Perianal cellulitis	Group A streptococcus
Preseptal cellulitis	*S. aureus, S. pyogenes*
Orbital cellulitis	*S. aureus, Streptococcus pneumoniae*
Facial cellulitis	*Haemophilus influenzae*[a]
Neonatal cellulitis	Group B streptococcus
Crepitant cellulitis	*Clostridium* species
Salt water exposure	*Vibrio vulnificus*
Freshwater exposure	*Aeromonas hydrophilia*
Hot-tub exposure	*Pseudomonas aeruginosa*
Soil exposure	*Clostridium* species
Dog/cat bite	*Pasteurella multocida, Capnocytophaga canimorsus*
Human bite	*Eikenella corrodens*
Immunocompromised	Often mixed infection with gram-negative organisms, fungi
Nosocomial	*Pseudomonas*
Handling of raw poultry, meat	*Erysipelothrix rhusiopathiae*
Handling of raw fish	*Streptococcus iniae, Erysipelothrix rhusiopathiae*
Intravenous drug use	*S. aureus*

[a] Less common since advent of vaccine

highlight the disease process. Cellulitis of the periocular soft tissue warrants ophthalmologic evaluation to differentiate preseptal SSTI from orbital cellulitis, a medical emergency. Computed tomography (CT) can quickly differentiate these two entities.

The differential diagnosis of cellulitis, especially if localized to the lower extremity, includes other inflammatory diseases such as stasis dermatitis, superficial thrombophlebitis, lipodermatosclerosis, vasculitis, and deep venous thrombosis.

THERAPY

In addition to systemic antimicrobial therapy, local measures including immobilization and elevation of the affected area are important adjuvant therapies in SSTIs. Skin hydration is paramount to improve barrier function. Treatment should be directed at both the infectious disease and the noninfectious comorbidities. If fluctuance is present, moist heat may help localize infection. All abscesses require incision and drainage with culture.

Table 21.2 Oral antimicrobial therapeutic options for the treatment of uncomplicated SSTIs

Class	Medication	Adult dosage
Penicillins[a]	Penicillin V	500 mg q6–12h
	Amoxicillin	500 mg q8h
	Amoxicillin/ clavulanate	875/125 mg q12h
	Dicloxacillin	500 mg q6–12h
Cephalosporins	Cephalexin[b]	500 mg q6–12h
	Cefaclor[c]	250–500 mg q8h
	Cefuroxime[c]	250–500 mg q12h
	Cefprozil[c]	250 mg q12h
	Cefdinir[d]	300 mg q12h
	Cefpodoxime[d]	400 mg q12h
Macrolides	Erythromycin	500 mg q6–12h
	Azithromycin	500 mg on day 1, then 250 mg daily days 2–5
	Clarithromycin	500 mg daily–q12h
Tetracyclines	Tetracycline	500 mg q6–12h
	Doxycycline	100 mg q12h
	Minocycline	100 mg q12h
Lincosamide	Clindamycin	300 mg q6–12h
Fluoroquinolones	Ciprofloxacin	500 mg q12h
	Levofloxacin	500 mg daily
Other	Trimethoprim–sulfamethoxazole	160/800 mg (DS) q12h

All treatment for 7 to 14 days unless otherwise specified.
[a] Adjustment in dosages required for renal impairment.
[b] First generation.
[c] Second generation.
[d] Extended spectrum.
Abbreviation: SSTIs = skin and soft-tissue infections.

Systemic antimicrobial therapy is the treatment of SSTIs, and many appropriate choices exist for uncomplicated cases (Table 21.2). Being familiar with particular patient populations and regional variations in bacterial susceptibility patterns is critical in selecting appropriate antimicrobial therapy, as is differentiating purulent from nonpurulent cellulitis. If standard therapy fails, a resistant or less common organism (Table 21.3) may be the causative agent. Treatment failure has been linked to both inappropriate antibiotic selection and insufficient antibiotic dosing.

For both erysipelas and nonpurulent cellulitis, empiric therapy should target *S. pyogenes* and

Table 21.3 Recommended antimicrobial therapies for specific organisms

Organism	First-line therapy	Alternative therapies
Aeromonas hydrophila	Fluoroquinolone	TMP–SMX
Clostridium perfringens	Piperacillin–tazobactam + clindamycin	Levofloxacin + metronidazole
Eikenella corrodens	Ampicillin/sulbactam	Levofloxacin + metronidazole
Erysipelothrix rhusiopathiae	Penicillin G, ampicillin	Fluoroquinolone
Haemophilus influenzae	Amoxicillin, ceftriaxone	Azithromycin, fluoroquinolone
Pasteurella multocida	Ampicillin, amoxicillin	Doxycycline, TMP–SMX
Staphylococcus aureus	Dicloxacillin, oxacillin, nafcillin	Clindamycin, macrolide
MRSA	Vancomycin, TMP–SMX, doxycycline	Linezolid, daptomycin, tigecycline
Streptococcus pyogenes	Penicillin V, amoxicillin	Other β-lactams, macrolide
Vibrio vulnificus	Doxycycline + ceftazidime	Cefotaxime, fluoroquinolone

S. aureus. Empiric therapy for purulent cellulitis should be directed against MRSA. Penicillins or other β-lactam antibiotics, including first- and second-generation cephalosporins, are typically considered the treatment of choice for uncomplicated SSTIs. For penicillin-allergic patients, alternate therapies include either a cephalosporin if the penicillin allergy is not type I (immunoglobulin E [IgE]-mediated immediate hypersensitivity), a tetracycline, or trimethoprim–sulfamethoxazole.

Tetracycline antibiotics, including tetracycline, minocycline, and doxycycline, are effective in treating uncomplicated SSTIs, with satisfactory coverage of common causative organisms and MRSA. Trimethoprim–sulfamethoxazole is another reasonable choice for SSTIs, especially if infection with MRSA is suspected. Fluoroquinolones have demonstrated efficacy similar to β-lactam antibiotics, but increasing resistance has limited their use as an alternative therapy.

Clindamycin, a lincosamide, has good activity against *S. pyogenes* in addition to methicillin-susceptible *S. aureus* (MSSA) and MRSA, although inducible resistance to clindamycin has become a concern. Resistance to erythromycin indicates the possibility of inducible resistance to clindamycin, which can be screened for in the laboratory by the D test.

Some experts favor empiric combination therapy to optimally cover both MRSA and streptococci, e.g., with trimethoprim–sulfamethoxazole plus a first-generation cephalosporin.

Hospitalization for intravenous antimicrobial therapy and supportive care is warranted for neonates, immunocompromised patients, patients with extensive skin disease with or without signs of sepsis, patients with systemic symptoms, patients who have failed appropriate initial therapy or are rapidly progressing, and when necrosis is present. Vancomycin is typically considered the treatment of choice in this setting, especially with MRSA infection. Polymicrobial infection should be suspected in immunocompromised patients and broader coverage for gram-negative organisms is warranted. In such cases, combined treatment with vancomycin plus either an extended-spectrum antipseudomonal penicillin, an extended-spectrum cephalosporin, or clindamycin plus a fluoroquinolone, is appropriate.

If tissue necrosis is present, immediate surgical evaluation is required. Early and complete surgical debridement extending beyond the areas of necrosis to reach healthy tissue is necessary. Indicators of deep infection requiring debridement include gangrenous changes, severe pain or anesthetic skin, crepitus, poor response to antibiotic therapy, or abscess formation with multiple sinus tracts (see Chapter 22, Deep soft-tissue infections: necrotizing fasciitis and gas gangrene).

Although not recommended for first-line therapy, other appropriate medications that can be used in the hospital setting if vancomycin allergy is present or vancomycin-resistant organisms are confirmed include linezolid, daptomycin, or tigecycline (Table 21.4).

Linezolid is approved for the treatment of complicated SSTIs due to MRSA and other drug-resistant gram-positive organisms. The ability to convert from intravenous to oral therapy makes this an attractive option. Daptomycin, a cyclic lipopeptide, is bactericidal against gram-positive bacteria, including MRSA. Tigecycline offers broader coverage, including gram-positive, gram-negative, anaerobic, and multidrug-resistant organisms, and is approved for the treatment of complicated SSTIs. Dalbavancin was recently approved for once-weekly

Table 21.4 Intravenous dosing regimens for complicated SSTIs

Medication	Adult dosage
Vancomycin[a]	1 g q12h
Piperacillin–tazobactam[a]	3.375 g q6h
Clindamycin	600 mg q8h
Linezolid[b]	600 mg q12h
Daptomycin[b]	4 mg/kg q24h
Tigecycline[c]	50 mg q12h after 100-mg loading dose

[a] Adjustment in dosage interval required for renal impairment.
[b] Same dose for oral conversion.
[c] Adjustment in dosage required for severe hepatic impairment.
Abbreviation: skin and soft-tissue infections = SSTIs.

treatment of acute bacterial SSTIs caused by gram-positive pathogens, including MRSA.

Recurrence is especially common in patients with SSTIs of the legs who have impaired circulation. In such instances, continuous antimicrobial prophylaxis may be necessary, coupled with weight reduction, support stockings to reduce edema, and good skin hygiene with emollients and possibly topical antifungal therapy.

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22. Deep soft-tissue infections: necrotizing fasciitis and gas gangrene

Stephen Ash and Louis E. Kennedy

Necrotizing fasciitis (NF) and gas gangrene (GG) are serious infections of the deep soft tissue. They both carry a high morbidity and mortality. Early diagnosis and treatment is important and is the key to improving outcome. Broadly speaking, NF is an infection primarily of the fascia and deep soft tissue of the skin, whereas GG is usually an infection of the skeletal muscle.

The incidence of NF in the western world is approximately 4:100 000 with a mortality rate of 15% to 20%.

Previously, NF has been subdivided into different categories based on anatomical site, etc., but such classification is unhelpful with regards to the diagnosis and management of these dangerous conditions. More recently, NF has been classified into three etiologic types (Table 22.1).

Type I is polymicrobial with usually at least one anaerobic species present. This is more common in patients with a strong predisposition for NF, such as intravenous drug users and postoperative patients. It is more likely to be present on the trunk, abdomen, perineum, or perianally.

Type II is monomicrobial and caused by group A streptococci and is less often associated with a predisposing factor. It is more common on the head and neck, and arms and legs. Thirty percent of cases are complicated by streptococcal toxic shock syndrome.

Type III occurs in the extremities and is caused by marine vibrio or aeromonas organisms following injury in sea water.

Various other forms of NF have been described including that caused by Panton-Valentine leukocidin (PVL) staphylococcus, *Klebsiella pneumoniae*, and also a number of cases of necrotizing cutaneous mucormycosis following injuries incurred during a tornado.

Both GG and, particularly, NF are strongly associated with numerous underlying, premorbid risk factors (Table 22.2), each of which requires medical management in order to improve the prognosis of an individual patient.

Again, both conditions may be caused by one bacterial organism, or commonly, they may be polymicrobial and require treatment with broad-spectrum or multiple antibiotics.

Table 22.1 Necrotizing fasciitis: classification

Type I	Polymicrobial, including anaerobes
Type II	Group A β-hemolytic streptococci
Type III	Marine vibrios and aeromonas

Table 22.2 Factors predisposing to deep soft-tissue infection (necrotizing fasciitis and gas gangrene)

• Trauma, sometimes trivial and including insect bites
• Recent surgery
• Malignancy, particularly intra-abdominal and carcinoma of colon
• Diabetes mellitus
• Intra-abdominal sepsis
• Alcoholism
• Injecting drug use
• Obesity
• Malnutrition
• Recent chickenpox
• Immunocompromised states
• Chronic renal failure
• Systemic steroid use
• Peripheral vascular disease
• Old age

NECROTIZING FASCIITIS (NF)

Diagnosis of NF

NF is an uncommon, but severe infection with a fulminant course and high mortality often following a history of trauma or surgery. The

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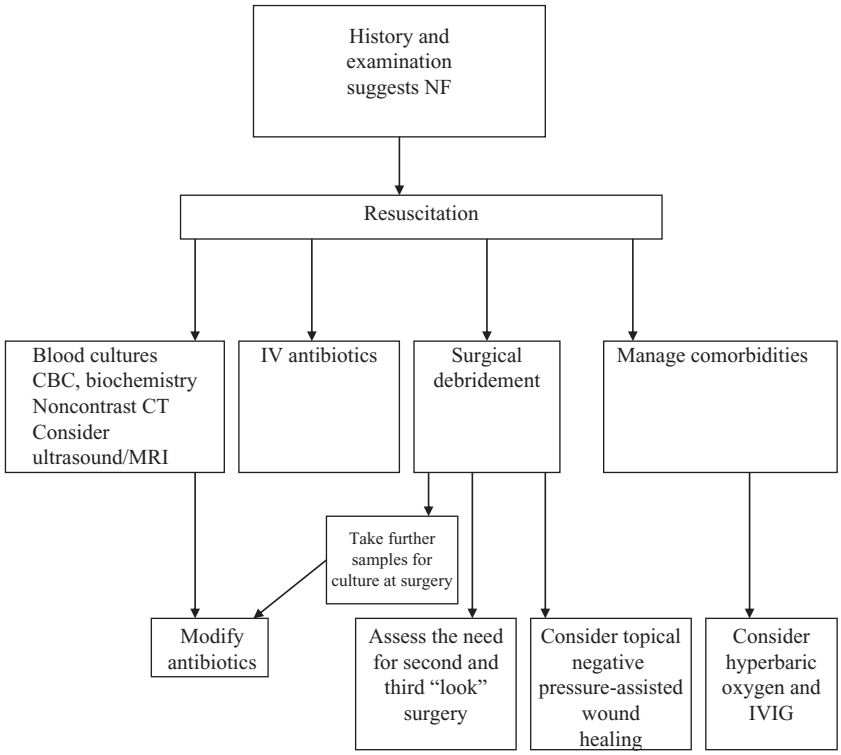

Figure 22.1
Management of necrotizing fasciitis. CBC = complete blood count; IV = intravenous; IVIG = intravenous immunoglobulin.

patient may go into rapid decline with necrosis of soft tissue and multisystem organ failure. The latter would appear to result from superantigenic overstimulation of the immune system and excessive production of cytokines.

NF can affect any part of the body, but has a predilection for the limbs, abdominal wall, perineum, and occasionally the neck and periorbital area. Although to begin with, there may be only slight redness, or other discoloration, and swelling, the clue to the patient having NF is often the disproportionate severity of pain as well as systemic upset. The condition is rapidly progressive, with systemic inflammatory responses, shock, and multiorgan failure. Early diagnosis is crucial in optimizing outcome. The diagnosis is predominantly clinical with surgical confirmation, but noncontrast CT and ultrasound may be of use in supporting such a diagnosis. These tests as well as plain x-ray may sometimes show gas or a localized abscess in the soft tissue. Differentiating early NF from the more common cellulitis may be difficult; one clue may be the severe pain that often accompanies early NF. Occasionally, one may find an area of anesthetic skin overlying the inflamed and indurated area, although this is usually a late feature. One report suggests tissue oxygen saturation of the affected limb may help distinguish between cellulitis and NF.

If left untreated, there is progressive discoloration and darkening of the tissue with subcutaneous hemorrhage accompanied by tachycardia, hypotension, acidosis, and fever or occasionally a fall in body temperature.

Some authorities have used a laboratory scoring system: the *L*aboratory *R*isk *I*ndicator for *NEC*rotizing fasciitis (LRINEC) to determine and assist in the diagnosis of NF. This uses a panel of hematologic and biochemical test results (C-reactive protein [CRP], serum creatinine, total white cell count, hemoglobin, blood glucose, and serum sodium) to provide a scoring system for the risk for having NF. However, recent studies strongly suggest that this system has a high specificity and high negative predictive value but limited sensitivity.

Treatment of NF

The principles of management of NF are outlined in Figure 22.1. Rapid *resuscitation* takes precedent, followed by the empiric administration of *broad-spectrum antibiotics*. The choice of antibiotic is further discussed below and summarized in

Table 22.3 Empiric antibiotic choices for necrotizing fasciitis

- Benzyl penicillin + nafcillin + metronidazole + quinolone
- Clindamycin + quinolone
- Carbapenem, eg. Meropenem (+/− fluconazole)
- Piperacillin with tazobactam
- Consider vancomycin or linezolid or daptomycin or tigecycline for possible MRSA
- *Clindamycin should be considered for inclusion in all antibiotic regimens because of its special immunomodulatory mechanisms.*

Table 22.3. *Surgery* with exploration and excision of necrotic tissue should not be delayed. Surgery should involve thorough debridement of all non-viable and affected tissue; there is no role for an "incision and drainage" approach to surgery. Repeat surgical explorations on subsequent days should be considered.

Samples for microbiology such as blood cultures should be taken at presentation and also at the time of surgery. Administration of antibiotics should not be delayed whilst waiting for results. Treatment of *comorbidities* such as diabetes and malnutrition is important.

Some clinicians suggest considering the following three adjuvant measures to try to improve outcome, although their usefulness remains controversial:

1. The use of *hyperbaric oxygen* has been tried in many cases of NF. The current consensus is that it is of little or no value.
2. *Topical negative pressure-* or *vacuum-assisted wound* healing has been tried in patients after surgical excision to promote efficient wound healing of what is often a large surface area of tissue.
3. Because it is thought that some of the systemic proinflammatory effects of NF, mediated by cytokines, are a result of superantigenic effects of bacteria such as group A streptococci there is a hypothesis that the administration of pooled, polyvalent *intravenous immunoglobulin* (IVIG) may be beneficial in modifying this response. There is a growing amount of evidence that this is of value.

Choice of antibiotic

Possible choices of antibiotic are given in Table 22.3, and may be modified according to local policies and the circumstances around individual patients. The initial choice of antibiotic is likely to be empiric and should cover gram-positive and -negative organisms as well as anaerobic bacteria, and should be administered intravenously, as absorption from the gut is likely to be unreliable in patients with severe systemic upset. It is widely accepted that clindamycin should be included in any antibiotic regimen to treat NF because of its immunomodulatory effects. These effects are thought to include stimulation of opsonization and phagocytosis of bacteria, as well as reducing the production of M proteins and exotoxins from group A streptococci bacteria.

Over the past few years there have been reports of methicillin-resistant *Staphylococcus aureus* (MRSA) as the causative agent in some cases of NF, both in patients with infections acquired nosocomially and from the community. Some of the newer antibiotic agents with activity against MRSA may have use in this scenario, such as linezolid, tigecycline, and daptomycin.

GAS GANGRENE (GG) (CLOSTRIDIAL MYONECROSIS)

GG is most often caused by the anaerobic spore-forming bacillus *Clostridium perfringens*, an organism that causes infection of skeletal muscle following surgery or trauma. Necrosis and gas formation are characteristic features of the infection. There is rapid advancement of infection and muscle necrosis over just a few hours, if untreated.

Myonecrosis can also occur spontaneously, caused in this case by *Clostridium septicum*. This occurrence may be associated with underlying colonic abnormalities, or leukemia.

The first symptom of post-traumatic or post-surgical gas gangrene is the sudden onset of pain at the infected site. The area becomes tender and discolored, although it may be pale to begin with. Gas may be detected in the muscle on plain x-rays and also on both CT and MRI scans. However, with all but deep-seated infections, crepitus is palpable, demonstrating the presence of gas in the muscle tissue. The patient will become systemically unwell, with a bacteremia in many instances. Hemolysis may ensue, and renal failure may follow as a consequence.

Urgent surgical debridement, and antibiotic therapy are the essential mainstays of treatment and the prognosis may well be improved with the additional use of hyperbaric oxygen. Antibiotic therapy may be chosen from penicillins, clindamycin, and metronidazole. Tetracyclines and chloramphenicol can also be used. Antitoxin is no longer available.

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23. Animal and human bites

Ellie J. C. Goldstein and Fredrick M. Abrahamian

In the United States, more than 5 million animal bites and an untold number of human bite wounds occur each year. These account for 10 000 hospitalizations and 1% (300 000) of all emergency department visits annually. Patients with bite wounds are also commonly seen as outpatients in primary care physician and specialist (orthopedics, plastic/hand surgery, infectious diseases physicians) offices. Some patients will attempt to conceal the nature of the injury with human bite wounds. The bacteriology of these wounds is diverse and comprises both aerobic and anaerobic organisms from the oral flora of biting animal/human, the victim's skin flora, and occasionally environmental isolates.

ANIMAL BITES

Microbiology

An extensive number of bacterial species are isolated from infected dog and cat bite wounds. *Pasteurella* species, especially *Pasteurella multocida* and *Pasteurella septica*, will be present in 50% and 75% of dog and cat bite wounds, respectively. Anaerobes will be present in 50% of dog bite wounds and 67% of cat bite wounds. Streptococci are present in 46% of dog and cat bite wounds, whereas staphylococci are present in 46% of dog and 35% of cat bite wounds. *Streptococcus pyogenes*, if present in a cat bite wound, usually comes from the victim's skin because it is rarely isolated from cat oral flora. *Staphylococcus aureus* is also a secondary invader originating as skin flora and is present in 20% of dog bites but only 4% of cat bites. *Capnocytophaga canimorsus* is an uncommon wound isolate but has been associated with bacteremia, some fatal, in asplenic and cirrhotic patients. Other animal bite-associated species of bacteria are often isolated, but are difficult for the routine laboratory to identify.

Table 23.1 Components of care for patients with animal and human bite injuries

History
Situation, pet ownership/identity
Geographic location
Examination
Nerve, tendon function
Blood supply (pulses)
Presence of edema, crush injury
Proximity to joint and bone penetration
Wound care
Irrigation
Debridement, if necessary
Elevation
Antimicrobials
Prophylaxis, 5–7 days (orally)
Therapy for established infection
Empirical versus specific (animal specific)
Culture (if infected)
Baseline radiograph (if suspect bony injury)
Tetanus immunization if required
Rabies prophylaxis if needed
Health department report (if required)
Decision regarding the need for hospitalization

Wound evaluation and care

The elements of wound care are outlined in Table 23.1. The most important principle of wound care is for the patient to wash the wound with soap and water as soon as possible after the injury. This will reduce any bacterial or viral (rabies prevention) inoculum. The addition of topical antiseptics or other remedies does not appear to affect the outcome or the incidence of infection. Washing the wound and keeping it clean and dry is sufficient for minor wounds. Minor injuries to compromised hosts (Table 23.2) can potentially lead to more extensive infection. Wounds that are on the hands, have associated

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severe crush injury or edema, are near a joint or may have penetrated a bone or a joint, and are moderately extensive should be treated aggressively. Bites, especially those around the head and neck, may penetrate a blood vessel and rarely cause exsanguination. In addition, nerves and tendons may be injured or severed, and their function should be evaluated, especially when wounds involve the hand. If edema is present, develops, or is pre-existing, 24-hour-a-day elevation to reduce the edema is an important component of primary therapy. The use of a sling can be helpful, and this should be worn at the level of the heart when hand injury results in edema.

Cat scratches are more prone to infection than dog scratches, which are generally minor and rarely cause infection. Any eschar of a wound should be removed if there is more than 1 to 2 mm of erythema surrounding it or if it is obviously infected. Puncture wounds are prone to infection, especially when associated with edema. They should be irrigated with sterile normal saline (no added iodine or antimicrobials) using an 18-gauge needle or catheter tip with a 20-mL syringe. This system functions as a high-pressure jet and reduces bacterial inoculum, whereas surface cleansing may not. Tears or avulsion should be copiously irrigated, any debris removed, and necrotic tissue cautiously debrided. Overly aggressive debridement can cause a defect that requires subsequent surgery.

Closure of infected wounds is generally not recommended. Wounds to the head and neck seen less than 8 hours after injury may be closed if there is copious irrigation, debridement, no

Table 23.2 Compromised hosts with animal bite wounds requiring prophylactic antimicrobial therapy and aggressive care

Local defense defects
Pre-existing edema
Prior lymph node dissection
Prior radiation therapy
Medications
Systemic steroids
Immunosuppressives
Diseases/conditions
Chronic alcoholism
Asplenia
Cirrhosis
Leukemia
Lymphoma
Mastectomy (radical or modified radical)
Myeloma
Neutropenia
Systemic lupus erythematosus

Table 23.3 Activity of selected antimicrobials against animal bite isolates

	Pasteurella multocida	*Staphylococcus aureus*[a]	Streptococci	Capnocytophaga	Anaerobes
Penicillin	+	–	+	+	V
Ampicillin	+	–	+	+	V
Amoxicillin–clavulanate	+	+	+	+	+
Ampicillin–sulbactam	+	+	+	+	+
Dicloxacillin	–	+	+	–	–
Ertapenem/carbapenems	+	+	+	+	+
Cephalexin	–	+	+	–	–
Cefuroxime	+	+	+	+	–
Cefoxitin	+	+	+	+	+
Tetracyclines	+	V	–	V	V
Moxifloxacin	+	+	+	+	+
Erythromycin	–	+	+	+	–
Azithromycin	+	+	+	+	–
Clarithromycin	V	+	+	+	–
Trimethoprim–sulfamethoxazole	+	+	V	+	–
Clindamycin	–	+	+	–	+

Abbreviations: +, active; –, poor or no activity; V, variable activity against listed pathogen.

[a] β-lactams (with the exception of ceftaroline), fluoroquinolones, and macrolides do not have adequate activity against methicillin-resistant *Staphylococcus aureus* (MRSA); clindamycin and tetracyclines (doxycycline, minocycline) have variable but often adequate activity against MRSA.

undue tension on the suture lines, and antimicrobials are given. Approximating the edges with a tape bandage or delayed primary closure is often used.

Elevation is vital to decrease edema and prevent the spread of infection and cannot be overemphasized. The failure of the patient to properly elevate the area is a common cause of therapeutic failure. In the hospital, elevation of the hand should be carried out using a 4-inch tubular stockinette, numerous safety pins, and an intravenous pole. A knot is placed at the elbow and the forearm placed between two layers of uncut stockinette held together by strategically placed safety pins.

If there is a need, tetanus immunization should be updated. Rabies prophylaxis will depend on local patterns of infection among the animals, the circumstance leading to the bite, mode of contact, and the patient's prior history of rabies immunization (refer to Chapter 192, Rabies, for details of rabies prophylaxis).

Table 23.4 Hospitalization criteria for patients with bite wound infections

Signs and symptoms of systemic toxicity
Sepsis syndrome
Compromised host (see Table 23.2)
Advance of cellulitis
Worsening infection
Patient noncompliance
Septic arthritis
Osteomyelitis
Severe and extensive crush injuries
Tendon/nerve injury
Tenosynovitis

Antimicrobial selection

The pre-emptive selection of antimicrobials should take into account the microbiology of these wounds. Fortunately, most dog and cat bite isolates are susceptible to penicillin and

Table 23.5 Causes of therapeutic failure for bite wound infections

Incorrect antimicrobial selection
Resistant isolates
Delay in seeking follow-up care
Noncompliance with medications or wound care
Failure to elevate
Underlying abscess or joint/bone involvement

Table 23.6 Activity of selected antimicrobials against human bite wound isolates

	Eikenella corrodens	*Staphylococcus aureus*[a]	Streptococci	*Haemophilus* species	Anaerobes
Penicillin	+	–	+	–	–
Ampicillin	+	–	+	V	–
Amoxicillin–clavulanate	+	+	+	+	+
Ampicillin–sulbactam	+	+	+	+	+
Dicloxacillin	–	+	+	–	–
Cephalexin	–	+	+	–	–
Cefuroxime	+	+	+	+	–
Cefoxitin	+	+	+	+	+
Carbapenems	+	+	+	+	+
Tetracyclines	+	V	–	V	V
Moxifloxacin	+	+	+	+	+
Erythromycin	–	+	+	–	–
Azithromycin	+	+	+	–	–
Clarithromycin	V	+	+	–	–
Trimethoprim–sulfamethoxazole	+	+	V	+	–
Clindamycin	–	+	+	–	+

Abbreviations: +, Adequate activity; –, poor or no activity; V, variable activity against listed pathogen.

[a] β-lactams (with the exception of ceftaroline), fluoroquinolones, and macrolides do not have adequate activity against methicillin-resistant *Staphylococcus aureus* (MRSA); clindamycin and tetracyclines (doxycycline, minocycline) have variable but often adequate activity against MRSA.

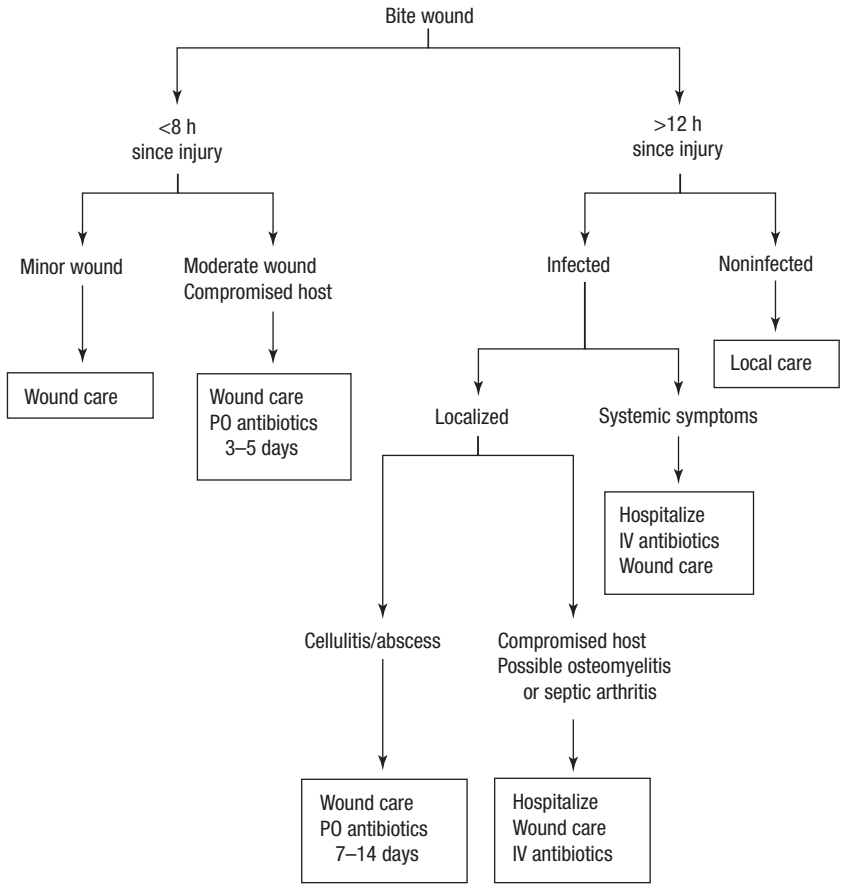

Figure 23.1 Bite wound therapy.

ampicillin. Antimicrobial selections are outlined in Table 23.3. Of note is the relatively poor activity of cephalexin, cefaclor, cefadroxil, and erythromycin against *Pasteurella multocida*.

Patients who present more than 24 hours after injury without clinical signs of infection rarely require antibiotics. Patients who present for care less than 8 hours after injury and without signs of established infection should be given prophylactic antibiotics for 5 to 7 days if they have moderate to severe wounds, especially if edema or extensive crush injury is present; are immunocompromised patients (including those with splenectomy, splenic dysfunction, severe liver dysfunction, or chronic steroid use); have multiple deep puncture wounds, especially to the hands; have bone or joint space penetration; or have wounds adjacent to a prosthetic joint.

Unreliable patients should also be managed more aggressively and may require intramuscular antimicrobials and/or inpatient observation. Follow-up should be within 48 hours or sooner, and the patient should be instructed to seek medical care sooner if the condition worsens.

The most common complications are septic arthritis, osteomyelitis, and residual joint stiffness. Long-standing pain should raise suspicion for complications such as septic arthritis or osteomyelitis. Immediate pain out of proportion to the injury when in proximity to a bone or joint should raise the issue of periosteum penetration.

Patients who present with established infection should receive proper wound care with irrigation, cautious debridement, tetanus and rabies evaluation, and courses of antibiotics. The decision to hospitalize a patient should follow the items in Table 23.4. The course of antimicrobial therapy for cellulitis is typically 7 to 14 days, for septic arthritis 3 to 4 weeks, and for osteomyelitis 4 to 6 weeks. Abscesses should be drained, and infected wounds should be cultured. Therapeutic failure of outpatient therapy, including those listed in Table 23.5, should lead to hospitalization.

HUMAN BITES

Human bites are either occlusional, where the teeth bite directly into flesh, or clenched-fist (closed-fist) injuries (CFIs). Most occur during fights, and the patient often has a delayed presentation. They tend to be more severe than other animal bites and often result in infection.

Occlusional bites may be to any part of the body and include "love nips." Bites to children or the elderly may be the result of abuse. Occlusional injuries to the hand are often particularly severe and may result in abscess or osteomyelitis. The bacteria associated with these infections include *Streptococcus anginosus*, *Streptococcus pyogenes*, *Staphylococcus aureus, Haemophilus* species, *Eikenella corrodens*, and, in more than 55% of cases, oral anaerobes. Antimicrobial therapy is outlined in Table 23.6. Of note is the poor activity of cephalexin and erythromycin against *E. corrodens* and anaerobes.

The most severe form of human bite wounds is the CFIs. These injuries usually require hospitalization and are often complicated by septic arthritis and osteomyelitis. Elevation and splinting are usually required, as are intravenous antimicrobials. An algorithmic summary of the approach to bite wounds is presented in Figure 23.1.

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24. Scabies, lice, and myiasis

Gentiane Monsel and Olivier Chosidow

Arthropod infestations of humans are most commonly caused by mites, head or body lice (pediculosis), pubic lice (pthiriasis), or fly larvae (myiasis). Although many mite species may feed on human tissue, scabies are the most common mites living on human hosts. All of these arthropods can cause irritation and inflammation of the skin, but fly larvae may penetrate more deeply into the body. Diagnosis of each of these parasitic problems is dependent on accurate identification of the infesting arthropod. Lice and scabies mites are readily transmitted between close contacts, whereas myiasis is not a contagious condition.

SCABIES

Scabies is a common parasitic infection caused by the mite *Sarcoptes scabiei* var. *hominis*, an arthropod of the order Acarina (Fig. 24.1). The worldwide prevalence has been estimated at about 100 million cases annually. In general, transmission occurs by direct skin-to-skin contact. In crusted scabies, transmission may also occur through infected clothing or bedding. Skin eruption with classical scabies is attributable to both infestation and hypersensitivity reaction to the mite. Moreover, because the eruption is usually itchy, prurigo and superinfection are common. The main symptom is pruritus that typically worsens at night, and it is often associated with itching experienced by other family members in the household or amongst people in close physical contact with an infested individual. The lesions are commonly located in the finger webs, on the flexor surfaces of the wrists, on the elbows, in the axillae, and on the buttocks and genitalia. The elementary lesions are papules, burrows, and nodules. In crusted scabies, clinical signs include hyperkeratotic plaques, papules, and nodules, particularly on the palms of the hands and the soles of the feet, although areas such as the axillae, buttocks, scalp, and genitalia in men, and breasts in women may also be affected.

The definitive diagnosis relies on the identification of mites. Multiple superficial skin samples should be obtained from characteristic lesions by scraping with a scalpel. The specimens are examined under a microscope, looking for mites, eggs, empty eggs, and scybala. Biopsy may help. Failure to find a mite is common and does not rule out scabies.

Therapy

People with scabies and their close physical contacts, even without symptoms, should receive treatment at the same time.

Topical treatment includes 5% permethrin, 10% to 25% benzyl benzoate, esdepalletrine, lindane (withdrawn from the market in most western countries), crotamiton, and precipitated sulfur. Topical scabicides have neurotoxic effects on mites and larvae. Despite the weak level of evidence of randomized controlled trials (RCTs), a recent meta-analysis suggested that topical 5% permethrin is the most effective.

Oral ivermectin interrupts the gamma-aminobutyric acid-induced neurotransmission of many parasites, including mites. However, oral ivermectin is not licensed for scabies in most countries. It is prescribed at 200 µg/kg as a single dose in patients >2 years of age and >15 kg of weight. A second dose is mandatory one to two weeks later due to the lack of ovicidal action of the drug. Ivermectin may be used as first-line therapy, but its higher cost in some countries supports consideration of initial therapy with topical agents. Ivermectin should be routine therapy for patients who have no response to a topical scabicide, and it may be the appropriate first choice for the elderly, patients with generalized eczema, and other patients who may be unable to tolerate or to comply with topical therapy.

Patients should received detailed information about scabies infestation and therapeutic options, including the amount of drug to be used and

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Figure 24.1 Scabies mite *Sarcoptes scabiei* female. (Courtesy of Dr. Arezki Izri, Université Paris 13 and Department of Parasitology, Hôpital Avicenne, Bobigny, France.)

proper administration. Topical treatment should be applied to the entire skin surface, including the scalp, face (in children and in the elderly), all folds, groin, navel, and external genitalia, as well as the skin under the nails and reapplied again 7 to 14 days after the first treatment. Hands should not be washed during therapy (protection mandatory in infants), otherwise the treatment should be reapplied.

After completion of treatment, patients should use clean clothing and bedding. If possible, potentially contaminated articles should be washed at high temperature (>50°C) or kept in a plastic bag for up to 72 hours, because mites that are separated from the human host will die within this time period. The use of insecticidal products should be restricted to unwashable materials.

Patients should be informed that itching may persist, especially in atopic individuals. After 4 weeks, the cause of itching should be reinvestigated.

PEDICULOSIS CAPITIS

The most common form of louse infestation is caused by the head louse, *Pediculus humanus* (designated *Pediculus humanus capitis* in the past

Figure 24.2 Adult human louse *Pediculus humanus*. (Courtesy of Dr. Arezki Izri, Université Paris 13 and Department of Parasitology, Hôpital Avicenne, Bobigny, France.)

to differentiate it from the body louse, formerly designated *Pediculus humanus humanus*, which has now been found to be genetically identical to the head louse). Since the 1970s, the prevalence has increased in many countries. Head lice predominantly infest schoolchildren (and their mothers) of all socioeconomic groups; transmission occurs through head-to-head contact, with the classroom being the main source of infestation. Active infestation is based on the finding of live lice. The stage of the louse most commonly seen is the nit. Each nit is oval, opaque, and white (about 0.8×0.3 mm) and is firmly attached individually to a single hair by the female louse. Nymphs or viable-appearing nits (louse eggs) are located about 1 mm from the scalp surface. Three immature stages (nymphs) precede the formation of the adult louse. Adult and immature lice are wingless and, as in all insects, have six legs. Each leg ends in a claw used for gripping hair. The adult lice are about 2 to 3.5 mm long and are white or cream in color (Figure 24.2).

Infested individuals usually first notice itching of the scalp, most often in the postauricular and occipital regions, but this pruritus occurs in a variable proportion of children. All immatures and adults require blood and, as a result of feeding, produce erythematous, papular lesions that are the cause of the pruritus. Some patients react to louse saliva with urticaria or lymphadenopathy. Secondary bacterial infection may occur as a result of scratching, and concomitant head-louse infestation should always be considered in cases of scalp impetigo or posterior cervical lymph node enlargement in the absence of other lymphadenopathy.

Table 24.1 Therapeutic regimens for scabies, lice, and myiasis

Infestation	Recommended therapy	Alternative therapy	Additional measures
Classical scabies	Two applications of permethrin 5% or benzyl benzoate 10–25%	Two doses of oral ivermectin, 200 μg/kg (at day 1 and day 7–14)	People in close physical contact, even without symptoms, should receive treatment at the same time
Head lice	Two applications of topical permethrin 1% or malathion 0.5%	Bug busting Dimethicone Topical ivermectin Two doses of oral ivermectin (failure of all other treatments) 400 μg/kg (at day 1 and day 7)	Remove nits with lice combs
Body lice	Decontamination of clothes and bed linen Application of permethrin or malathion for 8–24 h	Oral ivermectin used in indigent population to reduce reinfestation	Decontamination of furniture and mattresses
Pubic lice	Two applications of permethrin or malathion Shaving	Two doses of oral ivermectin, 200 μg/kg (at day 1 and day 7–14)	Treatment of all hairy area of the body and all sexual contacts when necessary
Myiasis	Mechanical or surgical removal of the maggots	One dose of oral ivermectin	Disinfection to prevent secondary infection

Therapy

Management of head-louse infestation is difficult because good comparative-effectiveness research is still lacking and louse resistance to pyrethroid has emerged. A Cochrane systematic review is in process. DNA sequencing showed that "knock-down resistance" (kdr) to permethrin was linked to a three-point mutation (M815I-T917I-L920F) in the louse voltage-gated sodium channel α-subunit gene, conferring nerve insensitivity. However, genetic resistance might not be predictive of clinical or parasitologic failure. It is recommended to use 1% permethrin or pyrethrin insecticide as first-line therapy. If resistance in the community has been proven or live lice are present 1 day after the completion of treatment, a switch to malathion may be necessary. Other options include wet combing, also called "bug busting," or treatment with dimethicone or other topical agents (see below), depending on the availability of the agents in the country. All treatments should be applied two times a week apart, because of insufficient ovicidal activity. A recent RCT showed that a single oral dose of ivermectin (400 μg per kilogram of body weight) repeated within 7 days achieved higher louse-free rates on day 15 than 0.5% malathion lotion among patients with difficult-to-treat head lice. The safety of such dosage of ivermectin in patients with head-louse infestation remains unknown, and subsequently should only be used in the case of failure of all other topical treatments (off-label). Topical ivermectin has shown greater efficacy than placebo in a recent RCT and has been approved by the US Food and Drug Administration (see Table 24.1).

All family members and close contacts should be screened and only those with signs of infestation should be treated. Dead nits may be removed with a fine-toothed comb. All materials that touched the heads of infested persons, such as hats, scarves, bedding, and cushions, should be thoroughly washed in hot water (50°C at least). Any infested materials kept in plastic bags for 3 days may be safely used. Hair grooming aids, such as brushes, combs, and curlers, should be discarded or decontaminated with an insecticidal powder.

PEDICULOSIS PUBIS (PTHIRIASIS)

Pubic louse infestation is caused by the crab louse (*Pthirus pubis*), named for its crablike appearance caused by the enlargement of the second two pairs of legs. Adult crab lice are 1 to 2 mm long and equally wide and are gray, yellow, or brown. Extreme pruritus in the inguinal region is usually the first sign of infestation. Dried serous fluid, blood, or louse feces in the pubic hair are indicative of an infestation. Heavily infested individuals may have blue or gray macules that do not blanch under pressure. Nits are usually laid on the pubic and perianal hair, but infestations of facial hair, including eyebrows, eyelashes, mustache, and beard, may occur, as do less frequent infestations of the axilla. Transmission occurs most often during sexual contact. Definitive

diagnosis requires identification of the nits or lice. As with head lice, pubic lice are not known to transmit any pathogens to humans, so the sole aim of therapy is removal of the insect parasite infestation.

Therapy

Pubic lice are treated with the same insecticidal creams or lotion as pediculosis capitis, with a second application after 1 week as the products have poor ovicidal activity. Resistance to pyrethrins has been shown. All hairy areas of the body should be treated at the same time (see Table 24.1). Shaving is sometimes necessary when nits are plentiful. Infestations of the eyelashes should be treated with permethrin 5% cream (wash off after 10 minutes) or only with petrolatum (applied twice a day for 8 to 10 days), followed by mechanical removal of the nits. Oral ivermectin has been used by some authors.

As in other louse infestations, all sexual contacts should be examined and treated when necessary. Bedding and clothes should be washed in hot water (50°C). Prepubertal children presenting with pubic louse infestations should be evaluated with regard to possible child abuse. Treatment failure is usually a result of an untreated hairy area or reinfestation from an untreated sexual contact. In addition, patients should also be screened for associated sexually transmitted diseases.

PEDICULOSIS CORPORIS

Body louse infestation is caused by *Pediculus humanus* (sometimes incorrectly called *Pediculus corporis*), a louse species virtually identical in morphology to the head louse, except that it is usually slightly larger, about 2 to 4 mm long. Body lice feed on blood, but retreat to hide in clothing on which the nits are laid. Infestations are most commonly found in homeless individuals, refugees, and victims of war and natural disasters. Infestations are recognized by extreme pruritus in conjunction with observation of nits firmly attached to clothing fibers. Lice are rarely seen. The erythematous, maculopapular feeding lesions are often scratched beyond recognition, leaving only serous or bloody crusts, or secondary infection. Postinflammatory pigmentation is seen in chronic cases.

Unlike head and pubic lice, body lice may act as vectors of human bacterial pathogens in those areas of the world where these organisms are endemic. Louse-borne (epidemic) typhus, caused by *Rickettsia prowazekii*, still occurs in parts of Africa and Central and South America. It is a serious, and sometimes fatal, disease that may become epidemic in crowded, unsanitary living conditions. Symptoms include fever, headache, rash, and confusion. Louse-borne relapsing fever, caused by *Borrelia recurrentis*, is also sometimes fatal but has been rarely seen in recent years, except in Ethiopia. Trench fever, caused by *Bartonella quintana*, is rarely fatal, but may cause endocarditis. As the name implies, it was most common during World War I and re-emerged in epidemic form in Europe during World War II. The recent emergence of trench fever has been confirmed in France, the United States, and Burundi. It is becoming more prevalent in populations of homeless and displaced persons. Symptoms include fever, myalgias, headache, meningoencephalitis, chronic adenopathies, and transient maculopapular exanthema, but it may be asymptomatic.

Therapy

Unlike the other forms of louse infestations, the lesions caused by body lice are the main focus of treatment. Antibiotics are needed to treat louse-borne infectious disease. Bed linen and clothes must be systematically decontaminated, and this action suffices for some physicians. Others recommend thorough washing of the body with soap followed by application of pyrethrins/pyrethroids or malathion for 8 to 24 hours (see Table 24.1). Recently, ivermectin (three doses of 12 mg each, given at 7-day intervals) greatly reduced the number of body lice infesting a population of homeless men. Such treatment may be effective in limiting the viability of body lice in patients living in an institution or routinely returning to a treatment center or shelter. Depending on the geographic location of the infested individual and his or her contact with other similarly infested individuals, the physician should consider the possibility of louse-borne disease. Infested furniture, mattresses, and box springs should be discarded or fumigated to destroy lice and nits. Infested materials sealed in plastic bags may be used safely after 3 days.

MYIASIS

Myiasis is the invasion of living vertebrate (including human) tissue by fly larvae. Various species of flies that normally deposit eggs or

larvae on garbage, carrion, or corpses may occasionally deposit these stages on wounds or skin adjacent to draining infections. Other fly species deposit eggs that hatch into larvae that penetrate intact skin. Flies in the former group include various house flies, blow flies (greenbottles and bluebottles), and flesh flies. The true myiasis producers in the second group are bot flies and warble flies. Although bot fly and warble fly larvae usually infest nonhuman hosts, these larvae occasionally invade human tissues. Myiasis is most often cutaneous, but fly larvae may also invade the nose and throat, eye, ear, and intestinal and genitourinary tract.

Dermal (furuncular) myiasis, arising in intact skin, as caused by the human bot fly (*Dermatobia hominis*) in Central and South America and the tumbu fly (*Cordylobia anthropophaga*) in Africa, appears as a painful or itchy swelling with an opening at the skin surface. Observation of the opening under low magnification will reveal the posterior end of a moving larva, on which will be two dark circular areas, the respiratory openings (spiracular plates), which allow the larva to breathe while it is feeding with its anterior end embedded in the skin. If the larva is left in the skin, it will continue to feed just below the skin surface for several days to weeks and eventually back out and drop to the ground to complete development.

Therapy

Myiasis of the nose and throat, eye, ear, or internal organs may require surgical intervention or at least the use of anesthetics for manual removal of the larvae with forceps. Invasive rhinoorbital myiasis has been treated successfully with one dose of oral ivermectin prior to surgery. However, the use of ivermectin is an off-label treatment in many countries and should be reserved for selected cases.

In dermal myiasis, early diagnosis and removal of the larva will relieve the irritation and discomfort caused by its movements and feeding under the skin. Direct removal involves application of a local anesthetic, followed by grasping the larva with a forceps and pulling with constant pressure to dislodge its hold, which may be strong because of the teeth or spines surrounding the anterior part of its body. Indirect methods of removal involve application of an occlusive dressing containing petrolatum or even a piece of meat or animal fat if medical supplies are not readily available. Within a few hours, the suffocating larva will back out of the opening into the dressing or embed itself in the occlusive tissue. Secondary infections are rare, and little further treatment beyond disinfection is usually needed. To prevent cutaneous myasis in an endemic area, it is necessary to use insect repellents (*Dermatobia hominis*) and not to wear clothes dried outside or to rest in sandy areas (*Cordylobia anthropophaga*). Wound myiasis, which may even occur in modern medical facilities, can be prevented by frequent changes of dressings and isolation of patients, especially immobile ones, within screened rooms. Myiasis of wounds is treated by removal of the feeding maggots, irrigation, and disinfection. Because fly larvae feed on dead tissue, secrete antibiotic chemicals, and may even expedite healing, sterile maggot therapy (with greenbottle fly larvae) has been used successfully in the treatment of persistent surgical wounds or ulcers.

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25. Tungiasis and bed bugs

Tania F. Cestari and Simone Pessato

TUNGIASIS

In recent years, increased ecotourism and international travel to tropical countries has produced a growing incidence of infestations formerly limited to certain regions.

Tungiasis is a common ectoparasitic infestation that occurs mainly in the tropics, particularly where poverty and poor standards of basic hygiene exist. Despite recent progress in the treatment and prevention of tungiasis, diagnosis can present a challenge to those unfamiliar with the disorder, especially when happening in nonendemic countries.

Tungiasis is caused by the penetration of the female sand flea, *Tunga penetrans*, a hematophagous ectoparasite, into the epidermis of the host. The infestation is usually self-limited and presents few complications. It is known by several popular designations, including – *chigoe flea, jigger flea, pico, nigua* (Mexico, Caribbean islands, Peru), *pique* (Argentina), *bicho dos pés, pulga da areia* (Brazil), *moukardan* (Sudan), *puce chique, ogri eye* (South America).

Epidemiology

Tunga penetrans is one of the few parasites that has spread from the western to the eastern hemisphere. Sand flea disease is common in resource-poor communities in South America and sub-Saharan Africa, with a prevalence of up to 60% in the general population. The parasite originally lived only on the American Continent and came to Angola with the sand carried by travelers from Brazil. Within a few decades, it spread from Angola to sub-Saharan Africa, East-Africa, and Madagascar. At present, tungiasis is endemic in many countries in Latin America (from Mexico to Northern Argentina), in the Caribbean islands, and in sub-Saharan Africa. Recent studies in Nigeria, Cameroon, and Brazil reported a similar high prevalence of tungiasis, from 45% to 51%; the higher rates occur in some communities of Brazil, Nigeria, and Trinidad and Tobago. The infestation happens mostly in underdeveloped communities in the rural hinterland, in secluded fishing villages along the coast, and in the slums of urban centers. The seasonal variation of tungiasis in endemic communities shows a highest incidence that corresponds to the peak of the dry season in the tropics.

In nonendemic areas, tungiasis is rare and usually appears on travelers returning from endemic countries. There are isolated reports of infection acquired in nonendemic regions, most likely by fleas that were imported from contaminated areas and completed their free-living life cycle at sites such as sandy beaches. Tungiasis is more common in adults. Considering the thinness of their stratum corneum and epidermis, children ought to be more susceptible; however, the infestation is rare in children living in nonendemic regions. There is no statistically significant difference between the prevalence of tungiasis in males and females, considering the same chance of exposure and disease-related behavior.

Etiology

Tunga penetrans belongs to the genus *Tunga* of the order Siphonaptera; it is the smallest flea, measuring around 1 mm in length, and the only species of the genus that affect humans. The parasite development requires dry and warm soil with an optimal temperature ranging between 22 and 31°C in the upper level of the soil. Male and female *T. penetrans* are bloodsuckers, but the male leaves its host after feeding, whereas the female burrows into soft skin regions of the body. Here, it remains for up to 5 weeks, completing its life cycle. Besides humans, various animals (domestic or wild mammals) may act as hosts for *T. penetrans.* Pigs have been considered the main reservoir, but the parasite has been reported to affect cows, dogs, cats, goats, and rats as well.

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Table 25.1 Biologic cycle and development of *Tunga penetrans* infestation in humans[a]

Stage/phase	Time after onset of penetration	Clinical findings: parasite	Clinical findings: host
Stage 1 Penetration	30 min–7 h (average 3 h)	Penetration of the gravid flea; the abdominal segments 1–3 separate toward the cephalic direction	Penetration at an angle of 45–90°; slight erythema; mild stink; tiny reddish spot
Stage 2 Hypertrophy	1–2 days	The abdominal segment enlarges and the parasite is visible	Itching and painful nodule with a central black dot; erythematous inflammatory area
Stage 3 White halo	4 days	Correspond to the maximum growth of the parasite; the lesion resembles a white pearl with a central opening from which the enlarged flea eliminates feces and eggs	Painful foreign-body reaction
Stage 4 Involution	3–4 weeks	Dark crust containing the parasite remains	The lesions may be numerous and close-set like a honeycomb; secondary infection is frequent
Stage 5 Residual scar	Days after the involution phase		Reorganization of the epidermis continued; the site occupied by the parasite is flattened and becomes indistinguishable from normal skin

[a] Fortaleza Classification, based on: Eisele M, Heukelbach J, Marck EV, Mehlhorn H, Menckes O, Franck S, Feldmeier H. Investigations on the biology, epidemiology, pathology and control of *Tunga penetrans* in Brazil: I. Natural history of tungiasis in man. *Parasitol Res.* 2003;90:87–99.

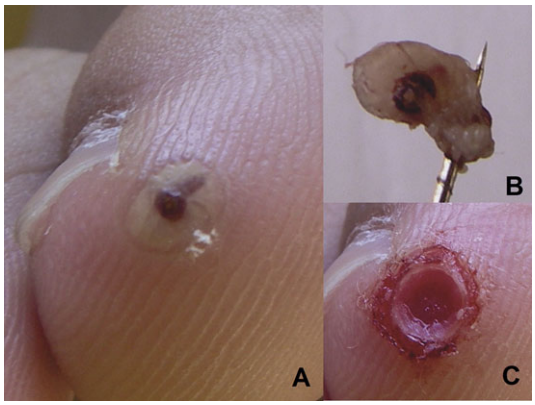

Figure 25.1 Tungiasis. (A) Isolated lesion on the first toe, corresponding to the parasite in its maximum growing stage, and presented as a white nodule with central opening. (B) Parasite removed with a needle, after gentle debridment, showing the intact abdomen full of eggs. (C) Circular ulceration, with clean walls, after removing the female *Tunga*.

Clinical manifestations

About 90% of all lesions occur on the feet, and areas of soft skin, such as the interdigital spaces, the periungual regions, under the toenails, and along the medial border of the feet, are the favored sites for flea embedding. Occasionally, genital and perianal areas, thighs, hands, and other sites may be affected, especially when the infestation is massive.

The female flea burrows into the skin of its host, starting a complex five-stage sequence of structural and morphologic changes; the cycle is accompanied by different degrees of inflammatory reaction, known as the *Fortaleza classification* (Table 25.1). The clinical diagnosis of tungiasis is based on the presence of papular or nodular lesions, either single or multiple, white, gray, or yellowish in color, with a small brown-black central opening, usually localized to the feet, in a patient who recently visited endemic areas (Figure 25.1).

Dermoscopy has been shown to be helpful in confirming the clinical diagnosis of *Tunga* infestation. The exam in vivo shows an annular brown ring with a central black pore. After extraction of the intact parasite, ex vivo, the diagnosis is confirmed by the visualization of the flea head on a distended "jelly sac" that corresponds to the abdomen full of eggs.

The histopathology of a typical lesion shows hyperkeratosis, parakeratosis, and acanthosis. The body of the flea locates in the upper dermis, and it is surrounded by a pseudocystic cavity. Inside the cavity, annular-shaped digestive and respiratory organs as well as ovaries rich in eggs may be observed. Eggs are oval or, less frequently, round, with a thickened wall and pale center. A perilesional, inflammatory infiltrate, mainly consisting of lymphocytes, neutrophils, and numerous eosinophils, is also present.

The differential diagnoses of tungiasis include *talon noir*, plantar or subungual warts, subungual exostoses, myiasis, abscesses, verrucae, ecthyma, tick bite, and melanocytic and nonmelanocytic skin tumors, especially melanoma.

Tungiasis is usually a self-limited condition, resolving in 4 to 6 weeks, with few complications

consequent to the infestation. Colonial documents and travel reports from the early twentieth century indicate that the disease used to cause severe morbidity among the indigenous populations, such as grave inflammation in the feet, deep ulcers, gangrene, lymphangitis, and septicemia. Nowadays, the degree of morbidity depends on the intensity of infestation, hygiene conditions, and associated clinical disorders.

In economically depressed urban neighborhoods, however, poor housing conditions and inadequate health care lead to a high transmission potential, resulting in high parasite loads and secondary complications. The most common problems associated with tungiasis infestation are: acute painful inflammation and edema, abscess formation, lymphangitis, sepsis, tissue necrosis or gangrene, erysipelas, or even contamination by other infectious agents such as fungi, causing atrophy or loss of nails, toe deformations, and difficulty in walking and gripping. As an additional risk, clinical and epidemiologic evidence suggests that, in populations with low vaccination coverage, untreated tungiasis is a risk factor for tetanus.

Treatment and control

Standard therapy for tungiasis consists of surgical extraction of the embedded parasite under sterile conditions, followed by appropriate care of the resulting wound. During the excision, care should be taken to prevent tearing of the flea and to avoid parts of the flea being left behind due to the risk of severe inflammation.

Topical application of kerosene, plant extracts, chlorophenothane, chloroform, 4% formaldehyde solution, turpentine, and yellow mercury oxide has been used, but without controlled studies. Chemotherapeutic approaches to attempt to kill embedded fleas without mechanical extraction include administration of oral niridazole, thiabendazole, and ivermectin, none of them completely effective.

Superinfection of the lesions may lead to pustule formation, suppuration, and ulceration. In this case, oral antibiotics should be prescribed and appropriate local care administered. Tetanus prophylaxis is recommended, especially for those individuals living in endemic areas.

The reduction of prevalence and intensity of tungiasis is possible through regular treatment of infested humans, elimination of animal reservoirs, and environmental changes. Prevention measures include paving of public areas and house floors, and implementing basic hygiene measures. Animals living close to humans should also be treated using insecticidal compounds, such as collars, sprays, shampoos, or topical products. The early and late stages of the flea could be eliminated by spraying environmental insecticide on sandy areas, on beaches, and close to animal housing facilities. Biologic repellents, composed of coconut and jojoba oils (Zanzarin®), may be recommended. A regular twice-daily application of Zanzarin®, for a period of 3 weeks, reduced the rate of newly embedded fleas by 92%, and reversed tungiasis-associated clinical pathology almost completely. Sanitary disposal of domestic garbage, proper vector control, housing of animals, wearing of protective shoes, and periodic self-examination in endemic areas are also mandatory.

CIMICIDAE INFESTATION: BEDBUGS

Bedbugs and their relatives belong to the family Cimicidae and are all blood-sucking ectoparasites of mammals or birds. The species *Cimex lectularius* is the most common. They are cosmopolitan and may be found in homes, in poultry houses, and around small caged pets or near bird and bat nests and roosts, parasitizing humans and also bats, chickens, and other domestic animals. At houses, they live in tufts, seams, and folds of mattresses, bed covers, bed frames, windows and door casings, bird nests, floor cracks, under carpets, behind loose wallpaper or wall pictures, and in furniture and luggage. Infestations of bedbugs can often be detected by their offensive odor, caused by an oily secretion produced by special glands.

Laboratory techniques have demonstrated that bedbugs could harbor some pathogenic microorganisms. However, they are not vectors of human infections and it appears unlikely that those insects could be a significant risk for the transmission of HIV.

After World War II, bedbugs became uncommon. However, an increase has been observed recently and may be associated with international trade and traveling.

Epidemiology and etiology

The common bedbug is a wingless, ovoid, flat, reddish-brown, blood-sucking insect that grows up to 7 mm in length and has a lifespan from 4 months to 1 year (Figure 25.2). They are nocturnal insects that are attracted by warmth and carbon dioxide, feed on sleeping patients, and

Figure 25.2 Bedbug – *Cimex lectularius* nymph, in the process of ingesting a blood meal from the arm of a "voluntary" human host, showing the partially filled insect abdomen. (Image from the Center for Disease Control and Prevention, Public Health Image Library, available at: http://phil.cdc.gov/phil/quicksearch.asp.)

hide during the day. When feeding, the insect grasps the skin with its forelegs, and injects saliva containing anticoagulant, vasodilator, and anesthetic fluids. After a blood meal, female bugs lay between one and five eggs that hatch in 4 to 5 days. The female deposits eggs on rough surfaces of cracks and crevices, where nymphs could survive more than 260 days in case of starvation.

Clinical features

Bedbug bites are often observed in linear groups of three, so-called "breakfast, lunch, dinner" pattern. The lesions range from erythematous pruritic macules in previously unexposed patients, to pruritic papules, wheals, vesicles, or bullae in sensitized individuals. Exaggerated local responses occur in patients with a high degree of immunity, those sensitive to other insects, and after repeated bites. Type I hypersensitivity allergic cutaneous and asthmatic reactions have also been observed as well as widespread bullous eruption, with urticated hemorrhagic papules, due to multiple bedbug bites.

The differential diagnosis of bedbug bites includes scabies, flea bites, and urticarial prurigo reactions.

Treatment and control

Many physicians are unfamiliar with bedbugs and their bites. Awareness of the possibility of infestation is important to institute correct medication and parasite control measures. Treatment of the reaction secondary to the contact with bedbugs involves the use of antihistamine or corticosteroids, and topical antimicrobials for secondary bacterial infection, if necessary. Cleaning of bedbugs' hiding places with elimination of cracks and crevices as well as the use of insecticides will decrease the infestation of houses. Pesticides containing dichlorvos, malathion, and pyrethrins are effective, taking into account the surface being treated. Bedbug control by repellents or permethrin-impregnated bed nets has proved its effectiveness in actual use.

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26. Superficial fungal diseases of the hair, skin, and nails

Gian L. Vinelli, Evelyn K. Koestenblatt, and Jeffrey M. Weinberg

The vast majority of fungal infections of the skin, hair, and nails are caused by the dermatophytes, and yeasts including *Candida* species and *Malassezia furfur*. Proper diagnosis of these conditions is essential as they can present in a similar fashion to nonfungal disease. Moreover, some fungi causing systemic infections may begin as cutaneous lesions. In most cases, potassium hydroxide (KOH) preparation, culture, and/or biopsy can provide a definitive diagnosis. Treatment of these conditions may include topical and/or systemic antifungal therapy.

THE DERMATOPHYTES

The dermatophytes are organisms that are found in specific ecologic niches and consume the structural protein, keratin. Those found in the soil are referred to as geophilic while those that are transmitted from human to human, resulting in primarily infections of the hair, skin, and nails, are termed anthropophilic. Zoophilic organisms are those that are mainly found in fur, feathers, skin, and nails of animals. Zoophilic and geophilic organisms, when transmitted to humans, tend to be much more inflammatory than anthropophilic organisms. Factors precluding a dermatophyte infection or dermatophycosis include inoculum size, host immune status, the particular organism, a suitable environment, fungal growth rate exceeding epidermal turnover, and in certain instances, the host genetics.

The term *tinea* refers to a dermatophycosis due to one of the following genera: *Epidermophyton, Trichophyton*, or *Microsporum*. Dermatophyte infections are described by their location on the body: tinea capitis (scalp), tinea corporis (glabrous skin), tinea faciei (face), tinea cruris (groin), tinea manuum (hand), tinea pedis (feet), tinea barbae (facial hair), and tinea unguium (nails). Onychomycosis refers to any fungal infection (dermatophytes and nondermatophyte organisms) of the nails. Most infections in the United States are due to five species: *Trichophyton rubrum, Trichophyton tonsurans, Trichophyton mentagrophytes, Microsporum canis,* and *Epidermophyton floccosum*.

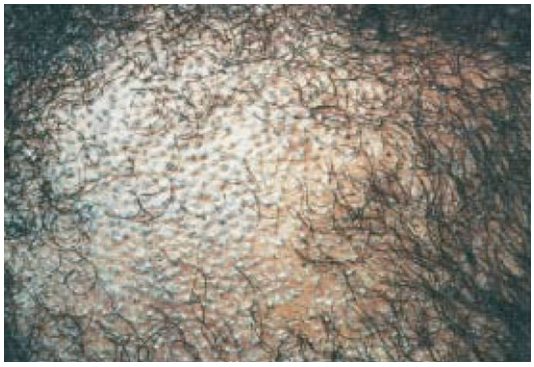

Figure 26.1 "Black dot tinea capitis" due to *T. tonsurans*. (Courtesy of Evelyn Koestenblatt.)

Tinea capitis

In the United States, tinea capitis (scalp ringworm) is most commonly due to *T. tonsurans* and most often seen in children. Clinically, this form of tinea capitis begins with the appearance of papules and progresses to a scaly area of irregular or well-demarcated alopecia with black dots (Figure 26.1). The black dots are due to spore-filled hairs (endotrix invasion) breaking at the surface of the scalp. This type of infection is the most common form of tinea capitis and is seen more frequently in African American and Hispanic children. An inflammatory boggy, tender, purulent mass called a kerion may be present, often in African American children. A short course of systemic steroids along with antifungal treatment will reduce the inflammation and discomfort, as well as the chance of scarring alopecia. Other organisms causing black dot tinea, including *Trichophyton soudanense* and *T. violaceum*, are being recovered with greater frequency in the United States.

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Table 26.1 Treatment for tinea capitis

Griseofulvin	Terbinafine	Itraconazole	Fluconazole
20–25 mg/kg/d for 6–8 weeks (liquid microsize)	62.5 mg/d ≤20 kg 125 mg/d 20–40 kg 250 mg/d >40 kg For 2–4 weeks	5 mg/kg/d for 4–8 weeks	6 mg/kg/d for 3–6 weeks

Gray patch ringworm is another form of tinea capitis, caused by the organisms *Microsporum canis* and *M. audouinii*. In this case the fungus is on the outside of the hair shaft (ectothrix invasion), causing it to have a grayish appearance. Some of these organisms produce a yellow-green fluorescence visible with a Wood's (UV) lamp. Favus or tinea favosa is generally associated with malnutrition and poor hygiene, is rarely seen in the United States, and is most frequently due to *T. schoenleinii*. Clinically, favus appears as diffuse alopecia with yellow crusts or scutula, which are made up of hyphae, neutrophils, and skin debris. Microscopically, hyphae and air spaces are seen within the hair shaft.

The most common methods for diagnosing tinea capitis are KOH preparation and fungal culture. Collection of infected hair is necessary for diagnosis of tinea capitis. The hairs may be obtained for both KOH prep and culture in two ways: a scalpel blade or glass slide may be used to scrape the area or a soft toothbrush or moist gauze can be firmly rubbed over the involved scalp (Figure 26.2). The hairs are placed onto a glass slide and mixed with 10% to 20% KOH, a coverslip is applied, and the sample is then examined under a microscope. The hairs are inspected for evidence of fungal infection with spores either inside (endothrix) or outside (ectothrix) of the hair shaft. For culture, the hairs are gently placed on the surface of the fungal media for a period of several weeks. Only the specimen should be placed inside of the media tube.

The gold standard of therapy for tinea capitis is oral griseofulvin. Topical therapy is most often unsuccessful because the medication cannot penetrate the hair follicle. Griseofulvin is usually given to children in conjunction with a fatty meal which stabilizes the gastric pH. The use of a warm compress to induce sweating and ultimately cutaneous excretion of the drug may also improve efficacy.

For patients who fail therapy with griseofulvin or cannot tolerate the medication, treatment with itraconazole (Sporanox), fluconazole (Diflucan), or terbinafine (Lamisil) is an option (Table 26.1). Terbinafine is an accepted alternative first-line agent for patients suffering from tinea capitas which is suspected or found to be caused by *Trichophyton*. Terbinafine may also be used for *Microsporum* infections but requies higher and longer dosing. In addition, brushes, combs, hats, hair ribbons, barrettes, and bed linen should be thoroughly washed. Children and caretakers of patients may be asymptomatic carriers of infection and ultimately sources for reinfection which necessitates further evaluation and the use of 2.5% selenium sulfide or 2% ketoconazole shampoo three times per week for at least 5 minutes by all family members to reduce the spread of infectious spores.

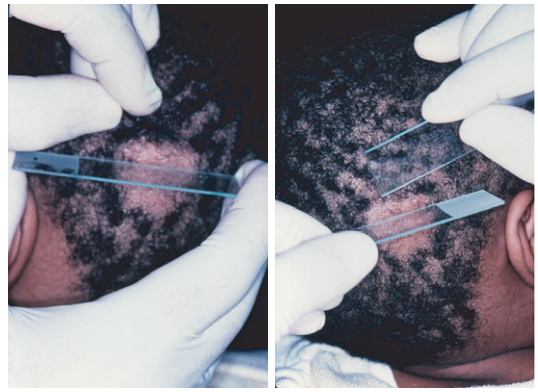

Figure 26.2 Tinea capitis techniques for collecting hair for KOH and culture. (Courtesy of Evelyn Koestenblatt.)

Tinea corporis

Tinea corporis (Figures 26.3 and 26.4) refers to dermatophycosis of the glabrous skin. The infection may present as sharply demarcated annular lesions with a scaly border, bullous lesions, granulomatous eruptions, pustular lesions, psoriasiform plaques, and/or verrucous lesions. The disease is most prevalent in tropical areas but may be found across the world. In the United States, *T. rubrum* is the most common etiologic agent of tinea corporis. *T. mentagrophytes* and *M. canis* are also common. Infections caused by *M. canis* and some strains *of T. mentagrophytes* typically present with multiple lesions and are often more inflammatory and symptomatic than those caused by *T. rubrum*. Tinea corporis may also be seen in caretakers of children suffering from black dot tinea capitis due to *T. tonsurans*.

Tinea cruris

Tinea cruris refers to a dermatophyte infection of the groin, including the suprapubic areas,

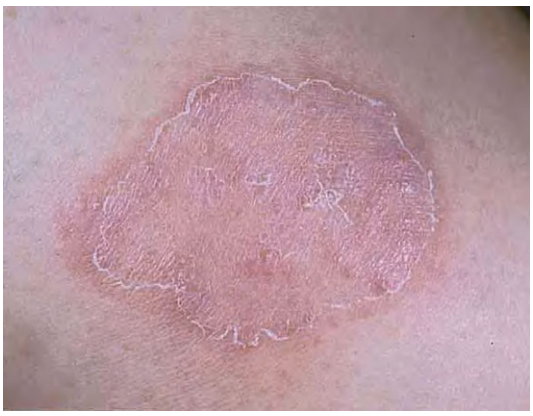

Figure 26.3 Tinea corporis. (Courtesy of Evelyn Koestenblatt.)

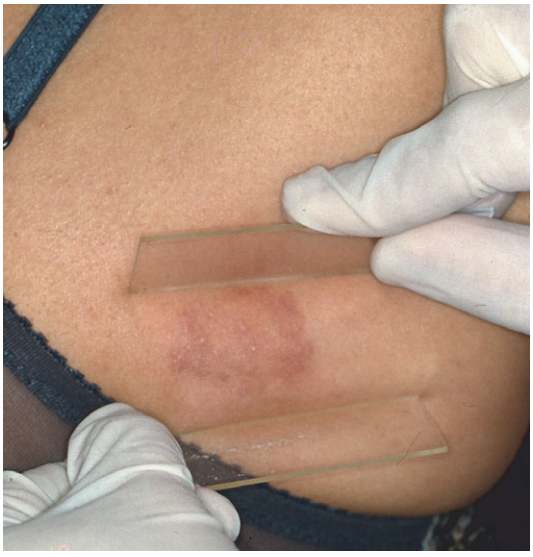

Figure 26.4 Erythematous tinea corporis with small pustules. (Courtesy of Evelyn Koestenblatt.)

proximal medial thighs, perineum, gluteal cleft, and buttocks. Infection is more often seen in men than women and is commonly caused by *T. rubrum, T. mentagrophytes*, and *E. floccosum*. Women more often suffer from candidiasis than tinea cruris.

Tinea pedis

Athlete's foot or tinea pedis is the most common fungal infection (Figure 26.5). The moisture, friction, maceration, heat, darkness, and occlusion present in the feet are perfect for fungal growth. *T. rubrum* is the most common etiologic agent and

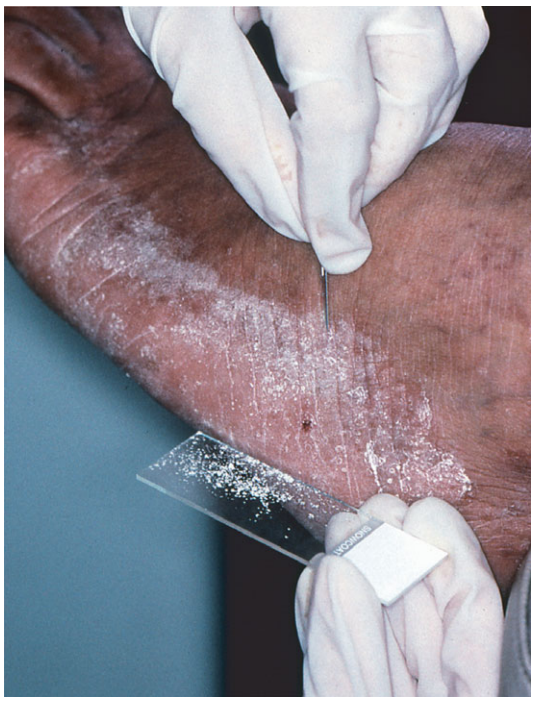

Figure 26.5 Moccasin type tinea pedis. Scrape the active border with a #15 blade for KOH preparation and culture. (Courtesy of Evelyn Koestenblatt.)

causes a "moccasin" distribution of scale and erythema. *T. rubrum* is associated with a familial autosomal-dominant predisposition to this type of infection. Dermatophytosis occurring between the toes is referred to as interdigital tinea pedis. *T. mentagrophytes*, *T. rubrum*, or *E. floccosum* may be recovered with or without bacterial organisms and/or yeast. *T. mentagrophytes* may also cause a vesicular-type tinea pedis characterized by vesicles with serous exudate on the plantar surface.

Tinea manuum

The patients commonly have dermatophycosis of both feet and one hand. Tinea manuum presents as a fine scale with some erythema covering the surface of the palm, like the feet; *T. rubrum* is usually recovered.

Tinea faciei and tinea barbae

Tinea faciei occurs in women and children generally on the upper lip and chin (involvement of similar area in men is termed tinea barbae) and is frequently acquired from pets (Figure 26.6). *T. rubrum, T. mentagrophytes*, and *M. canis* are typically recovered.

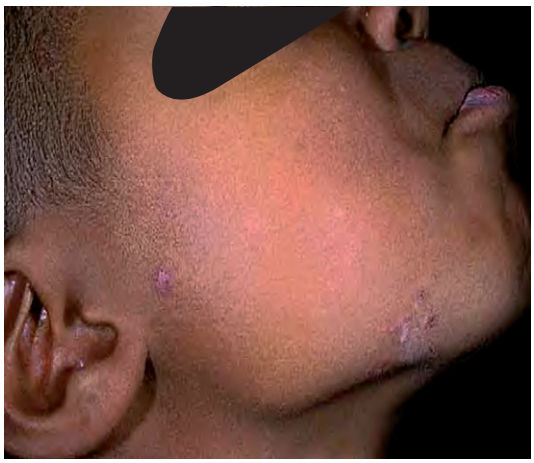

Figure 26.6 Tinea faciei. (Courtesy of Evelyn Koestenblatt.)

Tinea barbae or ringworm of the beard is seen in men and associated with exposure to animals (cattle, horses, cats, and dogs). The inflammatory type causes a deep, nodular, pyogenic reaction. *T. mentagrophytes* and *T. verrucosum* tend to cause this kerion-like response, whereas *T. violaceum* and *T. rubrum* usually cause a more superficial infection with scaling and alopecia. Extracted hairs are necessary for diagnosis by KOH preparation and culture. In some instances biopsy may be necessary to rule out other dermatoses. Given the organisms affect the hair, oral antifungal therapy is necessary as topical therapies will not adequately penetrate the hair follicle.

Dermatophytid (id) reactions

The id reaction, or autoeczematization, is a pruritic, disseminated, papulovesicular eruption secondary to a variety of inflammatory and infectious skin disorders. Dermatophytid reactions can be seen following infections of tinea capitis, tinea corporis, tinea cruris, tinea pedis, and tinea manuum but no fungal forms are recovered from dermatophytid lesions. Treatment involves eradication of the underlying infection with topical corticosteroids and oral antihistamines providing symptom relief.

Treatment

The first-line therapy for tinea corporis, cruris, manuum, faciei, and pedis consists of topical antifungals. Topical antifungal agents utilized in the treatment of dermatophytosis include several classes: allylamines, benzylamines, hydroxpyridones, and imidazoles (Table 26.2).

Commonly used imidazoles include clotrimazole (Lotrimin, Mycelex), miconazole (Desenex, Micatin, Monistat), econazole (Ecostatin, Spectazole), ketoconazole (Nizoral), oxiconazole (Oxistat), sertaconazole (Ertaczo), and sulconazole (Exelderm). The allylamines are fungicidal and include terbinafine (Lamisil AT), naftifine (Naftin), and butenafine (Lotrimin Ultra, Mentax). Ciclopirox (Loprox) is fungicidal and has antibacterial, anti-inflammatory, and antifungal properties. Treatment regimens for topical medication are generally for 2 to 4 weeks twice a day. Treatment with oral antifungals may be necessary, especially when the infection is deeper, more widespread, or involves hair-bearing areas.

ONYCHOMYCOSIS

Onychomycosis is more than an embarrassing cosmetic problem as it can be exquisitely painful and lead to serious infections, especially in diabetic and immunocompromised populations. The dermatophytes account for approximately 90% of toenail infections, whereas yeasts account for the majority of infections affecting the fingernails. Up to 50% of nail dystrophy is due to fungal infections. There are four types of onychomycosis: (1) distal subungual onychomycosis, (2) white superficial onychomycosis, (3) proximal subungual onychomycosis, and (4) candida onychomycosis.

The most common form is distal subungual onychomycosis, most frequently caused by *T. rubrum*. The nail, of the toe or the finger, appears thickened, with subungual debris, discoloration, and onycholysis (separation of the nail plate from the nail bed). The infection begins at the distal and/or lateral nail fold and involves the nail bed and hyponychium.

White superficial onychomycosis involves the surface of the toenail, imparting a chalky white appearance. The most common etiologic agents are *T. mentagrophytes* or nondermatophytes such as *Acremonium, Aspergillus, Cephalosporium, Fusarium, or Scopulariopsis*. *T. rubrum* is most often recovered in the HIV population. For diagnosis of white superficial onychomycosis, a curette can be used to scrape the white chalky material off the surface of the nail (Figure 26.7).

Proximal subungual onychomycosis is the least common form and may be a sign of HIV infection; it begins at the proximal nail fold, causing an opaque white area near the lunula. The opaque areas grow distally along with the nail.

Table 26.2 Antifungal topical agents

Name	Concentration/ Vehicle	Formulation/ Class	Antibacterial activity	Anti-inflammatory activity	Pregnancy category	Indications	Dosage	Activity
Ertaczo	2% cream	Sertaconazole Imidazole	Gram (+) Gram (−)	Yes	C	T. pedis	BID 4 wk	Efloc, Tment, Trub
Exelderm	1% cream 1% solution	Sulconazole Imidazole	No	No	C	T. pedis/cruris/ corporis TV	QD/BID 3–4 wk QD-BID 3 wk	Efloc, Mcanis, Tment, Trub Calb Mfur
Lamisil AT	1% cream, spray solution	Terbinafine topical Allylamine	Gram (+)	No	B	T. pedis/cruris/ corporis TV (solution only)	QD/BID 1–4 wk BID 2 wk	Efloc, Tment, Trub Mfur
Loprox	0.77% cream, gel, suspension, 1% shampoo	Ciclopirox Hydroxpyridone	Gram (+) Gram (−)	Yes	B	T. pedis/cruris/ corporis TV (cream or suspension)	BID 1–4 wk BID 2–4 wk	Efloc, Mcanis, Tment, Trub, Calb Mfur
Lotrimin	1% cream, lotion, solution	Clotrimazole Imidazole	Gram (+)	No	B	T. pedis/cruris/ corporis TV	BID 2–4 wk BID 2–4 wk	Efloc, Tment, Trub, Calb Mfur
Lotrisone	0.05%, 1%, cream, lotion	Betamethasone/ clotrimazole Imidazole	Gram (+)	Yes	C	T. pedis T. cruris/corporis	BID 4 wk BID 2 wk	Efloc, Mcanis, Trub, Calb
Mentax	1% cream	Butenafine HCl Benzylamine	No	Yes	B	T. pedis T. cruris/corporis TV	BID 7 days QD 14 days QD 14 days	Efloc, Tment, Trub, Tton Efloc, Tment, Trub, Tton Mfur
Mycelex	1% cream, solution	Clotrimazole Imidazole	No	No	B	T. pedis/cruris/ corporis TV	BID 2–4 wk	Efloc, Tment, Trub, Calb Mfur
Naftin	1% cream, gel	Naftifine Allylamine	Gram (+) Gram (−)	Yes	B	T. pedis/cruris corporis	BID 1–4 wk (gel) QD 1–4 wk (cream)	Efloc, Tment, Trub,
Nizoral	2% cream 2% shampoo	Ketoconazole Imidazole	Gram (+)	No	C	T. pedis T. cruris/corporis Cutaneous candidiasis TV	QD 6 wk QD 2 wk QD 2 wk QD 2 wk	Efloc, Tment, Trub Efloc, Tment, Trub Mfur
Oxistat	1% cream, lotion	Oxiconazole Imidazole	Gram (+)	Yes, weak activity	B	T. pedis T. cruris/corporis TV	QD/BID 4 wk QD/BID 2 wk QD 2 wk	Efloc, Tment, Trub Mfur
Penlac Nail Lacquer	8% solution	Ciclopirox Hydroxypyridone	No	No	B	T. unguium finger/toe nails	QD 48 wk	Trub
Spectazole	1% cream	Econazole Imidazole	Gram (+) Some gram (−) No Pseudomonas	No	C	T. pedis T. cruris/corporis Cutaneous Candidiasis TV	QD 4 wk QD 2 wk BID 2 wk QD 2 wk	Maud, Mcanis, Mgyp, Tment, Trub, Tton Maud, Mcanis, Mgyp, Tment, Trub, Tton

Abbreviations: TV = tinea versicolor; Maud = *Microsporum audounii*; Mcanis = *Microsporum canis*; Mgyp = *Microsporum gypseum*; Tment = *Trichophyton mentagrophytes*; Trub = *Trichophyton rubrum*; Tton = *Trichophyton tonsurans*; Calb = *Candida albicans*; Mfur = *Malassezia furfur*; QD = once a day; BID = twice a day.

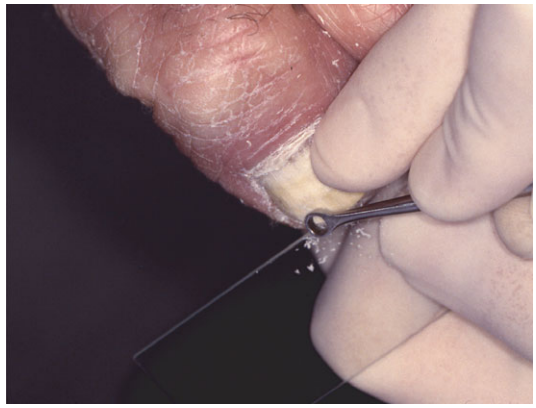

Figure 26.7 White superficial onychomycosis on the surface of the nail is scraped and small pieces are used for KOH preparations and culture. (Courtesy of Evelyn Koestenblatt.)

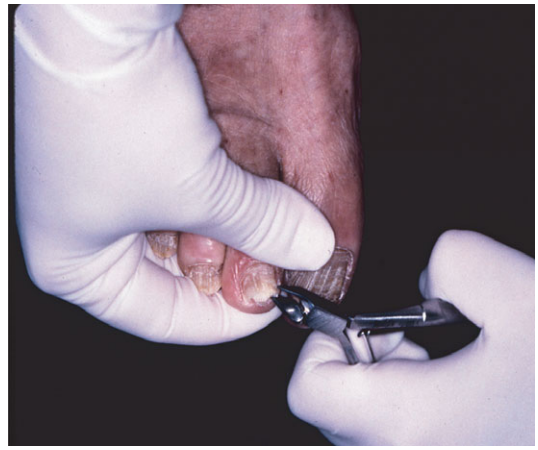

Figure 26.8 Clip back the nail as far as possible to the juncture of the nail plate and nail bed. (Courtesy of Evelyn Koestenblatt.)

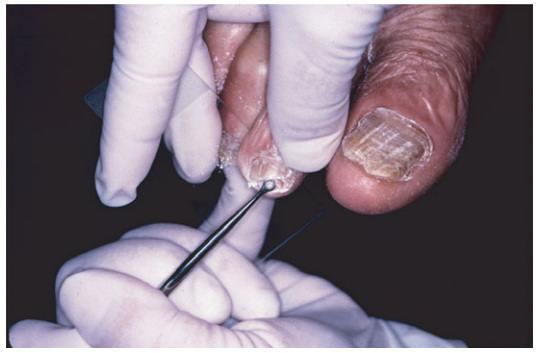

Figure 26.9 Curette small thin pieces of nail and debris for KOH preparation and culture. (Courtesy of Evelyn Koestenblatt.)

T. rubrum and occasionally *T. megninii* are the common etiologic agents. Material for KOH and culture from proximal subungual can be obtained by a punch biopsy into the affected area, or after deep scraping below the surface of the nail.

Candida onychomycosis is mainly due to *Candida albicans* and causes yellowing of the nails with onycholysis. Before initiation of therapy, it is important to document the presence of fungi utilizing one or more diagnostic techniques including: KOH preparation, fungal culture, and nail plate biopsy with PAS (periodic acid–Schiff) stain. However, lab results are only as good as the manner in which the specimen was taken. When managing distal and lateral onychomycosis (Figures 26.8 and 26.9), it is important to trim the nail back as close to the juncture of the nail plate and nail bed as possible. A curette can then be used to collect thin small pieces of nail and debris for KOH and culture.

KOH preparation is a simple, inexpensive, and reliable way to diagnose fungal infections (Figures 26.10 and 26.11). The scraping is collected on a clean glass slide, a couple of drops of 10% to 20% KOH are then added and mixed with the specimen. A coverslip is applied, and the slide is gently heated to promote breakdown of the keratin. The slide is microscopically examined for the presence of hyphal elements and yeast cells.

Material for culture should be gently placed on the surface of the agar using a wooden applicator stick that was premoistened with condensation from the tubed media (Figure 26.12). Sticks and blades should not come in contact with the inside of culture media tubes.

Proper diagnosis of onychomycosis is necessary because other disorders can present similarly including: psoriasis, irritant dermatitis, and trauma. Topical treatment of onychomycosis is generally insufficient to clear the infection. Naftin gel and 8% solution of ciclopirox have been used with moderate success. In the past, only 25% of patients treated with griseofulvin were disease free after 1 year of therapy for toenail disease. Over the past several years, the emergence of itraconazole and terbinafine has allowed much shorter and more effective courses of therapy with fewer incidents of relapse.

Itraconazole has a broad spectrum of activity and shows activity against dermatophytes and nondermatophyte molds as well as yeasts and can be administered in a continuous or pulse fashion. In the continuous regimen, the dosage

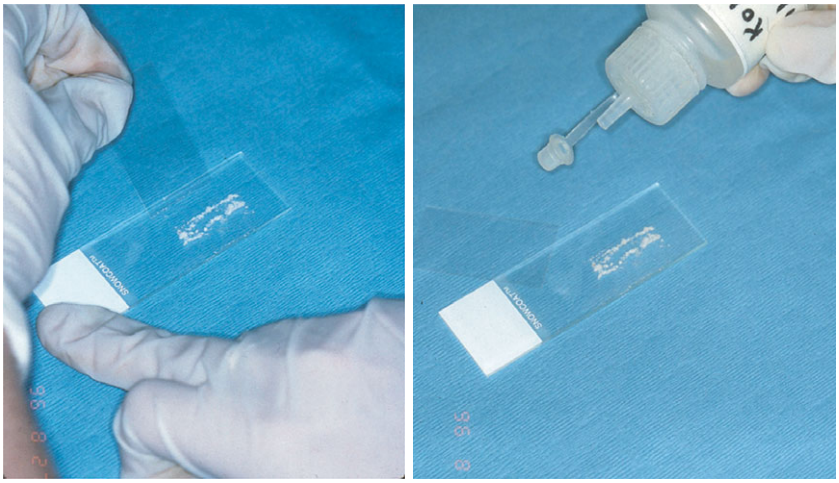

Figure 26.10 Method for KOH: Gather material on a clean glass slide and add a couple of drops of 10–20% KOH and mix with specimen. Add a coverslip. (Courtesy of Evelyn Koestenblatt.)

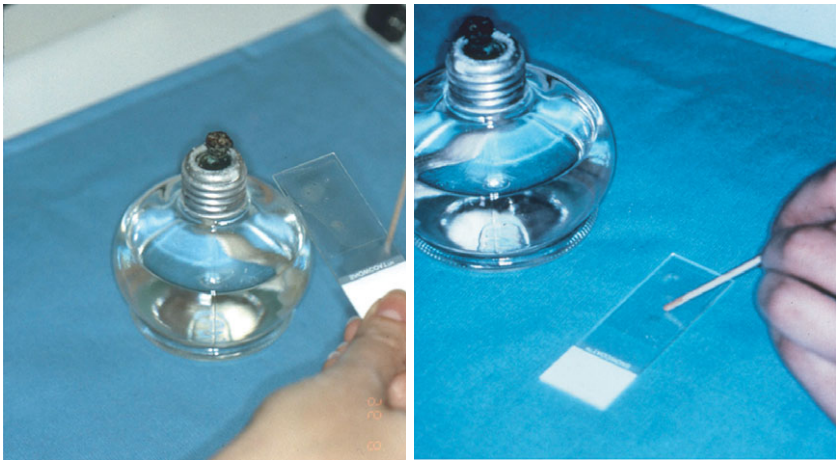

Figure 26.11 Heat slide gently and press coverslip to flatten scale. (Courtesy of Evelyn Koestenblatt.)

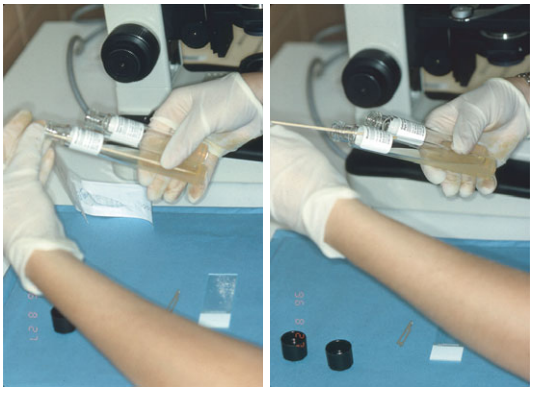

Figure 26.12 Specimen should be placed on the surface of the culture media with a wood applicator stick. (Courtesy of Evelyn Koestenblatt.)

of itraconazole is 200 mg daily for 12 weeks for toenail disease and 8 weeks for fingernail disease. Pulse dosing of the medication involves a dosage of 200 mg twice daily for only 1 week of a given month. Toenails are treated for 3 months, whereas fingernails are treated for 2 months (Table 26.3). Unlike itraconazole, terbinafine is fungicidal, blocking cell membrane synthesis. This may account for terbinafine's higher efficacy for both mycologic and clinical cure rates as compared to other systemic antifungals. Terbinafine dosage is 250 mg daily for 12 weeks for toenails and 6 weeks for fingernails.

The combination of clipping and debridement of the affected nail with systemic antifungal therapy improves clearance of the infection. Other

Table 26.3 Treatment for onychomycosis

	Fingernails	Toenails
Itraconazole	200 mg/day for 8 consecutive weeks OR 200 mg twice a day for 1 week per month for 2–3 months	200 mg/day for 12 consecutive weeks OR 200 mg twice a day for 1 week per month for 3–4 months
Terbinafine	250 mg/day 6 weeks	250 mg/day 12 weeks
Fluconazole	150–200 mg/week for 6 months	150–200 mg/week 9–12 months

helpful measures include: the use of white cotton socks and antifungal powder, properly fitting shoes, discarding prior fungus-laden shoes, and not walking around barefoot in public areas.

It is recommended for patients receiving either itraconazole or terbinafine to undergo liver function tests prior to and during treatment. Serious liver failure has been reported with the use of both therapies. Patients taking other medications metabolized by the cytochrome P450 pathway should not take itraconazole due to significant drug interactions. The use of itraconazole also carries a slight risk of developing congestive heart failure. Interactions have been reported in patients taking terbinafine and tricyclic antidepressants as well.

Although not approved by the US Food and Drug Administration fluconazole is used to treat onychomycosis at a dose of 150 to 450 mg once a week for more than 3 months for fingernails and 6 to 12 months for toenails in those unable to tolerate other therapies.

MALASSEZIA FOLLICULITIS

Malassezia folliculitis, previously called pityrosporum folliculitis, presents with a chronic history of perifollicular erythematous and pruritic pustules and papules on the neck, torso, and upper arms. KOH preparation will reveal numerous spores and budding yeast forms. A confirmatory diagnosis in atypical locations can be made with the microscopic examination of a skin punch biopsy. Treatment is with topical antifungal therapies such as shampoos containing selenium sulfide or ketoconazole, propylene glycol 50% in water, or ciclopirox olamine cream. For more serious disease systemic oral therapies are warranted. For refractory cases, topical photodynamic therapy with methyl aminolevulinate has shown some efficacy.

Malassezia furfur (formerly *Pityrosporum ovale*) has also been associated with seborrheic dermatitis. Although the etiology of seborrhea is not known, Malassezia's involvement may be due to its lipase degradation of sebum into inflammatory fatty acids such as arachidonic acid and to its activation of the alternative complement pathway. Whether its contribution is through immune response activation or as an irritant is still unknown. Indirect evidence supports its involvement in the pathogenesis as antifungal azole therapies have been shown effective in the treatment of seborrheic dermatitis.

PITYRIASIS VERSICOLOR

Pityriasis versicolor is also known as tinea versicolor but this is a misnomer as it is due to yeast, not a dermatophyte. The etiologic agent is *Malassezia furfur*. The skin lesions appear as sharply demarcated, superficial macules that may be hyper- or hypopigmented with fine scaling, located on the trunk, shoulders, neck, upper arms, back, abdomen, and rarely the face. Predisposing factors that cause the yeast form to convert to phialides (short hyphae with a fertile end) and spores include Cushing's disease, malnutrition, systemic steroid therapy, genetic predisposition, oral contraceptives, application of oils to the skin, immunosuppression, heat, and humidity.

Diagnosis is made by KOH preparation. Phialides and round short chains or clusters of budding thick-walled spores, commonly referred to as "spaghetti and meatballs," are seen microscopically. Culture is not generally performed as these organisms require an exogenous source of lipids for growth. Examination of the lesions with a Wood's lamp reveals a pale yellow fluorescence. A biopsy will show a thick basket-weave stratum corneum with phialides and spores.

Topical treatments are the most common therapy used. 2.5% selenium sulfide lotion should be applied daily for 10 minutes, then washed off, for a week. To prevent recurrence the lotion may be used monthly for 3 months and a shampoo with selenium sulfide can be used to prevent colonization of the scalp. Ketoconazole shampoo, imidazoles, triazoles, terbinafine spray, and propylene glycol are other useful topical treatments.

Oral therapies are effective but must also be continued to prevent recurrence. Itraconazole 200 mg/day for 5 to 7 days is effective, followed by 200 mg twice a day on a monthly basis for prophylaxis. Ketoconazole 200 mg/day for 10 days or single dose 400 mg repeated monthly

can be effective. Fluconazole taken as a single dose of 300 to 400 mg has been shown to be effective as well.

Patients should be counseled that prophylaxis is necessary to avoid recurrence of infection and that the return to normal pigmentation takes time.

CANDIDIASIS

Skin folds are the most common site of cutaneous candida infections. The lesions appear as erythematous, sometimes erosive, areas with satellite pustules. The intertriginous zones (submammary, inguinal creases, finger spaces) are often affected because of their predilection for moist conditions, as well as the nails, scrotum, and diaper area. Topical therapy including the azoles, nystatin, and clotrimazole are generally effective. It is also important to keep the area dry. Fluconazole and itraconazole are useful if systemic therapy is required.

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27. Eumycetoma

Ncoza C. Dlova, Anisa Mosam, and Antoinette Chateau

Mycetoma refers to a chronic subcutaneous granulomatous infection found predominantly in India, South America, and Africa. It is characterized by disfigurement, draining sinuses, and grains which commonly involve the feet. Although mycetoma can be clinically diagnosed, effective therapy requires etiologic characterization of the causative organism by pathology and culture. Where the causative agents are bacterial, mycetoma is subclassified as actinomycetoma and where the organisms are fungal it is termed eumycetoma. This chapter will focus on eumycetoma, which is difficult to treat and hence requires a combined approach for the best results. A combination of debulking surgery and antifungals: azoles as first line (ketoconazole, itraconazole) followed by allylamines for long periods until clinical cure is obtained. In resistant cases second-line azoles (posaconazole and voriconazole) or a combination of azoles and allylamines are used. However, greater awareness and health worker education is necessary to diagnose and treat eumycetoma early and effectively. This, together with community awareness, is imperative for putting into place preventative measures due to the chronic and disfiguring nature of eumycetoma.

EPIDEMIOLOGY

Although eumycetomas are endemic worldwide, they are predominantly found in the tropical regions of the world. The continents most affected are Asia and Africa, with India, Pakistan, and Sudan reporting the highest number of cases. Eumycetomas are caused by organisms living in soil and plants that are spread by direct contact or by traumatic implantation of, for example, wooden splinters into the skin. They occur most often in the feet of those walking barefoot but may also occur on the back and neck. This is due to the organisms resulting in direct implantation into the feet of those walking barefoot. Although worldwide males are most commonly affected, females and children are not spared.

ETIOLOGY

At variety of causative agents have been associated with eumycetomas, however >90% of eumycetomas reported worldwide are due to the four organisms below:

Madurella mycetomatis (black grain)
Madurella grisea (black grain)
Scedosporium apiospermum (white grain)
Leptosphaeria senegalensis.

CLINICAL FEATURES

Eumycetomas are slow-growing painless nodules that develop on the feet. As a result of the insidious and painless nature of the disease, patients usually delay in seeking help. The implanted organisms set up an inflammatory reaction which involves the subcutaneous tissues, causing protracted disfigurement of the tissues (Figure 27.1). The characteristic clinical diagnostic features

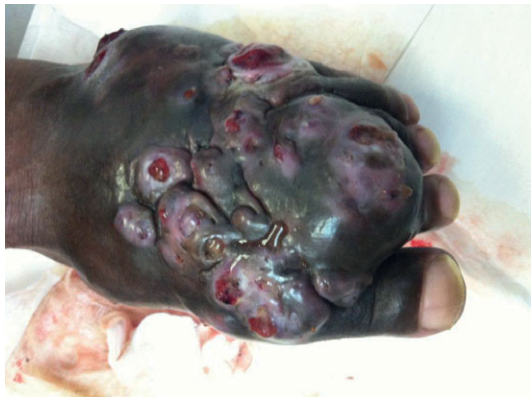

Figure 27.1 Eumycetoma in a 35-year-old black male, showing a distorted foot with multiple nodules and sinuses.

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include a triad of disfigurement, sinuses, and grains. The color of the grains depends on the causative organism, and this is usually black or gray-white when it is due to fungal infection. With chronicity, the foot tends to become a large mass with resultant spread of infection to the underlying bone. Eumycetomas have a tendency of forming cysts which can be walled off, thereby preventing distant spread, and thus creating a therapeutic challenge. Although the commonest site is usually unilateral involvement of the foot, the legs, hands, neck, and back may also be affected.

DIFFERENTIAL DIAGNOSIS

There are several other conditions that need to be taken into account that can mimic eumycetoma, hence the need for biopsy and culture. These are:

- Foreign-body granulomas
- Soft-tissue neoplasms
- Tumors, e.g., Kaposi's sarcoma
- Other deep fungal infections, e.g., sporotrichosis; chromomycosis, conidiobolomycosis
- Cysts
- Botryomycosis
- Leishmaniasis
- Tuberculosis.

DIAGNOSIS

Histopathology

Histologically the lesions are characterized by granulomatous inflammation with organisms within the center of the abscesses. Occasionally maze-shaped structures called clubs are found in the vicinity of the granules.The clinical presentation of mycetoma remains the same irrespective of the implicated organism, although the histologic features, namely the size, shape, and color of the granules can be suggestive of the causative agent. Using special stains (Grocott, periodic acid–Schiff, and hematoxylin and eosin) assists in ascertaining the various types of grain. Fine-needle aspiration is an alternative to obtaining samples for cytology.

Laboratory diagnosis

Direct examination, culture, and histopathology are the various methods that are used to identify the causative species and genus. Suggestions of the etiologic agent can be drawn from the size, form, presence or absence of clubs or pseudoclubs. The most commonly isolated organism in eumycetoma is *Madurella mycetomatis*, with countries such as Sudan reporting up to 70% of cases.

Contamination of cultures with bacteria, as well as challenges in identifying the morphology of the organism when cultures are positive, can sometimes pose a problem in diagnosing the genus and species when studying pathology specimens. This has led to the introduction of various methods of molecular diagnostic techniques, for example polymerase chain reaction (PCR) amongst which are PCR restriction fragment length polymorphism (RFLP), real-time PCR, and DNA sequencing, and these have been used to identify the species of eumycetoma from lesional biopsies and the environment.

Below we describe a few of the common organisms.

MADURELLA MYCETOMATIS

Inspection reveals oval, spherical, or lobulated black grains measuring 0.5 to 1 mm which sometimes coalesce to form 5-mm oval grains. Hyphae are light brown, ranging from 1 to 5 mm in diameter with reddish–brown grains on microscopy.

Culture Initially the hyphae look white and membranous, and then later change to yellow-brown with a dark pigment that spreads into the culture medium. Growth is at 26 to 30°C. Oval conidia (3.5–5 μm) are produced and these are derived from the simple or branched conidiophores.

MADURELLA GRISEA

They have spherical or multilobed black grains ranging from 0.5 to 1 mm in diameter that are soft to start but then become hard and brittle. Microscopically, a clear center which is surrounded by brown, pigmented hyphae is seen.

Culture Slow-growing gray–green hyphae with peripheral folds and short hyphae are observed with growth at temperatures between 26 and 30°C. Occasionally a reddish–brown pigment is detected. A pigmented wall is seen around septate hyphae (1–3 μm) and there are no spores, although numerous pycnidia and chlamydoconidia are seen sometimes.

IMAGING

Ultrasound and magnetic resonance imaging have been used to determine the extent of disease and bone involvement, with an increase in

soft-tissue volume (93%), bone sclerosis (56%), bone cavities (32%), periosteal reaction (27%), and osteoporosis (19%) often seen. Ultrasound usually reveals the "dot in circle" sign, which is considered to be typical of mycetoma. Computed tomography appears to be more sensitive in picking up early bone changes than magnetic resonance imaging.

MANAGEMENT OF MADURA FOOT

Management of mycetoma is challenging, protracted, and sometimes disappointing. Combination of surgical and medical management is the gold standard of treatment in limited disease. There are no randomized controlled trials regarding the management of mycetoma and treatment is based on occasional case reports.

Medical management

Azoles: imidazole and triazoles:

Treatment is protracted, from 9 to 12 months but may extend to up to 18 to 24 months.

- Ketoconazole 400 mg daily has been shown to be effective. This drug, however, is limited by its side effects, the most important being hepatotoxicity, others being hyperpigmentation and gynecomastia.
- Itraconazole 200 mg BID is better tolerated and is thought to have greater efficacy than ketoconazole.
- Posaconazole 200 mg QID has been used in recalcitrant cases of mycetoma with some success.
- Voriconazole 200 mg two or three times a day has been shown to be effective. Side effects such as visual disturbances, skin rashes, and elevated liver function profile frequently result in discontinuation of the drug.
- Fluconazole has shown poor results.

Allylamines:

- Terbinafine at a dose of 500 to 1000 mg/day has shown a cure rate of 50%.

Polyenes:

- Amphotericin B has not been shown to be effective. However, there have been isolated reports of efficacy at doses ranging from 0.5 to 1.25 mg/kg/day.

Griseofulvin has shown very poor results.

A study conducted in Brazil showed improvement in patients receiving a combination of itraconazole and trimethoprim–sulfamethoxazole. The latter was thought to exert an antibacterial effect against secondary bacterial infection as well as exerting an effect on the fungi itself.

Surgery

Surgery is advocated in limited disease. Antifungal therapy is used to debulk the lesion, followed by surgery and then continuation of oral therapy. Extensive disease with bone involvement may necessitate amputation in a subset of patients. Topical negative pressure therapy following surgery has been shown to be effective.

SUMMARY

Eumycetomas are a neglected disease prevalent in the tropics, particularly in India, Pakistan, and Sudan. It is a chronic, smoldering disease where diagnosis is delayed due to the painless nature and difficulty in confirming the causative organism by microbiologic culture. Therapy is prolonged due to the poor response rates, attributed, in part, to encapsulation and depth of inflammation. Hence treatment of this chronic condition is expensive and efforts need to be directed to prevention. Due to chronicity and subsequent disfigurement, many are subjected to debulking surgery and amputation. This poses a challenge in young males, who are the most frequently affected and the most productive workforce. Further research and education should be directed towards prevention, awareness, improved noninvasive diagnostic techniques and combination therapies.

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28. Lymphadenopathy/lymphadenitis

Sheela Shenoi and Gerald Friedland

Fever and lymphadenopathy is a commonly encountered presentation in clinical practice. It is important to have a logical and systematic approach for the accurate diagnosis and treatment of patients with this syndrome (Figure 28.1). Careful history-taking and physical examination are essential in the initial patient evaluation and the following questions are requisite:

1. Is the adenopathy local or generalized?
2. Is the process acute or chronic?
3. Is the cause infectious or noninfectious?
4. Is there a primary peripheral lesion?

Important elements of the history should also include the presence or absence of pain, occupational and animal exposures, geographic residence, travel history, sexual and drug use behavior, trauma and presence or absence of systemic symptoms, and/or history of underlying disease.

A thorough examination must include the location of lymphadenopathy including an evaluation of all accessible lymph node-bearing areas, the size and consistency of palpated nodes, whether they are discrete or matted and whether tenderness is present and, if so, at what level of severity.

As a general rule, a node larger than 1 cm should be considered abnormal. Stony-hard nodes are usually a sign of malignancy. Very firm, rubbery nodes suggest lymphoma. Softer nodes are the result of infectious or inflammatory conditions and when suppuration is present, these nodes may tend to be fluctuant. The term *shotty* refers to small nodes that feel like "buckshot" under the skin, as found in the cervical nodes of children with viral illnesses. A group of nodes that feel connected and seem to move as a unit is said to be *matted* and can be either benign (e.g., tuberculosis [TB], sarcoidosis, lymphogranuloma venereum, and human

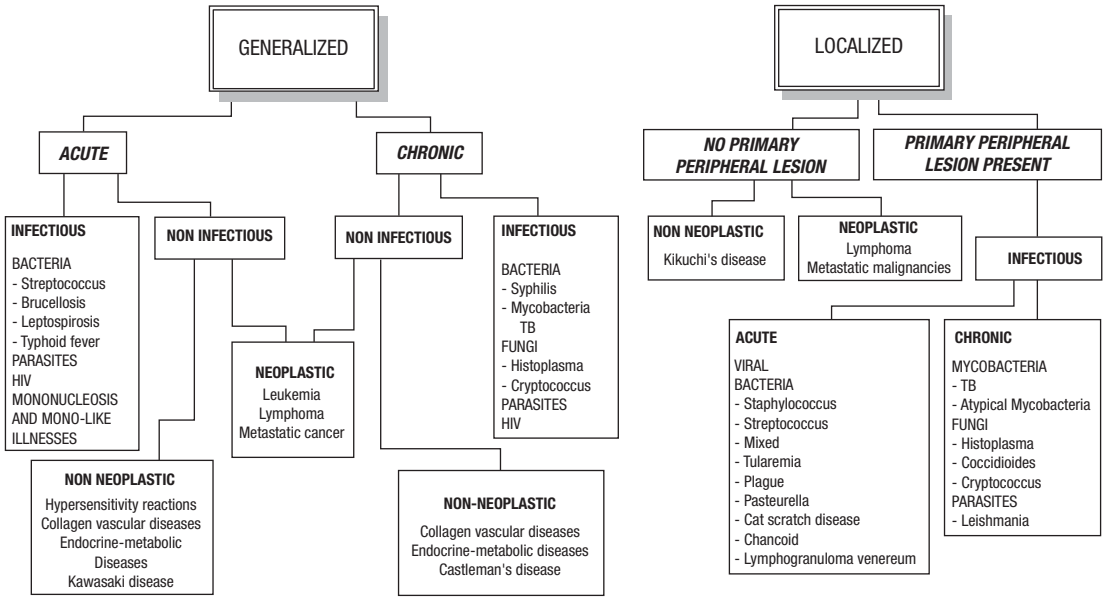

Figure 28.1 Differential diagnostic scheme for fever and lymphadenopathy.

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immunodeficiency virus [HIV]) or malignant (e.g., metastatic carcinoma and lymphoma). Pain and tenderness is usually the result of an inflammatory process or suppuration within the nodes but may also represent hemorrhage into the necrotic center of a malignant node. The presence or absence of tenderness does not reliably differentiate benign from malignant nodes.

LOCALIZED LYMPHADENOPATHY

Lymphadenopathy is considered localized if no more than two contiguous lymph node groups are involved. Anatomically and clinically, the node-bearing areas are divided into five major groups, namely (1) the head and neck area, (2) the axilla, (3) the inguinal area, (4) the mediastinal-hilar areas, and (5) the retroperitoneal and para-aortic areas. Basic knowledge of the anatomy and areas drained by these lymph nodes can help in narrowing the differential diagnosis (see Table 28.1). Infectious local adenopathy may be acute or chronic. It is usually associated with a primary lesion. At times, the peripheral lesion may be subtle or inapparent. In patients with unexplained localized lymphadenopathy and a reassuring clinical picture, a 3- to 4-week period of observation may be appropriate before considering biopsy. It is important to bear in mind and examine carefully the areas of drainage of each nodal group, as this will often reveal the primary site of infection or other pathology. The lymph nodes of the head and neck are collectively called cervical nodes and occipital and auricular nodes and are more accurately subdivided into several anatomic and clinical areas (see Figure 28.2). The occipital and posterior auricular nodes drain large areas of the scalp and face. Adenopathy of these groups may be associated with primary infectious lesions in these areas (usually from staphylococcal and streptococcal infections) but can be a common feature of acute viral illnesses as well. In children, secondarily infected wounds from insect bites and ringworm (dermatophyte infection) are common causes. The anterior auricular nodes drain the eyelids, palpebral conjunctivae, external auditory meatus, and pinna of the ear. Conjunctivitis and anterior auricular adenopathy (the oculoglandular syndrome) is classically associated with *Francisella tularensis* via direct inoculation of the conjunctival sac but may also be seen with

Table 28.1 Localized lymphadenopathy: anatomic areas drained and associated conditions

Lymph node area	Anatomic area	Areas drained	Associated conditions/comments
Head and neck	Occipital and posterior auricular	Scalp, face	Local infections with skin pathogens: *Staphylococcus*, *Streptococcus*, acute viral illnesses Children: secondarily infected insect, tick, or spider bites, dermatophyte infections (ringworm), viral infections
	Anterior auricular	Eyelids, palpebral conjunctivae, external auditory meatus, pinna	Conjunctivitis, oculoglandular syndrome (*Francisella tularensis*, *Neisseria gonorrheae*, *Bartonella henselae*), keratoconjunctivitis
	Tonsillar, submaxillary, submental	Pharynx, mouth, teeth, lips, tongue, and cheeks	Infections of the head, neck, sinuses, ears, scalp, pharynx, teeth, and oral mucosa
	Posterior cervical	Scalp and neck, skin of arms and pectorals, thorax, cervical, and axillary nodes	Mononucleosis, Kikuchi disease, tuberculosis, lymphoma, head and neck malignancies
Axillary		Upper extremity Thoracic wall, breasts, and back	Acute pyogenic infection, cat scratch disease, brucellosis, melanoma, breast malignancy
Inguinal		Lower extremities Abdominal wall Genitalia: penis, scrotum, vulva, vagina, perineum, and perianal region	Pyogenic infections of the lower extremities Sexually transmitted diseases: herpes simplex, syphilis, chancroid, lymphogranuloma venereum Pelvic and perianal malignancy
Mediastinal-hilar		Lungs, trachea, esophagus	Granulomatous disease (infectious and noninfectious) Malignancies
Abdominal Retroperitoneal Para-aortic		Abdominal viscera Retroperitoneal organs: kidneys Pelvic organs	Usually granulomatous disease: *Mycobacterium tuberculosis*, *Mycobacterium avium* complex Malignancies: lymphoma

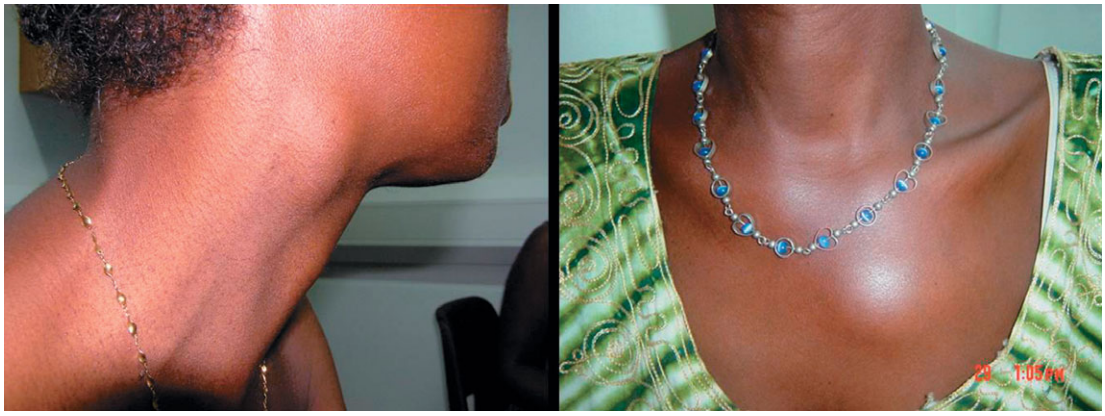

Figure 28.2 These pictures demonstrate palpable lymph nodes in the anterior cervical area (left image) and left parasternal areas (right image).

conjunctival infection from *Neisseria gonorrhoeae*, *Bartonella henselae* (cat scratch disease), and epidemic keratoconjunctivitis. The sternocleidomastoid muscle divides the cervical nodes into anterior and posterior sections, each with different drainage areas and resultant clinical importance. The anterior nodes, including the tonsillar, submaxillary, and submental nodes, are most commonly involved as they drain the tonsils and other structures in the pharyngeal area, including the teeth and gums. Enlargement of these nodes should prompt careful inspection of the contents of the mouth. In addition, this group also drains the external structures of the medial face including the lips, chin, cheeks, and medial aspects of the conjunctivae. The posterior cervical nodes are in the occipital triangle of the neck, posterior to the sternocleidomastoid muscle and above the inferior belly of the omohyoid muscle. The drainage of these nodes is more limited and if enlarged, systemic disease should be considered including infectious mononucleosis and mononucleosis-like syndromes, including HIV infection.

Kikuchi disease, or histiocytic necrotizing lymphadenitis, is a rare self-limited disorder involving the cervical lymph nodes. This condition was first recognized in Japan and has been predominantly described in females of Asian and Middle Eastern origin, commonly younger than 40 years of age. Clinical manifestations of this entity include fever or flu-like symptoms, rash, localized and sometimes tender cervical lymphadenopathy, elevated erythrocyte sedimentation rate (ESR), and leukopenia. The involved nodes are usually rubbery or firm, discrete, and rarely greater than 2 cm in diameter. Its etiology is still obscure, but it has been associated with Kaposi's sarcoma-associated herpesvirus (KHSV-HHV-8). This condition does not respond to antibiotics but usually resolves spontaneously in 1 to 2 months. Because of its association with systemic lupus erythematosus (SLE) and Still's disease, it is also thought to be autoimmune in origin. Recognition of this disease is important because pathologists who are unfamiliar with it commonly mistake it for other conditions that require treatment, such as malignant lymphoma and Kawasaki disease.

The inferior deep cervical nodes lie below the level of the inferior belly of the omohyoid muscle and anteroposterior to the sternocleidomastoid muscle. These nodes receive drainage from the scalp; the superior deep cervical nodes; the axillary nodes; and the nodes of the hilum of the lung, the mediastinum, and abdominal viscera. Infectious and noninfectious entities that involve these structures should be considered when these nodes are involved. Adenopathy in this area is usually subtle and not recognized clinically, but may be detected with the Valsalva maneuver.

Supraclavicular lymphadenopathy has been associated with malignancy in the majority of patients older than 40 years of age. The left supraclavicular (Virchow) node receives lymphatic flow from the thorax and abdomen and may indicate pathology involving the testes, ovaries, kidneys, pancreas, prostate, stomach, or gallbladder. Mediastinal and hilar adenopathies are usually detected only on radiography. These nodes are infrequently involved in acute suppurative disease. Acute suppurative mediastinal lymphadenitis, if present, can be a fulminant process, typically a complication of progressive infections of the upper respiratory tract, or perforation of the esophagus or bronchial tree as a

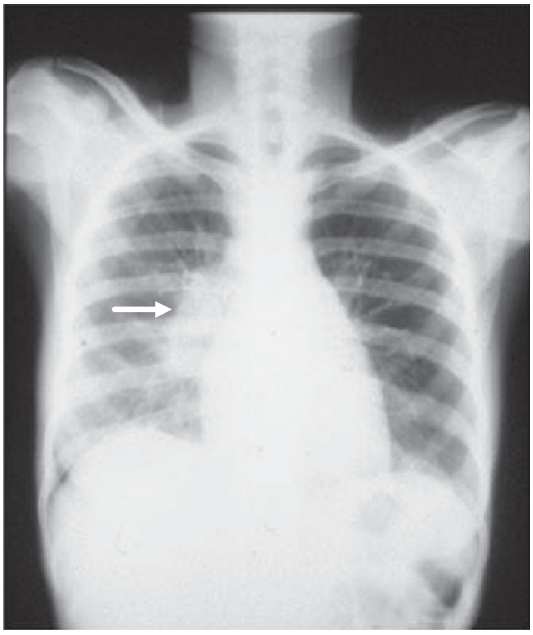

Figure 28.3 This chest x-ray depicts unilateral (right) hilar lymphadenopathy (as indicated by the arrow) in a patient with pulmonary tuberculosis.

result of trauma or surgery. A useful diagnostic criterion is whether the lymphadenopathy is unilateral or bilateral. Unilateral enlargement most frequently suggests granulomatous disease of both infectious (e.g., *Mycobacterium tuberculosis* and histoplasmosis) and noninfectious (e.g., sarcoidosis) origin (see Figure 28.3) and an ipsilateral malignant pulmonary process. Bilateral hilar adenopathy is seen in approximately three-fourths of patients with sarcoidosis. When dealing with mediastinal and hilar adenopathy, the diagnostic approach includes *M. tuberculosis* skin test (purified protein derivative [PPD]) or interferon-gamma release assay (IGRA) blood test, sputum cultures (routine, fungal, acid-fast bacillus [AFB]), and lymph node culture (routine, AFB, anaerobic) as well as cytology. Computed tomography (CT) is useful in assessing the size and location of these lymph nodes. Biopsy should be considered in any node >1 cm in the absence of a primary diagnostic lesion. Tissue for histologic examination may be obtained through inferior cervical node biopsy, transbronchial lung biopsy, mediastinoscopy, or percutaneous or surgical biopsy of hilar nodes (see Figure 28.4).

The axillary nodes drain the entire upper extremity as well as the lateral parts of the chest wall, back, and breasts. This cluster of nodes is most frequently involved in acute pyogenic

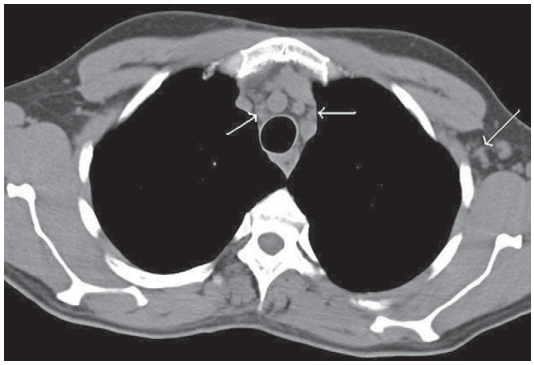

Figure 28.4 An example of chest CT in a patient with HIV and atypical mycobacterial pulmonary infection who presented with multiple hilar and left axillary lymphadenopathy (as indicated by the arrows).

infections of these drainage areas. By far, the most common etiologic organisms include staphylococci and streptococci, associated with furunculosis, cellulitis, or lymphangitis. The extremities are also often the site of zoonotic infections from other organisms acquired from the environment, including *F. tularensis* (tularemia), *Yersinis pestis* (plague), *Pasteurella multocida* (from dog or cat bites or scratches), *Erysipelothrix rhusiopathiae* (erysipeloid), and *B. henselae* (cat scratch disease).

Inguinal lymphadenopathy is very common, partly due to frequency of trauma or prior infections in the lower extremities and the wide watershed drainage area. These nodes not only drain the lower extremities but also the lower abdominal wall, the genitalia, perineum, and perianal areas. Acute pyogenic bacterial infection caused by the same organisms encountered in axillary adenopathy are the usual culprits. The drainage of the perineum and the perianal area suggests that enteric aerobic and anaerobic gram-negative organisms as well as gram-positive organisms are present. Because of the drainage of the genitalia and perianal area, sexually transmitted infections often involve the inguinal nodes as well. Those most likely to present with prominent inguinal adenopathy are syphilis, lymphogranuloma venereum, chancroid, and genital herpes simplex.

The abdominal and retroperitoneal nodes drain the abdominal viscera, and retroperitoneal and pelvic organs. They may receive drainage from the inguinal nodes as well. As they are not directly accessible by physical examination, their recognition and characterization usually requires CT or magnetic resonance imaging (MRI) (see Figure 28.5).

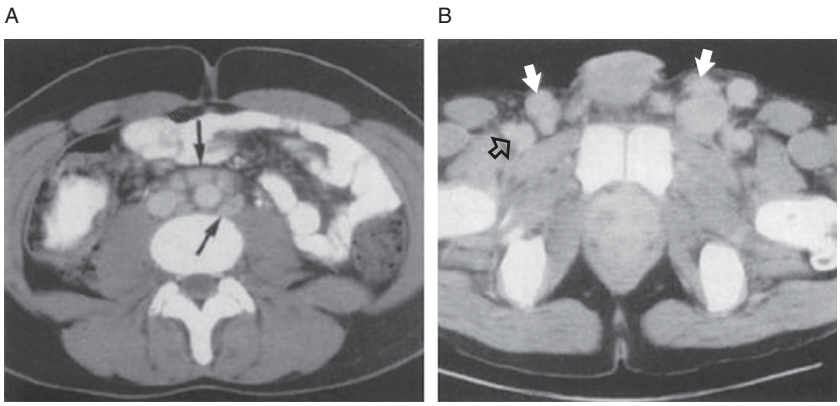

Figure 28.5 An example of high-attenuation lymph nodes (solid arrows) in the (A) retroperitoneum and (B) inguinal areas of patients with acquired immunodeficiency syndrome (AIDS) and Kaposi's sarcoma. Contrast-enhanced femoral vessels are seen on the right (open arrow).

GENERALIZED LYMPHADENOPATHY

Generalized lymphadenopathy is present if nodes in two or more noncontiguous major lymph node-bearing areas are enlarged. It is frequently a manifestation of disseminated infection. Clues may be provided by the age of the patient, presence or absence of rash, geographic factors (e.g., dengue fever, filariasis, localized leishmania lymphadenitis, histoplasmosis, TB), occupation and dietary history (brucellosis, toxoplasmosis), and exposure to animals and their excreta or standing water (leptospirosis). Acute generalized infectious lymphadenopathy, which is most often viral, is a common feature of many childhood viral infections, including rubella, measles, and varicella. Generalized lymph node enlargement may also be seen in the prodromal period of hepatitis A and B, Epstein–Barr virus (EBV), cytomegalovirus (CMV), HIV, and toxoplasmosis. These conditions initially present with the mononucleosis-like syndrome and generalized lymphadenopathy. Bacterial pathogens are much less often the cause of generalized lymphadenopathy, except in brucellosis and leptospirosis. In all these infections, the nodes are typically tender, discrete, firm to touch, and without fluctuance. Acute generalized noninfectious lymphadenopathy is frequently due to hypersensitivity reactions, most commonly drug induced. Sulfonamides, hydralazine, carbamazepine, and phenytoin are among the agents that have been most commonly implicated in such reactions. This condition rapidly disappears on withdrawal of the offending drug. Other offending medications include allopurinol, atenolol, captopril, quinine, primidone, and sulindac. Collagen vascular diseases, including rheumatoid arthritis and SLE, may also cause acute generalized lymphadenopathy and fever. Kawasaki syndrome (acute febrile mucocutaneous lymph node syndrome) is a disease of uncertain origin that is seen almost exclusively in infants and young children, and also presents with nonsuppurative cervical lymphadenopathy that may be unilateral.

Chronic generalized infectious lymphadenopathy is less likely to be viral, except for HIV. Its presence suggests more serious diagnostic possibilities. Disseminated bacterial and fungal diseases, including TB, syphilis, histoplasmosis, and cryptococcosis, should be considered. In children, persistent lymphadenopathy and fever may suggest an immunodeficiency state, including chronic granulomatous disease. Castleman's disease, associated with HHV-8, the same etiologic agent as for Kaposi's sarcoma, also presents with fever and chronic lymphadenopathy and is discussed later in this chapter.

Chronic generalized noninfectious lymphadenopathy is most often neoplastic. Lymphoreticular neoplasms (e.g., Hodgkin's disease, non-Hodgkin's lymphoma, chronic lymphocytic leukemia) predominate. Fever, when present, may be due to the underlying malignant disease or to secondary infection. Nonneoplastic diseases (with variable frequency) cause chronic generalized lymphadenopathy and fever and these include sarcoidosis, Still's disease, and hyperthyroidism. In patients receiving immunosuppressive therapy following a solid organ or bone marrow transplant, one should consider the diagnosis of post-transplant lymphoproliferative disorder (PTLD), which is a heterogeneous group of lymphoid proliferations, most of which are of B-cell lineage and associated

with EBV. These disorders can occur months to years after transplantation and would require reduction in immunosuppressive therapy with or without antiviral therapy.

LYMPHADENOPATHY AND HIV INFECTION

Lymphadenopathy is a common and important finding in people with HIV infection. Acute retroviral infection is a mononucleosis-like syndrome that occurs 2 to 10 weeks after exposure to HIV. Acute bilateral generalized lymphadenopathy, which may be accompanied by fever, sore throat, maculopapular rash, headache, mucosal ulcerations, myalgias, and malaise, is a common feature; occasionally signs and symptoms of meningitis are seen due to early neural invasion of the virus. Since HIV antibody tests are negative during the first 6 weeks and sometimes longer, during the early stage of HIV primary infection, the diagnosis is best made by testing for HIV RNA in plasma (viral load). Titers are extremely high during the acute infection and may be assayed by the reverse transcription–polymerase chain reaction (RT–PCR) method. The mean interval between the onset and resolution of symptoms during primary HIV infection is approximately 25 days, after which patients may remain asymptomatic for years. During this time, many infected individuals exhibit persistent generalized lymphadenopathy (PGL) which may last for several years. The nodes are typically nontender and firm to rubbery in consistency. In the untreated patient, as immunodeficiency worsens, symptoms may include fevers, night sweats, weight loss, and diarrhea and herald the presence of more severe complications including opportunistic infections and malignancies, defining acquired immunodeficiency syndrome or AIDS. In contrast to earlier stages in the natural history of HIV disease, lymphadenopathy is a less common finding in those with AIDS, and its presence suggests an infectious or neoplastic process involving the reticuloendothelial system. Of infectious causes, disseminated *Mycobacterium avium-intracellulare* infection, *M. tuberculosis*, histoplasmosis, CMV infection, toxoplasmosis, syphilis, and cryptococcosis are most common. Although high-grade B-cell lymphomas are common in AIDS, they are often extranodal. Kaposi's sarcoma may involve lymph nodes, occasionally without apparent skin lesions. The diagnosis of lymphadenopathy in people living with HIV is highly dependent on the geographic and social setting. In high prevalence TB settings, TB is usually the most frequent finding, occuring in up to 60% of cases. In contrast, in a recent retrospective multicentered biopsy study among people living with HIV in a non-TB endemic setting, 42.9% of peripheral lymphadenopathy was attributable to malignancy, 49.5% to reactive changes, and 7.5% to infections, with only 2.8% of all cases secondary to TB. Fevers, weight loss, antiretroviral use, and lower viral loads were significantly associated with nonreactive (malignant or infectious) lymphadenopathy. Multicentric Castleman's disease, associated with HHV-8, presents with persistent fever, marked splenomegaly, generalized lymphadenopathy in over 90% of patients, weight loss in 70%, and pancytopenia in 35%. These symptoms usually last more than 6 months and may represent acute infection with HHV-8 or reactivation of HHV-8 in the setting of immune suppression in AIDS. For more details on HIV and AIDS, please refer to Chapter 101, Differential diagnosis and management of HIV-associated opportunistic infections.

GENERAL DIAGNOSTIC APPROACHES

In most cases of infectious lymphadenopathy, clinical and laboratory findings short of biopsy often suggest the causative agent responsible for the enlarged nodes. Some of these findings are as follows:

1. Primary site of infection, e.g., streptococcal cellulitis, staphylococcal furuncle, syphilitic chancre
2. Associated symptoms: "B" symptoms with lymphomas, rash, serositis with SLE; arthritis with Still's disease, or rheumatoid arthritis
3. Characteristic rash, e.g., rubella, rubeola, drug eruption, acute HIV infection
4. Characteristic physical findings, e.g., splenomegaly in mononucleosis, lymphoma
5. Typical hematologic findings, e.g., eosinophilia (drug reactions), atypical lymphocytosis (mononucleosis syndrome), high ESR and/or C-reactive protein (CRP) (rheumatologic diseases)
6. Skin tests or IGRA, e.g., TB (though unreliable in immunocompromised hosts)
7. Serologic tests, e.g., EBV, hepatitis, syphilis, HIV, tularemia
8. Stains, cultures and histologic examination of material from peripheral primary lesions and pulmonary lesions (atypical mycobacteria, tuberculosis, plague, lymphoma).

Lymph node biopsy vs. fine-needle aspiration biopsy

The simplicity, safety, and cost-effectiveness of fine-needle aspiration (FNA) make it a useful test for the evaluation of persistent lymphadenopathy. The advent of radiologically guided FNA makes biopsy of the nodes of the hilum and retroperitoneum accessible, thus avoiding extensive surgical procedures. The presence of a cytopathologist on site to determine the adequacy of the specimen has been shown to increase the yield of FNA considerably. However, there are limitations to the procedure. FNA is useful in the diagnosis of benign reactive processes, certain infections, or metastatic disease, yet its accuracy in the diagnosis of lymphoma and primary malignancies as well as granulomatous infections remains controversial. Technical difficulties pose an obstacle for the effective differentiation of certain malignancies. Because the chemotherapeutic agents used for treatment of patients with lymphoma are selected on the basis of the specific type of lymphoma, excisional biopsy remains necessary for definitive subclassification of lymphoma in the majority of patients. Another limitation of FNA is insufficient material for histology, special stains, and culture, particularly when mycobacterial disease or other granulomatous infections are under consideration. These additional tests are often necessary to establish the diagnosis and select appropriate therapy. This is especially important for *M. tuberculosis* and nontuberculous mycobacteria, when establishing the species and the antitubercular medication resistance pattern is critical.

The following general guidelines are intended to suggest to the clinician circumstances in which excisional biopsy is appropriate:

1. Undiagnosed chronic lymphadenopathy of 1 month in adults, 3 months in children
2. Localized nonsuppurative lymphadenopathy without an accessible or apparent peripheral lesion
3. Enlarging undiagnosed lymphadenopathy after 2 weeks of observation
4. Nontender, matted to hard lymphadenopathy or a high clinical suspicion of neoplastic disease
5. Radiologic findings or systemic signs and symptoms suggesting granulomatous or lymphoproliferative disease when noninvasive tests are unrevealing
6. Positive tuberculin test in the absence of diagnostic pulmonary TB
7. New adenopathy in immunocompromised patients; otherwise, asymptomatic patients with HIV and PGL do not need biopsies
8. Lymphadenopathy in the setting of fever of undetermined origin
9. Persistently nondiagnostic or inconclusive FNA results.

TECHNIQUE

Approximately half of all lymph node biopsies lead to a specific diagnosis. Careful attention to several rules maximizes the usefulness of the invasive diagnostic procedure.

1. Discuss the differential diagnosis with the surgeon, pathologist, and the microbiology laboratory ahead of time so that any special considerations (e.g., fixation, staining, and special culture media) can be identified.
2. Select the best site. Lymph nodes frequently involved in minor inflammatory processes, such as the inguinal and submandibular nodes, should be avoided. In the presence of generalized lymphadenopathy, the inferior or posterior cervical nodes are preferred. The second choice is the axillary node.
3. The largest node in a cluster of enlarged nodes should be removed.
4. Remove nodes in their entirety with capsules intact. Dissect them, sending half of the specimen to the pathology laboratory and the other half to the microbiology laboratory for stains and culture of common pathogens, including mycobacteria, fungi, and other suspected organisms (see Figure 28.6).

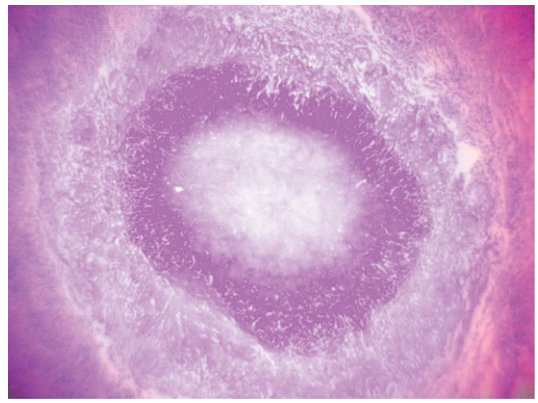

Figure 28.6 An example of a supraclavicular lymph node biopsy stained by H&E. This is a granuloma, with extensive necrosis in the center, caused by *Mycobacterium tuberculosis*. (Courtesy of Theresa Liu-Dumlao, MD.)

5. Request that the pathologist make additional sections of the excised tissue if the node is abnormal but not diagnostic.
6. Consider a repeat biopsy and the excision of more tissue if the node is abnormal but not diagnostic and the clinical picture is unclear.

INTERPRETATION

Entities discussed in this chapter that have a characteristic histologic pattern and for which a specific or strongly suggestive diagnosis can be made histologically are lymphoma, other neoplasms, TB, fungal disease, sarcoidosis, toxoplasmosis, and cat scratch disease. Most noninfectious nonneoplastic disorders and most acute viral infections show nonspecific lymphadenitis or hyperplasia only. However, a significant number of patients with initially nondiagnostic lymph node biopsies and persistent lymphadenopathy will ultimately prove to have a serious underlying disease. If the biopsy is not initially diagnostic, it is essential to follow the patient carefully and to consider repeat biopsy if adenopathy persists.

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Clinical syndromes: respiratory tract

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29. Acute bronchitis and acute exacerbations of chronic airways disease

Phillippa Poole and Mark Hobbs

Bronchial infections with viral and bacterial microorganisms cause considerable morbidity, as well as economic costs incurred through health care and loss of productivity. These infections affect all age groups. An important consideration is whether or not an individual has underlying chronic lung disease, as that alters the etiology, clinical presentation, laboratory findings, and indications for therapy. In this chapter, we discuss acute infectious bronchitis in individuals without underlying chronic lung disease, before outlining approaches when an individual has an acute exacerbation of a chronic lung disease such as asthma, chronic obstructive pulmonary disease (COPD), or non-cystic fibrosis bronchiectasis.

ACUTE BRONCHITIS

Acute bronchitis is a common condition in both children and adults. It has been defined as "an acute illness, occurring in a patient without chronic lung disease, with symptoms including cough, which may or may not be productive and associated with other symptoms or clinical signs that suggest LRTI [lower respiratory tract infection] and no alternative explanation (e.g., sinusitis or asthma)." Most people will experience this at some time during their lives, and in most cases it is self-limiting and will not result in those affected seeking medical attention.

Nonetheless, this condition is a frequent cause of attendance to primary care providers and has been identified as a potential target for reducing unnecessary antibiotic prescribing in the community. Additionally, those who seek medical care for acute bronchitis, especially if this is frequent, should be considered for investigation as to whether or not they have an underlying chronic airways disease.

Typical symptoms of acute bronchitis are the acute onset of cough with or without sputum production or discoloration, often preceded by or associated with upper respiratory tract symptoms such as sneezing, a runny nose, or a sore throat. The cough often lasts for 7 to 10 days but may persist for several weeks. Fever and wheezing are frequently associated, as is a burning sensation in the tracheal area. Some patients may have focal signs on chest auscultation. Abnormality of vital signs or the presence of focal chest signs suggesting consolidation should prompt consideration of a chest radiograph to exclude pneumonia.

Young infants may present with the syndrome of bronchiolitis. In addition to symptoms and signs above they may be off their food, and in severe cases, develop cyanosis or apnoea. Treatment may involve the use of nebulized adrenaline or hypertonic saline.

Acute bronchitis is usually a viral illness but it may also be caused by bacterial species including *Mycoplasma pneumoniae, Chlamydia pneumoniae*, or *Bordetella pertussis* amongst others. The relative frequency of implicated viral species varies with time, place, and patient age, with agents circulating in the community with epidemic-like characteristics. Common species include influenza, rhinovirus, coronavirus, and common pediatric pathogens such as respiratory syncytial virus, human metapneumovirus and parainfluenza virus.

Extensive investigation for a cause of acute bronchitis is not usually necessary or beneficial. While molecular testing (PCR) of upper respiratory tract secretions will often identify a viral pathogen, this finding seldom alters management. Limited investigation for specific pathogens may be of use in selected cases, such as for public or occupational health reasons during a whooping cough outbreak, or to decide on whether or not to offer influenza treatment in a suspected case.

Antibiotic treatment is commonly requested by patients with acute bronchitis, with wide variation in prescribing practice for this condition. There is observational evidence that antibiotic

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use may lead to a statistically significant but clinically nonsignificant reduction in symptom duration. Given the typically benign, self-limited course of the illness and increasing rates of antibiotic resistance in common bacterial pathogens, antibiotic use for this condition should be avoided. Unnecessary treatment also undermines the patient's ability to self-manage this common condition in the future. Several methods exist for dealing with patients' expectations of receiving antibiotics. These include education or printed information outlining the uncertainties involved, or the use of delayed prescriptions. This is where a prescription is given, to be used only under specific criteria which point to bacterial infection. Symptomatic treatment may be offered, but there is little evidence it alters any outcomes.

Treatment for influenza with a neuraminidase inhibitor may be appropriate in patients with a consistent illness during an epidemic, if the circulating strain is known to be susceptible to the available treatments and the patient has presented early enough in the course of their illness to derive a meaningful benefit. These medicines reduce the duration of symptoms by about 1 day but do not reduce rates of hospitalization or death.

Postviral bacterial pneumonia may occur following an episode of bronchitis, and may be severe. Investigation for this with a chest radiograph should be considered in patients who have deteriorated or failed to settle as expected. If pneumonia is confirmed, antibiotic treatment is appropriate and further microbiologic investigation may be required. Consideration should be given to specific cover for *Staphylococcus aureus* in patients with postinfluenza pneumonia.

ACUTE EXACERBATIONS OF CHRONIC AIRWAYS DISEASE

Disease definitions

The airways diseases asthma and COPD are relatively common, with each affecting 5% to 10% of people worldwide. By definition, asthma is a reversible airways disease characterized by steroid-responsive airways inflammation. It occurs in people with a genetic predisposition to develop allergic reactions to aeroallergens. In contrast, COPD is a persistent and progressive disease with an enhanced inflammatory response in the airways and the lungs to noxious particles and gases, such as smoke from cigarettes or fires. COPD as a disease entity encompasses patients with emphysema or chronic bronchitis. The latter term describes a clinical syndrome of chronic cough or sputum for 3 months in 2 consecutive years and should not be considered indicative of chronic infection. Instead, excess mucus is produced by goblet cells which have become hypertrophic due to the abnormal inflammatory response.

Bronchiectasis (BX) is a rarer condition which results in daily production of large amounts of sputum. It has a number of causes, including infection. BX is characterized by irreversible dilation of parts of the bronchial tree, resulting from destruction of the muscle and elastic tissue. The prevalence of BX is unknown but the condition is increasingly recognized in part because of greater use of chest CT scans.

It is increasingly recognized that chronic airways diseases may occur together: bronchial hyperreactivity may be a risk factor for COPD; COPD occurs in asthmatics who smoke; and BX may complicate severe asthma or COPD.

Common features of acute exacerbations

The role of infection in these three chronic airways diseases is discussed further below. All three are characterized by the occurrence of acute exacerbations (AEs) which may or may not be infective in origin. There are various definitions of AEs, but most are clinical, such as an acute worsening in the patient's shortness of breath, and/or cough, and/or sputum beyond the baseline, sufficient to warrant a change in management. AEs are more frequent in the winter months, suggesting viruses play an important role.

The frequency of AEs increases with disease severity and correlates with poorer quality of life. In turn, AEs may have a role in accelerating decline in lung function and thus contribute to morbidity and premature mortality. In economic terms, the cost of AEs, especially hospitalizations, far exceeds that of stable chronic disease management; amounting to billions of dollars annually in the United States alone.

The pathologic and physiologic abnormalities of airways that predispose patients with chronic airways disease to bacterial infection include impaired mucociliary clearance, bronchial obstruction by abnormal secretions, and bronchoconstriction. In patients with COPD or BX, there are colonizing bacteria in the bronchial epithelium which may become pathogenic, as well as impaired host defenses. For example,

there is reduction in bacterial phagocytosis, intracellular bactericidal activity by polymorphonuclear neutrophils, macrophage recruitment, and sputum immunoglobulin levels.

Although purulence of sputum is often equated with infection, the characteristic yellow-to-green color is caused by myeloperoxidase released from polymorphonuclear neutrophils and eosinophils, reflecting the stasis of secretions in the bronchial tree. Microscopic assessment of the sputum by Gram stain and simple wet preparation reveal the two essential characteristics of bacterial infection: first, increased numbers of bacteria; second, increased bronchial neutrophilic inflammation. To be significant, the Gram stain must have bacteria in numbers over 10 to 20 per oil immersion field, which is significantly above the average of two when a patient is stable. In addition, the majority of the inflammatory cells are neutrophils. This, when accompanied by an increase in the volume of sputum expectorated, reflects the outpouring of neutrophils into the bronchial lumen in response to bacterial infection.

Reducing the impact of acute exacerbations

In order to reduce morbidity and unnecessary healthcare utilization, including hospitalization, all patients with chronic airways disease at risk of AEs should use preventive approaches. Smoking cessation and influenza vaccination are essential preventive strategies for every patient with chronic airways disease. Pneumococcal vaccination has less of an evidence base to support its use, but is recommended every 5 years for those with COPD.

In airways diseases with copious sputum (usually chronic bronchitis or BX), sputum clearance techniques, such as postural drainage and active cycle of breathing, are safe and improve symptoms and quality of life. Physiotherapists have a role in teaching these techniques, as well as in clearance of secretions in severe AEs, although this lacks evidence of effectiveness.

Education is an important component in the management of all chronic airways diseases. Patients should be taught to recognize early symptoms and to seek escalation of therapy, including antibiotics where appropriate. Maintenance of physical fitness is critical. Many of these aspects are covered in pulmonary rehabilitation programs which have been shown to improve symptoms, quality of life, and healthcare utilization at all stages of COPD.

Exacerbation frequency in COPD has become an important end point in clinical trials. These have shown a reduction in AECOPD with inhaled corticosteroids and long-acting bronchodilators (beta-agonists and antimuscarinics); and possibly by oral phosphodiesterase inhibitors, mucolytics, and bacterial extract immunostimulants. Combining an inhaled long-acting bronchodilator and corticosteroid leads to an even greater reduction in exacerbations. The mechanism is unclear but is likely anti-inflammatory or immunomodulatory. A current controversy is the finding that overall, inhaled corticosteroids reduce AECOPD, yet are associated with an increase in the risk of pneumonia. The role of prophylactic antibiotics is discussed further below.

Symptoms of acute exacerbations

Patients with AEs of chronic airways disease present with similar respiratory symptoms. Among these are increased dyspnea, increased frequency and severity of cough, increased volume or purulence of sputum, or chest tightness. More general symptoms include malaise, anorexia, fatigue, chills or fevers. A viral cause may be suspected when the patient has antecedent coryzal symptoms. The presence of rigors, high fevers, or pleuritic pain suggest coexistent pneumonia. Physical examination may reveal wheeze, accessory muscle use, decreased breath sounds, tachypnea, or tachycardia. Measures of airflow such as FEV_1 or peak flow will be reduced from usual values. Chest radiography may assist in determining the presence of pneumonia or other conditions such as heart failure. Increasingly, patients with chronic lung diseases have other comorbidities that need to be incorporated into the differential diagnosis.

The goals of therapy for an infective AE of chronic airways disease are the expeditious resolution of the acute infection without significant early relapses, followed by a long infection-free post-treatment period. Implicit in these goals is the avoidance of further damage to the airways and lungs, along with maintenance of functional status and quality of life.

Role of infection in asthma

The role of infection in causing asthma is controversial. Respiratory syncytial virus (RSV) and rhinovirus are found more commonly in the airways of children with asthma, but this is not thought causal. On the other hand, viruses cause

about 75% of asthma exacerbations. Most commonly, infection is with rhinovirus, but other common viral pathogens are influenza, RSV, coronavirus, human metapneumovirus, parainfluenza, or adenovirus. Bacterial infections play only a minor role. Compared with non-asthmatic controls, people with asthma infected with a "common cold-causing rhinovirus show more severe lower respiratory symptoms and changes in airway physiology. This suggests the presence of abnormal airways responses to infection, such as defective interferon responses to rhinovirus. The bacteria *C. pneumoniae* and *M. pneumoniae,* primarily recognized as causative agents in "atypical" community-acquired pneumonia, may play a role in asthma.

Current treatment options for AE of asthma are limited and have developed little in recent years. Generally they consist of increased inhaled bronchodilator therapy and anti-inflammatory treatment with inhaled or oral corticosteroids. Antibiotics are reserved for when bacterial infection is suspected. Macrolides have been shown to have anti-inflammatory, bactericidal, and possibly antiviral activity, making them attractive agents in asthma. However, there is insufficient evidence yet of a disease-modifying effect in either acute or chronic asthma. Newer antiviral approaches such as either vaccination against, or enhancement of, the host response to respiratory viruses are under consideration.

Role of infection in COPD

An AECOPD is thought to occur as a result of the increased inflammatory burden in the airways from interactions among host, viruses, bacteria, and/or air pollution. In a third of AECOPD, no cause is found. Infections (bacterial, viral, or other) account for the majority of AECOPD, with air pollution and comorbidities such as heart failure, pneumonia, or pulmonary embolism making up the balance. During an infective AECOPD, the airways exhibit an increase in neutrophils, products of neutrophil activation, and oxidative stress, some of which may result in an increased systemic acute phase response.

Depending on the study, viruses account for 12% to 48% of AECOPD, with the common viral pathogens being influenza, parainfluenza, rhinovirus, adenovirus, coronavirus, and RSV. In some AECOPD, both viruses and bacteria are found. Where viruses are detected, the AECOPD is more severe and prolonged than when they are not detected.

The same bacteria seen in an AECOPD may colonize the airways of over half of patients while they are in a stable state. Features that suggest pathogenicity include a pure heavy growth of organism on sputum culture, or a change in organism from one known to be present in the stable state. The four commonest bacterial organisms found in COPD patients and in AECOPDs are *Streptococcus pneumoniae*, *Haemophilus influenzae* or *Haemophilus parainfluenzae*, and *Moraxella catarrhalis*. In very severe COPD, *Pseudomonas aeruginosa* is an important consideration, particularly in patients with frequent hospitalizations, more than four courses of antibiotics per year, recent oral steroid use, or who have not been vaccinated against influenza. The atypical organisms – *Chlamydia*, *Legionella*, and *Mycoplasma* – do not play a specific causative role in AECOPD.

In principle, the identification of a specific bacterial etiology in AECOPD allows for selection of appropriate therapy and avoids the costs and adverse effects associated with the use of unnecessary medications, including the emergence of resistant strains. Obviously, antimicrobials are not indicated for any AECOPD that is not bacterial in nature. A Cochrane review of antibiotics for AECOPD found that currently available antibiotics, as a group, do not reduce treatment failure in mild exacerbations, whereas they do in severe AECOPD. Yet there is no evidence of an effect on mortality or length of hospital stay, with almost no data on patient-reported outcomes.

In practice, the decision to treat with antibiotics is often based on clinical and not microbiologic grounds. Sputum cultures and antibiotic sensitivity testing are rarely indicated to guide empirical treatment for mild AECOPD in the community. In part this is due to the delay in getting a helpful result. Another problem is the difficulty in obtaining adequate sputum samples, free of saliva, that reflect the bronchial pathology. A final problem is the cost and availability of the test.

In contrast, a sputum culture and antibiotic sensitivity testing should be considered if the patient is having frequent AECOPDs treated with antibiotics; if the AECOPD is severe, especially where artificial ventilation is needed; or if the AECOPD does not respond to the initial choice of antibiotic. If gram-negative bacilli (other than *Haemophilus*-like organisms) or gram-positive cocci resembling staphylococci are noted on Gram stain, culture and sensitivity should be performed.

A useful heuristic is to treat empirically with antibiotics those AECOPDs which have no other cause, and with all three of the following: increased dyspnea, increased volume, and increased purulence of sputum. In addition, antibiotics are recommended for most exacerbations in those with severe COPD.

Antibiotics for AECOPD should be chosen with the following in mind:

- coverage of all common pathogens in AECOPD;
- local resistance patterns;
- risk factors for *P. aeruginosa;*
- route of delivery, with oral preferred where possible;
- a dosage regimen that favors compliance;
- minimization of undesirable side effects, interactions with other medications, and costs;
- a duration appropriate to treat the infection. This is usually 5 to 7 days unless there is coexistent underlying disease such as bronchiectasis.

Empirical oral treatments for infective AECOPDs suggested by global guidelines come from most of the major antimicrobial classes (i.e., penicillins, tetracyclines, quinolones, macrolides, cephalosporins, and sulfonamides). Oral antibiotics should suffice in most cases without pneumonia. The increase in β-lactamase-producing *H. influenzae* and *M. catarrhalis,* and the rising incidence of penicillin-resistant *S. pneumoniae* have forced a shift to newer antibiotics, or combinations such as a penicillin with a β-lactamase inhibitor such as clavulanic acid. Of the new quinolones, moxifloxacin appears to have the best efficacy and safety profile. If pseudomonas is suspected, a quinolone is the antibiotic of choice. In an AECOPD, parenteral therapy should only be needed if the patient is severely unwell. Switching from parenteral to oral therapy should be considered as early as possible, as it is cost-effective and permits earlier discharge from hospital. Antiviral therapy is not indicated for usual AECOPD.

In the United States, by far the most commonly used antibiotic for bronchitis is azithromycin, followed by amoxicillin and clarithromycin. This is despite concerns about the cardiotoxicity of azithromycin in patients at high risk of QT prolongation. Macrolide resistance is an emerging concern.

Thirty years ago the use of prophylactic antibiotics for chronic bronchitis was common, including cyclical treatment, but concerns about effectiveness and antibiotic resistance led to a decline in the use of this approach. Recently there has been renewed interest in whether or not prophylactic antibiotics prevent AECOPD. In part this is due to the observation that in addition to antibacterial effects, macrolides may be anti-inflammatory and immunomodulatory. Both continuous and pulsed approaches (several days per week or month) have been trialed. In one placebo controlled study of 250 mg azithromycin daily for a year in over 1000 patients with at least moderate COPD, there was a 40% reduction in the number of patients with an AECOPD, and a 20% reduction in the total number of AECOPDs. However, this benefit came at an increased risk of adverse effects and an increase in antibiotic resistance in the colonizing organisms. Furthermore, the participants had to be monitored carefully for cardiotoxicity. Because of ongoing safety concerns to both individual patients and to society, prophylactic antibiotics in COPD should be reserved for the small portion of patients with moderate to severe COPD and high morbidity from frequent bacterial AECOPD.

Role of infection in bronchiectasis

BX is the end result of a number of disease processes, several of which are noninfective, such as cystic fibrosis (CF); cilial or connective tissue diseases; or abnormal immunologic responses to *Aspergillus* spp. Infection does play a role in the development of some cases of BX, e.g., recurrent respiratory infections in childhood including with respiratory viruses, *Bordetella pertussis,* or tuberculosis.

Regardless of the cause, few studies have assessed the microbiologic pattern of airway colonization in established BX. Bacteria found in the airways during stable BX include *S. pneumoniae*, *H. influenzae*, *M. catarrhalis, S. aureus*, gram-negative enteric bacilli, *Mycoplasma pneumoniae*, and nontuberculous mycobacteria. *P. aeruginosa* is particularly a problem in BX of early onset or where there is severely reduced lung function.

Unfortunately, little is known about the microbiologic etiology of AEBX. Despite the lack of evidence, general recommendations for AEBX have been made, which include:

- consideration of periodic surveillance of colonization;
- antibiotic treatment for patients with exacerbations;
- obtaining a sputum sample for culture before starting antibiotic treatment in most cases, and particularly in those requiring hospitalization;

- for empirical antibiotic treatment, patients should be stratified according to the potential risk of *Pseudomonas* spp. infection;
- empirical antibiotics should be adjusted or modified according to sputum culture results.

Prolonged antibiotic therapy has shown only a small benefit in modifying the outcome of purulent BX. Nebulized antibiotics are not recommended for non-CF BX, in contrast to the situation with CF BX.

As in COPD, there is interest in the use of prophylactic treatment of patients with BX, using either continuous or pulsed regimens, with the main aim to reduce exacerbation frequency. While this approach does reduce exacerbations significantly in BX, it has no effect on lung function decline nor quality of life. Moreover, there is the potential for harm through adverse effects and in terms of driving antibiotic resistance, as discussed above in the COPD section. At present, this approach is not recommended in routine practice.

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30. Croup, supraglottitis, and laryngitis

Irmgard Behlau

CROUP

Croup is a clinical syndrome characterized by a seal-like barking cough, hoarseness, inspiratory stridor, and often some degree of respiratory distress. The term *croup* is usually used to refer to acute laryngotracheobronchitis. Other croup-like syndromes can include spasmodic croup and bacterial tracheitis (Table 30.1). Other potential infectious causes of stridor include supraglottitis (epiglottitis), peritonsillar abscess, retropharyngeal abscess, and rarely, diphtheria, whereas noninfectious etiologies include angioneurotic edema, foreign-body obstruction, hemangioma, trauma, neoplasm, subglottic stenosis, or extrinsic compression. Croup is primarily a disease of children between the ages of 1 to 6 with peak incidence between 6 months and 3 years. The parainfluenza viruses (1, 2, and 3) are the most frequent cause with outbreaks occurring predominantly in the winter months. Other occasional causes include respiratory syncytial virus (RSV), influenza, and adenovirus with rare cases secondary to *Mycoplasma*, *Corynebacterium diphtheriae*, and herpes simplex virus (HSV). In adults, the causes are also predominantly viral, including reported cases of influenza, parainfluenza, RSV, HSV, and cytomegalovirus (CMV). In either children or adults, most likely secondary bacterial infections with *Haemophilus influenzae* type b (Hib), staphylococci, *Moraxella catarrhalis*, and *Streptococcus pneumoniae* can be seen.

Croup usually follows a relatively mild upper respiratory infection. Its onset is commonly abrupt and occurs in the late evening and night. Viral infection with associated inflammation of the nasopharynx spreads inferiorly to the respiratory epithelium of the larynx and trachea. The subglottic region in children is normally narrow and surrounded by a firm ring of cartilage. Small swelling of this narrow subglottic area will significantly restrict air flow and produce audible inspiratory stridor, while the impairment of the mobility of the vocal cords will produce hoarseness.

Rapid, objective, and calm assessment of severity must be done to determine management and without respiratory compromise. The presence of chest wall retractions and stridor at rest are most critical (Table 30.2). Anteroposterior radiologic examination of the soft tissues of the neck (with medical monitoring) may be useful when the diagnosis is in question. The classic steeple sign is produced by the cone-shaped narrowing of the proximal 1-cm subglottic area of the trachea, at the conus elasticus to the level of the true vocal cords. It is produced by edema with elevation of the tracheal mucosa and the loss of the normal lateral convexities (shoulders) of the air column (Figure 30.1). Direct visualization of the airway can be attempted if the symptoms are not typical and the child is stable. If intubation appears imminent or there is a strong suspicion of epiglottitis, this should be performed under anesthesia. In croup, the supraglottic region appears normal.

Therapy

Management includes corticosteroids, nebulized budesonide, and nebulized epinephrine. Oxygen or heliox are often used as supportive treatment. No clear data exist on the benefits of mist or humidified air. Analgesics improve sore throat and overall comfort. Antitussives, decongestants, and "prophylactic" antibiotics are not beneficial.

Due to the sustained anti-inflammatory effects of corticosteroids, they have been shown to improve the status of not only severe croup but also mild to moderate croup. Dexamethasone in doses of 0.15 to 0.6 mg/kg has been shown to be beneficial and decreases the need for hospitalizations and unscheduled medical visits even in mild croup. Oral, intramuscular, and intravenous routes of administration are all effective, with nebulized dexamethasone possibly less effective. Nebulized budesonide, 2 mg, has been shown to be as effective as dexamethasone but is often reserved for patients with intractable vomiting

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Table 30.1 Comparison of croup-like syndromes

Characteristic	Spasmodic croup	Laryngotracheobronchitis	Bacterial tracheitis	Supraglottitis
Age range	6 mo–3 yr	0–6 yr (peak, 6 mo–3 yr)	1 mo–6 yr	Infants ≤2 mo, older children, and adults
Etiology	? Viral ? Airway reactivity	Parainfluenza virus (1, 2, 3) Influenza Respiratory syncytial virus Adenovirus	*Staphylococcus aureus* *Haemophilus influenzae* *Corynebacterium diphtheriae*	*Haemophilus influenzae* (Hib/non-b) *Streptococcus pneumoniae* Group A streptococcus *Haemophilus parainfluenzae*
Onset	Sudden	Insidious	Rapid deterioration	Sudden
Clinical manifestations	Afebrile Nontoxic Barking cough Stridor Hoarse	Low-grade fever Nontoxic Barking cough Stridor Hoarse	High fever Toxic Barking cough Stridor Hoarse	High fever Toxic Nonbarking cough Muffled voice Drooling Dysphagia Sitting, leaning forward
Endoscopic findings	Pale mucosa Subglottic swelling	Deep-red mucosa Subglottic swelling	Deep-red mucosa Copious tracheal secretions	Cherry-red epiglottis Arytenoepiglottic swelling
Complete blood count, differential	Normal	Mild leukocytosis Lymphocytosis	Normal to mild leukocytosis Marked Bandemia	Marked leukocytosis Bandemia
Radiographic findings	Subglottic narrowing	Subglottic narrowing	Subglottic narrowing Irregular tracheal border	Large epiglottis Thick arytenoepiglottic folds
Therapy	Mist Calm ?Racemic epinephrine ?Steroids	Corticosteroids Racemic epinephrine Nebulized budesonide Intubation (if necessary)	Intubation Antibiotics	Intubation Antibiotics
Response	Rapid	Transient	Slow (1–2 wk)	Variable (hours–days)
Intubation	Rare	Occasional	Usual	Usual

or for simultaneous administration with epinephrine in severe respiratory distress because it is substantially more expensive and more difficult to administer. The combination of oral dexamethasone and nebulized budesonide is no better than either alone. For the management of outpatient croup, oral prednisolone, 2 mg/kg/day as two divided doses per day, may be considered as an alternative, but comparison studies have been limited to oral dexamethasone.

Owing to the rapid onset of action, the use of nebulized racemic epinephrine has markedly reduced the need for intubation, even in hospitalized patients, to less than 2%. L-epinephrine (1:1000) is as effective as racemic epinephrine. Improvement occurs within minutes, but symptoms can recur within 2 hours; therefore, patients must be observed in the emergency room for 3 hours.

The administration of oxygen should be reserved for children with significant respiratory distress and hypoxia (oxygen saturation on room air ≤92%). Heliox, a lower density gas that is a mixture of oxygen (20%–30%) and helium (70%–80%), has been proposed to help reduce the need for intubation in the severely ill child by improving laminar gas flow through a narrowed airway. There remains insufficient evidence to advocate its general use.

If intubation is deemed necessary, an endotracheal tube one to two sizes smaller than would be used for the same-size healthy child will be needed to prevent pressure necrosis and resulting subglottic stenosis. For those children who appear to have a secondary bacterial infection, antibiotic therapy similar to that recommended for epiglottitis should be considered to treat the possibility of a secondary bacterial process. Table 30.2 outlines therapy recommendations depending on the clinical state of the patient.

ACUTE SUPRAGLOTTITIS (EPIGLOTTITIS)

Supraglottitis is characterized by inflammation and edema of the supraglottic structures, including the epiglottis, arytenoepiglottic folds, arytenoids,

Table 30.2 Recommended table algorithm for the management of croup (laryngotracheobronchitis)

Condition	Treatment
Mild	
No stridor *No* chest wall retractions *No* respiratory distress at rest	Analgesics, hydration as needed Single dose of oral dexamethasone (0.6 mg/kg body weight) Educate parents (illness, when to seek medical assessment)
Moderate	
Stridor at rest Mild chest wall retractions No agitation or significant respiratory distress	Above including oral dexamethasone, 0.6 mg/kg Observe in emergency room If improved with no stridor or retractions, educate, home If no or minimal improvement by 4 h, hospitalization
Severe	
Stridor may decrease with worsening airway obstruction Significant respiratory distress Severe chest wall retractions Agitation or lethargy Decreased air movement Possibly cyanosis	Nebulized racemic epinephrine 2.25% (0.5 mL/2.5 mL saline) or L-epinephrine 1:1000 (5 mL), may repeat Oral or parenteral dexamethasone 0.6 mg/kg, may repeat If contraindications to oral medication, consider nebulized budesonide 2 mg with epinephrine Humidifed oxygen ($\leq$92% room air 0_2 sat, consider heliox) ICU care, intubation as necessary

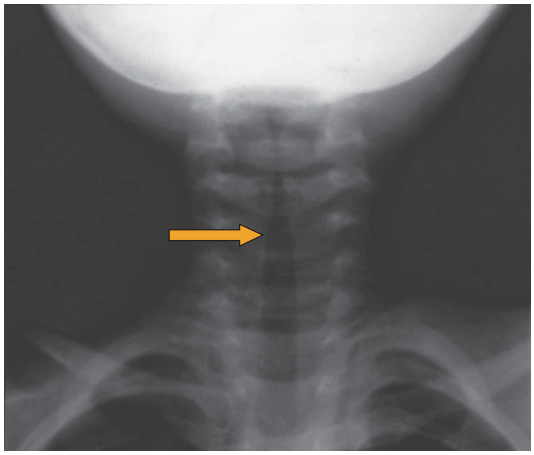

Figure 30.1 The "steeple sign" of croup. Anteroposterior radiograph of the upper airway (arrow) of a patient with croup. (Courtesy of Drs. A. Weber and H. D. Curtin, Dept. of Radiology, Massachusetts Eye and Ear Infirmary, Boston, MA.)

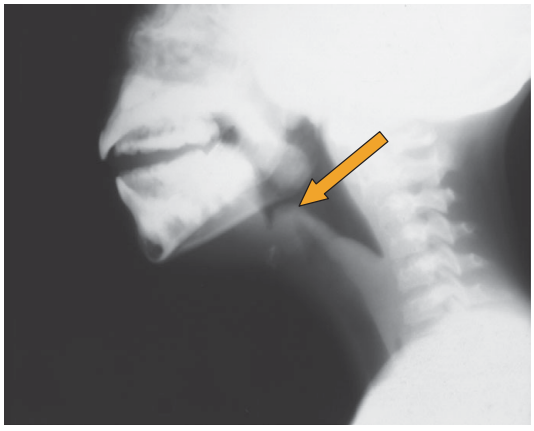

Figure 30.2 The "thumb sign" of supraglottitis. Lateral radiograph of the neck in a patient with supraglottitis; arrow indicates thickened epiglottitis. (Courtesy of Drs. A. Weber and H. D. Curtin, Department of Radiology, Massachusetts Eye and Ear Infirmary, Boston, MA.)

and false vocal cords; paradoxically, the epiglottis may be spared.

In children, acute supraglottitis is typically characterized by a fulminating course of severe sore throat, high fever, dysphagia, drooling, low-pitched inspiratory stridor, and airway obstruction, which, if left untreated, can lead to death. The child appears toxic and prefers an airway-preserving posture – sitting upright, jaw protruding forward, while drooling. In adults, the presentation is more variable; most adults have mild illness with a prolonged prodrome. In immunocompromised patients, there may be a paucity of physical findings.

Definitive diagnosis is made by examination of the epiglottis and supraglottic structures. No attempt should be made to visualize the epiglottis in an awake child; therefore, a severely ill child must be examined in the operating room at the time of control of the airway. In children, the epiglottis is typically fiery red and extremely swollen, but occasionally the major inflammation involves the ventricular bands and arytenoepiglottic folds, and the epiglottis appears relatively normal. In adults, awake indirect laryngoscopy may be performed, but only when it is possible to establish an artificial airway. In adults, the supraglottic structures may appear pale with watery edema. If indirect laryngoscopy is unavailable, lateral neck radiographs are also useful for evaluating supraglottitis (Figure 30.2), but they are not as sensitive and should never delay protecting the airway. The classic appearance is of an enlarged epiglottis bulging from the anterior wall of the hypopharynx with straightening of the cervical spine from the usual mild lordosis.

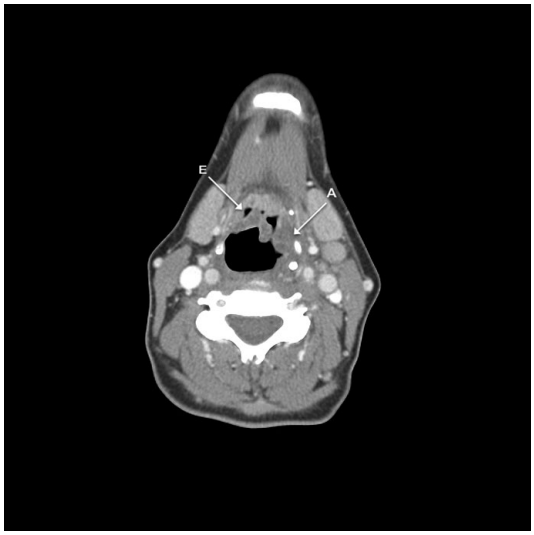

Figure 30.3 Computed tomography (CT) scan of the neck in an adult with acute supraglottitis due to group A β-hemolytic streptococci. Findings include an edematous epiglottis (E), narrowing of the larynx, and also a hypoattenuating area (A) at the level of the hyoid body suggestive of early abscess formation. (Courtesy of R. L. Reichle, MD and P. A. Rogoff, MD, Depart. of Radiology, Mount Auburn Hospital, Cambridge, MA.)

Computed tomography (CT) imaging may help to diagnose complicating conditions such as a parapharyngeal abscess (Figure 30.3).

The epidemiology of acute supraglottitis has changed dramatically since the introduction of the Hib vaccines in the mid to late 1980s. Supraglottitis, which most commonly had affected children 2 to 7 years of age, is now rarer in young children than adults, is primarily a disease of older children and adults, and is increasingly being caused by other microbial pathogens. The incidence of invasive Hib has decreased more than 99% compared to the pre-vaccine era. The organisms typically involved, in addition to Hib, are *S. pneumoniae*, *Staphylococcus aureus*, β-hemolytic streptococci, *H. influenzae* type non-b, *Haemophilus parainfluenzae*, rarely in adults *Pasteurella multocida*, and possibly increasing reports of *Neisseria meningitidis* since 1995. There are very rare reports of children developing Hib epiglottitis despite vaccination. The role respiratory tract viruses play as primary pathogens remains unclear. There have been reports of HSV type 1 and varicella as primary pathogens in immunocompromised hosts. Noninfectious causes include thermal and corrosive injury, lymphoproliferative disorders, and graft-versus-host disease.

Therapy

Treatment of acute supraglottitis is directed at establishing an airway and administering appropriate antibiotics. Children with epiglottitis should routinely have an artificial airway established; observation cannot be routinely recommended because the mortality rate is 6% to 25% and increases to 30% to 80% for those who develop obstruction. Most deaths occur within the first hours after arrival. The use of a "prophylactic airway" has reduced the mortality rate to less than 1%. The management of the airway in adult supraglottitis reflects the greater variability of clinical presentation and course. It has a range of mortality rates from 10% to 32%. Vigilant airway monitoring and continuous staging are needed for adults whose disease may progress to respiratory compromise. A formal written "acute airway obstruction protocol" should be followed. Factors associated with airway obstruction include symptomatic respiratory difficulty, stridor, drooling, shorter duration of symptoms, enlarged epiglottis on radiograph, and *H. influenzae* bacteremia.

An endotracheal tube is preferred over a tracheotomy for the following reasons: (1) ease of removal of the tube 2 to 3 days after the edema has subsided, thereby shortening the hospital stay; (2) no surgery; and (3) mortality and complication rates equal to or lower than those for tracheotomy.

Antibiotic therapy should include coverage for *H. influenzae*, *S. pneumoniae*, group A β-hemolytic streptococci, other streptococci, *H. parainfluenzae*, and *S. aureus*. Second- and third-generation cephalosporins are first-line agents. Pediatric dosages are intravenous cefuroxime, 150 mg/kg, 3 doses per day; cefotaxime, 150 mg/kg, 3 doses per day; ceftriaxone, 50 mg/kg/day; or ampicillin–sulbactam, 200 to 400 mg/kg, at 4 doses per day. The recommended adult dosages are intravenous ceftriaxone, 2 g/day; cefotaxime, 2 g every 4 to 8 hours; or ampicillin/sulbactam 1.5 to 3 g every 6 hours. Antibiotic therapy should be continued for 10 to 14 days. In patient populations with a significant prevalence of community-acquired methicillin-resistant *S. aureus* (MRSA) or penicillin-resistant *S. pneumoniae*, clindamycin, 30 to 40 mg/kg divided in 3 doses (max 2400 mg/day) or vancomycin, 40 to 60 mg/kg/day in 3 to 4 doses in children or 2 g/day in adults adjusted for renal function should be considered. Duration of therapy is usually 7 to 14 days, depending on patient response.

Steroids are commonly used for supraglottitis to theoretically decrease inflammation. There has been no evidence for any significant benefit, and in adults, there is no indication that steroids prevent the need for airway intervention. With epiglottitis being so uncommon and therefore all studies being small, it will be difficult to evaluate any beneficial role. The use of steroids remains controversial.

Prevention

Prophylaxis is indicated for supraglottitis secondary to Hib. Rifampin, 20 mg/kg, not to exceed 600 mg/day, daily for 4 days is recommended for: (1) all household contacts (except pregnant women) when there is a child younger than 12 months irrespective of vaccine status or there is a child younger than 4 years of age with incomplete vaccination; (2) day-care and nursery school classroom contacts (including adults) (a) if two or more cases of invasive disease have occurred within 60 days and unvaccinated or incompletely vaccinated children attend or (b) with one case and susceptible children 2 years or younger who attend for 25 hours or more per week (susceptible children should be vaccinated); if children are older than 2 years, rifampin prophylaxis need not be given irrespective of vaccination status. (3) The patient should receive prophylaxis before discharge if treated with ampicillin or chloramphenicol to prevent reintroduction of the organism into the household. Prophylaxis is not needed for those treated with the aforementioned recommended cephalosporins because they eradicate Hib from the nasopharynx.

Since the introduction of conjugated vaccines for infants beginning at 2 months of age, the incidence of supraglottitis resulting from Hib in this age group has declined by 99%, along with other invasive forms of Hib. There have been isolated rare reports of supraglottitis in children who have been vaccinated, but in general, we are seeing a near-eradication of Hib supraglottitis in young children. Supraglottitis caused by Hib occurs now primarily in undervaccinated children, infants too young to have completed the primary series of vaccinations, and older children and adults who have never been immunized.

LARYNGITIS

The larynx rests in the hypopharynx and consists of: (1) the supraglottic larynx, which includes the laryngeal inlet formed by the epiglottis anteriorly and the arytenoepiglottic folds bilaterally merging inferiorly into false cords, and (2) the glottic larynx, which consists of the true vocal cords.

Acute laryngitis often presents with hoarseness, odynophagia, and localized pain, which may also be referred and manifests as otalgia. Obstruction of the airway is uncommon in adults but more common in young children, especially if associated with tracheal inflammation as in croup, and must be distinguished from acute supraglottitis. Examination of the larynx reveals erythema, edema, secretions, and occasionally superficial mucosal ulcerations. The presence of exudate or membrane on the pharyngeal or laryngeal mucosa should raise the suspicion of streptococcal infection, mononucleosis, or diphtheria; granulomatous infiltration may be compatible with tuberculosis, sarcoidosis, fungal infection, or syphilis.

The respiratory viruses such as influenza virus, parainfluenza virus, rhinovirus, and adenovirus are most often isolated in cases of laryngitis (90%). *M. catarrhalis* has been isolated from the nasopharynx of 50% to 55% and *H. influenzae* from 8% to 15% of adults with laryngitis. It remains unclear whether these may represent a secondary bacterial invasion. Group A and G streptococci, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae* have also been associated with acute laryngitis. Laryngeal diphtheria is very rare and usually results from extension of pharyngeal involvement. It may occur in previously immunized persons.

Fungal infections such as histoplasmosis, coccidioidomycosis, blastomycosis, and cryptococcosis may cause laryngitis. Candidiasis is most often seen in immunosuppressed patients. *Treponema pallidum*, HSV, and herpes zoster virus may also be causes of acute laryngitis. Laryngeal tuberculosis is very rarely seen in the United States since the advent of effective antimycobacterial therapy. It is associated with a large tuberculous load, and patients often have very active pulmonary involvement. Sarcoidosis, Wegener's granulomatosis, and rhinoscleroma may be considered causes of laryngitis.

Therapy

Because most cases of acute laryngitis are viral in etiology and self-limited, treatment usually consists of resting the voice and inhaling moistened air. The role of empiric antibiotic therapy of laryngitis has been examined by prospective double-blinded studies. Penicillin V had no effect on the clinical course. Patients treated with erythromycin

(0.5 g twice a day for 5 days) had a marked reduction of *M. catarrhalis* carriage in the nasopharynx and reported a significant improvement of subjective voice disturbances after 1 week and cough after 2 weeks; however, there was no difference in laryngoscopic examination and voice evaluation. Because acute laryngitis in adults is self-limiting and subjective symptoms are spontaneously reduced after 1 week in most cases, empiric antibiotic treatment does not seem warranted as a general policy.

Antimicrobial therapy is indicated only in those patients with a bacterial infection or superinfection; therapy is directed toward the believed causative agent. Usual duration is for 10 to 14 days. The use of corticosteroids should be avoided due to their ability to mask vocal cord pathology.

Immunosuppressed patients who present with hoarseness or patients whose hoarseness has persisted longer than 10 to 14 days should have a laryngoscopic examination to exclude other more atypical causes such as HSV, bacterial, fungal, mycobacterial, and malignant etiologies of laryngitis.

SUGGESTED READING

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31. Atypical pneumonia

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ATYPICAL PNEUMONIA

The term "atypical pneumonia" was first termed over 60 years ago to describe cases of pneumonia caused by an unknown agent(s) and which appeared clinically different from pneumococcal pneumonia. It was initially characterized by constitutional symptoms, often with upper and lower respiratory tract symptoms and signs, a protracted course with gradual resolution, the lack of typical findings of consolidation on chest radiograph, failure to isolate a pathogen on routine bacteriologic methods, and a lack of response to penicillin therapy. In the 1940s an agent that was believed to be the principal cause was identified as *Mycoplasma pneumoniae.* Subsequently other pathogens have been linked with atypical pneumonia because of similar clinical presentation, including a variety of respiratory viruses, *Chlamydia pneumoniae, Chlamydia psittaci,* and *Coxiella burnettii*. Less common etiologic agents associated with atypical pneumonia include *Francisella tularensis, Yersinia pestis* (plague), and the Sin Nombre virus (hantavirus pulmonary syndrome), although these agents are often associated with a more acute clinical syndrome. In addition, although presently exceedingly rare, inhalation anthrax is included in part because of the concern for this pathogen as an agent of bioterrorism. Finally, pneumonia caused by *Legionella* species, albeit often more characteristic of pyogenic pneumonia, is also included since it is not isolated using routine microbiologic methods.

Although the original classification of atypical and typical pneumonia arose from the perception that the clinical presentation of patients was different, recent studies have shown there is excessive overlap of clinical manifestations of specific causes which does not permit empiric therapeutic decisions to be made solely on this basis. Thus, the designation of atypical pneumonia is controversial in relation to scientific and clinical merit; and many authorities have suggested that the term "atypical" be discontinued. However, the term remains popular among clinicians and investigators and remains prevalent in recent literature regardless of its clinical value. Moreover, options for appropriate antimicrobial therapy for the most common causes are similar, which is considered justification by some to lump these together.

M. pneumoniae, *C. pneumoniae*, and *Legionella pneumophila* are the most common causes of atypical pneumonia. Results of recent studies indicate they cause from 15% to as much as 50% (in selected outpatient populations) of cases of community-acquired pneumonia (CAP). However, these pathogens have not been identified often in clinical practice, because until recently there have not been specific, rapid, or standardized tests for their detection. The "other" causes of atypical pneumonia occur with much less frequency.

Treatment of atypical bacterial pneumonia in the spectrum of CAP has been controversial and is related to several issues, which include the relevance of terminology, imprecise diagnostic methods at present, and perceived contradictory results of published evidence. However, limitations of clinical trial methodology limit our interpretation of the actual benefit of providing coverage since many atypical pneumonias are eventually self-limited. Studies evaluating the time to clinical recovery and the use of earlier end points for evaluation suggest that appropriate therapy provides a benefit if an atypical pathogen is present. Similarly, a recent critical review concluded that available evidence does support treatment of the atypical pneumonia.

CLINICAL MANIFESTATIONS

Although the diagnosis of these specific pathogens is difficult to establish on clinical manifestations alone, there are several generalizations which may be helpful.

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Mycoplasma pneumoniae

M. pneumoniae is a common cause of respiratory infections which range from unapparent infection, upper respiratory infection, tracheobronchitis to pneumonia. Infection is transmitted from person to person by respiratory droplets with a usual incubation period of several weeks. Only 3% to 10% of infected persons develop pneumonia. Although commonly perceived as a cause of CAP predominantly in young healthy patients, the incidence of *M. pneumoniae* pneumonia increases with age, highlighting the importance of this pathogen in the elderly as well.

M. pneumoniae pneumonia is considered to be the "classic" atypical pneumonia. Many of the pathogenic features are believed to be immune mediated rather than induced directly by the bacteria (antibodies produced against the glycolipid antigens of *M. pneumoniae* may cross-react with human red cells and brain cells). Constitutional symptoms including headache, malaise, myalgias, and sore throat are frequently present. Cough is typically initially dry, may be paroxysmal and frequently worse at night; and may become productive of mucopurulent sputum. The physical findings often are minimal, seemingly disproportional to the patient's complaints. Auscultation of the lungs usually reveals variable scattered rales or wheezes. Bullous myringitis, first described in volunteer subjects infected with *M. pneumoniae*, has been infrequent in naturally occurring infection and is not a diagnostic sign. Chest radiograph findings are variable. Most common is peribronchial pneumonia.

The course of *M. pneumoniae* pneumonia is usually mild and self-limiting. However, significant pulmonary complications may occur and include: pleural effusion, pneumatocele, lung abscess, pneumothorax, bronchiectasis, chronic interstitial fibrosis, respiratory distress syndrome, and bronchiolitis obliterans. Extrapulmonary manifestations include rash, neurologic involvement (i.e., aseptic meningitis, meningoencephalitis, cerebral ataxia, Guillain–Barre syndrome, and transverse myelitis), hemolytic anemia (associated with cold agglutinins), myopericarditis, polyarthritis, and pancreatitis.

Chlamydia pneumoniae

Pneumonia caused by *C. pneumoniae* may be sporadic or epidemic. *C. pneumoniae* infections are often acquired early in life. Transmission is by person to person via respiratory secretions with an incubation period of several weeks. Reinfections or recrudescent processes, both referred to as recurrent infection, may occur throughout one's lifetime. Most adults who are hospitalized with *C. pneumoniae* pneumonia have recurrent infection.

The clinical manifestations of *C. pneumoniae* pneumonia remain somewhat unclear because of the lack of a gold standard of diagnosis and the contributing effect of co-pathogens. The onset is usually insidious. Infections often present initially with sore throat, hoarseness, and headache as important non-classic pneumonic findings. A subacute course is common and fever is low grade. Cough is prominent but unproductive and may last, if not treated early and effectively, for weeks or even months. Chest radiographs tend to show less extensive opacifications in relation to clinical findings than other processes. However, extensive infiltrates have been reported. Patients with primary infection are usually younger and tend to have higher fever. For older patients with reinfection, the presence of comorbid illness and the requirement for supplemental oxygen therapy are often the reason for hospital admission.

Legionella pneumophila

Legionellosis is primarily associated with two clinically distinct syndromes: Legionnaires' disease (LD), a potentially severe pneumonia, and Pontiac fever, a self-limited, nonpneumonic illness. Many of the clinical features of LD are more typical of pyogenic (bacterial) pneumonias. However, as LD has become increasingly recognized, less severely ill patients are seen earlier in the course of disease, and thus clinical manifestations of unusual severity are now less specific. *Legionella* is not spread person to person but usually by exposure to water. Outbreaks may be associated with infected water sources. The incubation period is 2 to 10 days.

The onset of LD is often acute; with high fever, myalgias, anorexia, and headache. Temperature often exceeds 40°C. Gastrointestinal symptoms are prominent, especially diarrhea. Hyponatremia and elevated lactate dehydrogenase levels (LDH) were common abnormal laboratory studies observed in our experience.

Other causes of atypical pneumonia

Other causes of atypical pneumonia include *Coxiella burnetii* (Q fever), psittacosis, tularemia, hantavirus pulmonary syndrome, plague, inhalation anthrax, and respiratory viruses.

Table 31.1 Common characteristics and therapy for the other atypical pneumonias

Pathogen	Epidemiologic or underlying condition	Clinical features	Recommended therapy
Chlamydia psittaci	Exposure to birds	HA, pharyngeal erythea, splenomegaly, Horder' spots (see text)	Doxycycline; alternatives: macrolide or respiratory fluoroquinolone (e.g., levofloxacin or moxifloxacin)
Coxiella burnettii (Q fever)	Exposure to farm animals (especially parturient)	HA prominent, liver involvement	Doxycycline (in combination with hydroxychloroquine if endocarditic); Alternatives: macrolide or respiratory fluoroquinolone
Francisella tularensis[a] (tularemia)	Exposure to rabbits	HA, chest pain prominent	Streptomycin or gentamicin considered as drug of choice; doxycycline effect for most cases (especially if nonsevere)
Yersinia pestis[a] (pneumonic plague)	Exposure to infected animals (rodents, cats, squirrels, chipmunks, prairie dogs)	For inhalation, acute onset with rapidly severe pneumonia; blood-tinged sputum	Streptomycin, gentamicin; tetracycline, doxycycline
Bacillus anthracis[a]	Wool mill worker	Biphasic (see text); hallmark radiographic finding – mediastinal widening	Ciprofloxacin plus one of the following for initial therapy: rifampin, vancomycin, β-lactam, or clindamycin; switch to monotherapy when clinically appropriate – see text
Viruses			
Influenzae	Influenza in community (Avian-poultry exposure)	Influenza pneumonia usually follows tracheobronchitis	Oseltamivir (orally), zanamivir (via inhalation)
Adenovirus		Pharyngitis prominent	No approved antiviral
Respiratory syncytial virus	Adults: cardiopulmonary disease, COPD	Bronchospasm	No antiviral agent currently recommended (ribavirin possibly for selected cases – see text)
Hantavirus pulmonary syndrome	Exposure to rodent excreta	Febrile prodrome; followed by noncardiogenic pulm edema with shock; thrombocytopenia	Supportive care
MERS-CoV	Travel to Arabian peninsula	Severe respiratory syndrome	Supportive care

[a] Potential infectious agent for biologic warfare

Abbreviations: HA = headache; COPD = chronic obstructive disease; MERS-CoV = Middle East respiratory syndrome coronavirus.

Several of the less common causes of the atypical pneumonia syndrome are zoonotic infections, i.e., transmitted from animals to humans. In such cases epidemiologic clues may be very important; and while specific manifestations cannot be considered diagnostic of a specific etiology, there are general findings which are characteristic of these diseases (Table 31.1).

Coxiella burnetii may be associated with exposure via any mammal, but most commonly cattle, goats, sheep, and pets, including cats and dogs. Infected mammals shed *C. burnetii* in their urine, feces, milk, and placenta. The mode of transmission is either aerosol or by tick bite; high concentrations of the organism can be found in birth products of infected animals. The incubation period is approximately 3 weeks. The acute disease is a self-limiting "flu-like" illness characterized by high fever, rigor, headache, myalgias, cough, and arthralgia. Pneumonia may be accompanied by granulomatous hepatitis. Radiologic findings include lobar or segmental alveolar opacities which may be multiple. Other manifestations may include maculopapular or purpuric rash, aseptic meningitis or encephalitis, hemolytic anemia, endocarditis, pericarditis, pancreatitis, or epididymo-orchitis. Rarely *C. burnetii* is associated with chronic Q fever, which is defined as infection lasting for more than 6 months and endocarditis is the predominant manifestation.

Pneumonia due to *C. psittaci* usually occurs after exposure to infected birds. Infection in birds is usually asymptomatic, or may cause illness associated with ruffled feathers, ocular or nasal discharge. The organism is shed in feces, urine, and respiratory secretions. Humans are usually infected by inhalation of organisms in dried feces or in bird feather dust. Cage cleaning may pose an infection risk The onset is often insidious with nonproductive cough, fever, and headache, but may be abrupt. The incubation

period is usually 5 to 15 days. Clinical clues include pharyngeal erythema, splenomegaly (which tends to occur toward the end of the first week), and a rarely seen specific rash (Horder's spots – pink blanching maculopapular eruption resembling rose spots of typhoid fever).

Francisella tularensis can cause primary tularemic pneumonia. Human infection occurs following contact with infected animals (hares or rabbits most common) or biting invertebrate vectors (most commonly ticks but also mosquitoes, horse flies, fleas, and lice). In one reported outbreak of tularemic pneumonia, a significant risk factor was mowing grass (presumably airborne transmission from close contact to rabbit habitats). Pneumonia may also occur from hematogenous spread after vector-borne (e.g., tick) infection. The incubation period following infection with *F. tularensis* is 3 to 5 days. The onset is usually abrupt with high fever, chills, cough (usually nonproductive, occasionally with hemoptysis), pleuritic chest pain, and diaphoresis.

Hantaviruses comprise a genus of enveloped viruses within the family Bunyaviridae and are associated with two severe, acute febrile illnesses: hemorrhagic fever with renal syndrome and hantavirus pulmonary syndrome (HPS). Hantaviruses are shed in the urine, feces, or saliva of acutely infected reservoir rodents; transmission to humans occurs via the aerosol route. Many patients describe encountering living or dead rodents or visible evidence of rodent infestation prior to illness. Typically the incubation period is 3 weeks after exposure. The clinical illness of HPS typically begins with a prodromal phase which is characterized by nonspecific manifestations such as fever, myalgias, headache, nausea, vomiting, abdominal pain, and cough. This phase typically lasts 3 to 8 days and is followed by the cardiopulmonary phase, which starts suddenly with tachypnea and shortness of breath and is followed by respiratory failure and shock. Chest radiograph shows noncardiogenic bilateral interstitial edema during this phase. Characteristically, the patient is hemoconcentrated and manifests significant thrombocytopenia.

Yersinia pestis, which causes plague pneumonia, is primarily a zoonotic infection of rodents and wild and domestic animals (most often a cat); humans are considered incidental hosts. Transmission occurs via bites of rodent fleas, scratches or bites from infected domestic cats, direct handling of infected animal tissues, or inhalation of respiratory secretions from infected animals. Infection in the United States is found mainly in the southwestern and Pacific coastal area. Incubation is usually 2 to 3 days. The disease may have an abrupt onset and usually begins with a painless cough with shortness of breath. Untreated pneumonic plague has a 40% to 90% mortality.

In the natural setting, inhalation anthrax is exceedingly uncommon and is classically referred to as woolsorter's disease, because of the association with workers in wool mills who may inhale *Bacillus anthracis* spores. However, the potential use as a biologic weapon has brought increased interest to this pathogen. In the 2001 outbreak of probable bioterrorism-associated anthrax conducted through the US postal system, nine cases of inhalation anthrax were identified, resulting in four deaths. The incubation is variable; often less than 1 week but can be 6 weeks or longer. Initial symptoms are nonspecific with fever, malaise, chest pain, and nonproductive cough. This may be followed by brief improvement and then severe respiratory distress, shock, and death. Widened mediastinum (associated with hemorrhagic mediastinitis) without parenchymal infiltrates found on radiographic imaging (CT scan is most sensitive) is characteristic of inhalation anthrax. The diagnosis is often established with positive blood cultures that may initially be dismissed as contaminants.

In addition to inhalation anthrax syndrome, pneumonic plague, and pneumonic tularemia are possible agents of bioterrorism. Clustered cases occurring without the expected epidemiologic exposures to animals, insects, or environmental activities should raise the possibility of a bioterrorism event. Specific epidemiological, clinical, and microbiologic clues should lead to early suspicion and rapid activation of the health alert system, since laboratory confirmation of the agent could be delayed.

Pneumonia caused by respiratory viruses

Viruses account for an important number of pneumonias in adults, especially during the winter months and amongst the elderly. Recent studies suggest that approximately one-third of adults hospitalized for pneumonia had a viral etiology. Many of the emerging infections have been associated with newly identified viruses (many zoonotic): Middle East respiratory syndrome coronavirus (MERS-CoV), and the new avian influenza A viruses (H5N1 and H7N9). Influenza and respiratory syncytial virus (RSV) are the most commonly identified viral pathogens; others

include parainfluenza virus, rhinovirus, coronavirus, and possibly human metapneumovirus (although pneumonia is uncommon). Influenza should be considered during periods of peak activity within a community and is often associated with sudden fever, myalgias, and cough. RSV is a more common cause of pneumonia in immunocompetent adults than previously appreciated. Characteristics include seasonal occurrence (winter), and association of bronchospasm. MERS-CoV is a novel coronavirus which was identified in the fall of 2012 in Saudi Arabia; it is different than the coronavirus previously associated with SARS (severe acute respiratory syndrome). Most persons who became infected developed a severe acute respiratory illness and about half died. Investigations are underway to determine the source; transmission from person to person and to healthcare providers has occurred. There have been no cases reported in the United States but clinicians are advised to consider this in patients with compatible illnesses who have traveled to the Arabian Peninsula or neighboring countries. A new strain of avian influenza (influenza A H7N9) was recently identified in China. Most of the people infected have had contact with poultry and available evidence suggests there has not been ongoing spread from person to person. Symptoms have started with high fever and cough. While mild cases have been seen, most patients have had severe respiratory illness with a mortality rate of 28% at the time of this writing.

DIAGNOSIS

Laboratory tests used for the diagnosis of the etiologic agents associated with atypical pneumonia are listed in Table 31.2. Until recently serologic tests were the most common means of laboratory diagnosis for most pathogens associated with atypical pneumonia, but are less valuable given the requirement for measurement during acute and convalescent specimens. However, advancements in molecular testing methods have brought forth new potentials for diagnosis, and more rapid identification of these pathogens. Nucleic acid amplification tests (NAATs), such as polymerase chain reaction (PCR), are becoming available with marked expansion of diagnostic capability for infectious diseases. There are several commercially available and/or institutionally developed NAATs for the atypical pathogens. US Food and Drug Administration (FDA)-approved tests are available for *Mycoplasma* and *Chlamydia* (as part of multiplex PCR) and most respiratory viruses.

Although the isolation of *M. pneumoniae* on specialized media is possible, culture requires 2 to 3 weeks and the organism is fastidious. As a result, most clinical laboratories do not attempt to culture this organism. For *C. pneumoniae*, culture on cell lines has traditionally been considered as a gold standard for diagnosis. However, cell cultivation is technically complex, and is associated with limited viability and slow growth such that it is restricted to specialized laboratories. *Legionella* can be readily isolated from respiratory specimens, but requires specialized media – buffered charcoal yeast extract agar (BYCE). A urinary antigen test is available for *L. pneumophila* serogroup 1, which represents the most common cause of *Legionella* pneumonia in the USA.

Several of the other causes of atypical pneumonia can be isolated by culture, including *Francisella*, *Yersinia*, and anthrax. Since these agents can be potentially transmitted from laboratory isolates, the laboratory should be notified if there is a clinical suspicion, to optimize growth conditions as well as to take proper precautions to reduce the risk of infection among laboratory personnel.

For most respiratory viruses, PCR is now the most sensitive diagnostic approach. PCR was vital for epidemiology during the recent 2009 influenza H1N1 pandemic because commercially available rapid influenza detection tests (RIDTs) were found to be relatively insensitive (sensitivity ranging from 10% to 70% depending in part on the method used).

ANTIMICROBIAL THERAPY

Antimicrobial agents generally considered effective for these atypical pathogens are included in Tables 31.1, 31.3, 31.4. Since most cases of atypical pneumonia are treated empirically, clinicians need also consider the possibility of other 'standard' pathogens (i.e., *S. pneumoniae, H. influenzae*) when deciding on antimicrobial therapy.

Mycoplasma and *Chlamydia*

Appropriate treatment (especially for *M. pneumoniae*) reduces the morbidity of pneumonia and shortens the duration of symptoms. Erythromycin and tetracyclines have been considered effective therapy. The new macrolides (clarithromycin and azithromycin) and the azalide, telithromycin, have good in vitro activity against these organisms, and

Table 31.2 Diagnostic studies for pathogens associated with atypical pneumonia

Pathogen	Rapid test	Standard culture or microbiologic test(s)	Serology[a], other tests
M. pneumoniae	PCR [95][b]	Throat or NP swab [90] (requires 7–10 days for preliminary growth)	ELISA, CF [75–80] (IgM may be present after 1 week but can persist 2–12 months) Diagnostic criteria: Definite: 4-fold titer rise Possible: IgG $\geq$ 1:64 (CF) IgM $\geq$ 1:16 (ELISA) Cold agglutinin [50] (less than 50% specificity; takes weeks to develop)
C. pneumoniae	PCR [80–90]	Throat or NP swab – requires cell culture technique, rarely done [50–90]	CF or MIF (latter not as available) (IgM may take up to 4–6 weeks to appear in primary infection) Diagnostic criteria: Definite: 4-fold titer rise Possible: IgG $\geq$ 1:512 IgM $\geq$ 1:32
Legionella pneumophila	Urine antigen (serogroup 1) [60–70] PCR[c]	Sputum, bronchoscopy [75–99] (selective media required, 2–6 days)	IFA; ELISA [40–75] Diagnostic criteria: Definite: 4-fold titer rise Possible: IgG or IgM $\geq$ 1:512 (titer of 1:256 has positive predictive value of only 15%)
C. psittaci	PCR[c]	Usually not done (considered laboratory hazard)	CF (presumptive IgG $\geq$ 1:32) MIF for IgM
Coxiella burnettii	PCR[c]	Usually not done (considered laboratory hazard)	IFA (current reference method)
Viruses			
Influenza	Rapid antigen detection (EIA)[d], PCR	Virus isolation	CF or HAI, ELISA
RSV	Antigen detection (IF or EIA; mainstay of diagnosis), PCR	Virus isolation	ELISA
Adenovirus	PCR PCR	Virus isolation	ELISA
Francisella tularensis		Culture (selective media; considered laboratory hazard)	ELISA preferred; passive hemagglutination
Yersinia pestis	Gram stain, morphology, gram-negative coccobacillus exhibiting bipolar staining ("safety pin"); PCR	Culture (considered laboratory hazard)	ELISA, IF
Bacillus anthracis (inhalation anthrax)	PCR	Culture (may be dismissed as *Bacillus* contaminant)	

[a] Paired sera generally required.

[b] [ ] =% sensitivity of test.

[c] In selected laboratories, reagents are not FDA cleared.

[d] Low sensitivity for 2009 influenza A N1N1.

Abbreviations: ELISA = enzyme-linked immunosorbent assay; CF = complement fixation; HAI=Hemagglutination inhibition; IF= Immunofluorescence; MIF = microimmunofluorescence, IFA = indirect fluorescence Ab; EIA = enzyme immunoassay; NP = nasopharyngeal.

have shown good results in clinical studies. Although resistance to the macrolides is relatively low in the United States (<10%), the prevalence of macrolide-resistant *Mycoplasma* in Asia is very high (up to 70%–90% in some areas). The newer fluoroquinolones (i.e., levofloxacin, moxifloxacin, gemifloxacin) are bactericidal and have been shown to be effective in clinical trials.

Table 31.3 Authors recommendation for antimicrobial therapy of *M. pneumoniae* and *C. pneumoniae* (adult doses[a])

Antimicrobial	Dose	Duration (days)
Erythromycin[b]	500 mg QID	7
Clarithromycin (Biaxin)	500 mg BID	7
Azithromycin (Zithromax)[b]	500 mg initially then 250 mg QD (alternative 500 mg QD)	5 (3)
Dirithromycin (Dynabac)	500 mg QD	7
Telithromycin (Ketek)	800 mg QD	7
Tetracycline	500 mg QID	10
Doxycycline[b]	100 mg BID	7
Levofloxacin (Levaquin)[b]	500 mg QD 750 mg QD	7 5 (data are limited)
Moxifloxacin (Avelox)[b]	400 mg QD	7
Gemifloxacin (Factive)	320 mg QD	5

[a] Oral except where noted

[b] Also can be administered intravenously in equivalent dose

The duration of therapy for optimal response of *C. pneumoniae* and *M. pneumoniae* has not been well established. In initial descriptions of *C. pneumoniae* pneumonia, observers found that respiratory symptoms frequently recurred or persisted after short courses (5 to 10 days) of erythromycin or tetracycline. In recent recommendations, the usual duration of therapy for *C. pneumoniae* or *M. pneumoniae* using more recently approved agents has been 7 to 10 days (shorter for azithromycin because of the longer half-life), however recent studies (mostly with the fluoroquinolones) have suggested that a minimum of 5 days may be adequate for immunocompetent patients if the patient has had a good clinical response within 48 to 72 hours.

Legionella

There is little debate concerning the need for therapy of *Legionella* pneumonia. Therefore, empirical anti-*Legionella* therapy should be included in treatment of severe CAP. Macrolides initially have been considered accepted as the treatment of choice for Legionnaires' disease. However, intracellular models as well as animal models of *Legionella* infection indicate that the systemic fluoroquinolones and the newer macrolides (especially azithromycin) show superior activity

Table 31.4 Parenteral therapy for serious *Legionella* infections[a]

Preferred antimicrobial	Alternative antimicrobial
Fluoroquinolone	
Levofloxacin (Levaquin) 500 mg IV q 24h (750 mg QD for 5 days possible for immunocompetent patients)	Erythromycin 1 g IV q 6h +/− rifampin[b,c]
Moxifloxacin (Avelox) 400 mg IV q 24h	Doxycycline 100 mg IV q 12h +/− rifampin
Azithromycin (Zithromax) 500 mg IV q 24h	

[a] Requiring hospitalization or in immunocompromised patients; can change to PO when clinically stable and can take PO.

[b] 300–600 mg IV q 12h.

[c] Not FDA approved for this indication.

compared with erythromycin. Several observational studies suggest quinolones produce superior clinical responses compared with macrolides. The addition of rifampin to erythromycin has been suggested for patients who are severely ill; however, there are no convincing laboratory data to show that adding rifampin to fluoroquinolones or the more active macrolide therapy improves bacterial killing. I prefer the newer fluoroquinolones because of greater activity in vitro against *S. pneumoniae* (including drug-resistant strains) and other common causes of CAP that need to be considered for empirical therapy (Table 31.4). Doxycycline has also been shown to be effective in limited, well-documented cases. Oral therapy for less serious cases or for step-down from intravenous therapy includes the oral macrolides and fluoroquinolones as well as doxycycline.

The usual duration of therapy for Legionnaires' disease of immunocompetent adults has been 7 to 14 days; one recent study showed good efficacy of 750 mg QD of levofloxacin for 5 days. For therapy of immunocompromised patients or more severe disease, longer duration is recommended.

Therapy for other pathogens associated with atypical pneumonia (see Table 31.1)

CHLAMYDIA PSITTACI

The tetracyclines (e.g., doxycycline 100 mg orally twice daily) are generally considered the drugs of choice with the macrolides as appropriate alternatives. The newer fluoroquinolones are active in vitro and in animal models but their efficacy for human infection is unknown.

COXIELLA BURNETTII

Doxycycline is the preferred agent; macrolides or fluoroquinolones are alternatives. Prolonged therapy (e.g., 18 months) with hydroxychloroquine in combination with doxycycline is the preferred treatment regimen for Q fever endocarditis.

FRANCISELLA TULARENSIS

The traditional choice of therapy for pneumonic tularemia is streptomycin (10 mg/kg every 12 hours up to 2 g/day for an adult) or gentamicin (3 to 5 mg/kg/day) for 7 to 14 days. Doxycycline (100 mg IV or PO BID) has often been used with good success, particularly in nonsevere pneumonia, and is easier to administer.

HANTAVIRUS PULMONARY SYNDROME

Treatment options are limited. The use of ribavirin has not been shown to be effective in one small study. Optimal cardiopulmonary and fluid management is critical for appropriate management.

YERSINIA PESTIS

Streptomycin (similar dose/day as for tularemia) is considered the drug of choice with 10 days being the minimum recommended course of therapy. Alternatives include gentamicin, tetracycline, and doxycycline. Close contacts of patients with pneumonic plague should receive tetracycline (500 mg QID) or doxycycline (100 mg BID) for 5 to 7 days for prophylaxis.

INHALATION ANTHRAX

The mortality rate remains high if treatment is not initiated prior to the development of clinical symptoms. Because of possible resistance, recent recommendations for initial therapy of inhalation anthrax are to use a multidrug regimen which can be switched to monotherapy once the patient has stabilized and possible susceptibility test results are known (Table 31.1). Treatment should be continued for 60 days due to the potential problem of prolonged incubation with delayed, but lethal, disease. If anthrax is a concern as an agent of bioterrorism, it is important to provide prophylaxis to the population at risk. The preferred regimens are ciprofloxacin (500 mg PO BID), levofloxacin (500 mg daily), or doxycycline (100 mg PO BID). Amoxicillin 500 mg TID for an adult is OK if the associated *B. anthracis* strain has an amoxicillin minimal inhibitory concentration $\leq$0.125 μg/mL. Prophylaxis should be continued for 60 days.

INFLUENZA

Because of the high rates of resistance in the United States amantadine and rimantadine are not recommended for treatment of seasonal influenza. A neuraminidase inhibitor (oseltamivir or zanamivir) is the recommended antiviral for treatment. Although there are no randomized clinical trials, oseltamivir is recommended for the treatment of avian influenza A (including H5N1 and the newly described H7N9). There does appear to be a mortality benefit for H5N1 based on an analysis of a registry from approximately 300 patients. While no data are available regarding treatment of persons with H7N9 influenza, laboratory testing indicates that most strains are susceptible to oseltamivir; but resistant strains have been identified.

RSV

The routine use of ribavirin is not recommended for infants and children with RSV. Several authorities recommend therapy in selected infants and young children who are at high risk for serious RSV disease. The benefit of ribavirin therapy for adults has not been established; however, it has been shown to reduce morbidity and mortality in adult bone marrow transplant recipients who develop RSV infections.

MERS-COV

No specific antiviral therapy is presently available.

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32. Community-acquired pneumonia

Keyur S. Vyas

Community-acquired pneumonia (CAP) causes significant morbidity and mortality worldwide. In developed countries, most episodes occur in the elderly with one or more chronic underlying disease. Children are more commonly affected in the developing world. Mortality from CAP averages 14% and has not decreased significantly since the early 1950s despite advances in antibiotic and intensive care therapy. Making the clinical diagnosis of pneumonia is usually not difficult; deciding which patients should be admitted to the hospital and selecting appropriate therapy, however, can be challenging.

DIAGNOSIS AND TREATMENT

Pneumonia is suspected when one or more of the following is present: cough, purulent sputum, dyspnea, pleuritic pain, fever, chest auscultation findings consistent with pneumonia, leukocytosis, or a new pulmonary infiltrate on imaging. Once the diagnosis is suspected, the physician must decide whether hospitalization is necessary and if intensive care unit (ICU) admission is appropriate.

A number of risk factors predict a complicated course (Table 32.1). Multiple scoring systems have been proposed to assess disease severity and predict mortality to assist in determining if hospitalization is necessary; two such systems are the CURB-65 score from the British Thoracic Society and the Pneumonia Severity Index (PSI) from the Pneumonia Patient Outcomes Research Team (PORT). The PSI assigns points for 19 variables based on age and comorbidities similar to those listed in Table 32.1. Patients are then assigned to one of five risk categories. Patients in risk groups I and II can be managed as outpatients whereas risk groups III–V should be hospitalized. The CURB-65 criteria include confusion, blood urea nitrogen (BUN) (>20 mg/dL), respiratory rate (>30 breaths/minute), blood pressure (systolic ≤90 mm Hg or diastolic ≤60), and age ≥65 years.

Table 32.1 Predictors of a complicated course in patients with community-acquired pneumonia

Suspicion of high-risk cause (*Staphylococcus aureus*, gram-negative bacilli, aspiration, or postobstructive process)
Age > 50 years
Prior episode of pneumonia
Consolidation, multilobe involvement, or pleural effusion on chest radiograph
Abnormalities on physical examination: Temperature ≤ 95ºF (35ºC) or >104ºF (40ºC) Systolic or diastolic blood pressures ≤90 mm Hg or ≤60 mm Hg, respectively Respiratory rate ≥30 breaths/minute Heart rate >125 beats/minute Extrapulmonary areas of infection
Laboratory factors Abnormal renal function (BUN >20 mg/dL or serum creatinine >1.2 mg/dL) Sodium ≤130 mg/dL Glucose ≥250 mg/dL Hematocrit ≤30% WBC count ≤4000/mm³ or >30 000/mm³ Metabolic acidosis (pH ≤7.35) PaO_2 ≤60 mm Hg breathing room air
Comorbid conditions Renal insufficiency Congestive heart failure Liver disease Diabetes mellitus Altered mental state Neurologic disease Alcoholism Immunosuppression Malignancy Splenectomy
No responsible person in the home to assist the patient

Abbreviations: BUN = blood urea nitrogen; WBC = white blood cell.

Patients with 0–1 of these findings can be managed as outpatients. Those with a score of 2 should be admitted to hospital, whereas those with 3 or more should receive ICU care. The PSI gives a more accurate prediction of which patients can

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be safely managed outside the hospital. The CURB-65 is less cumbersome and easier to use in the outpatient setting. Various biomarkers, including C-reactive protein, procalcitonin (PCT), and proadrenomedullin (proADM) have been proposed to assist in risk stratification. PCT is elevated in bacterial infections and has been used to determine need for antibiotics and discharge from the hospital. ProADM, when used with the PSI and CURB-65 risk scoring systems, improves prognostic accuracy for adverse outcomes. The use of these biomarkers is not currently routine but may be helpful if available. Risk stratification guides and biomarker measurements are useful, but the clinician's judgment remains the ultimate decision-making tool.

Accurate history, including occupation; travel; exposure to animals, birds, and insects; sick contacts; recent dental work; and history of alcohol or drug abuse may suggest a causative agent (Table 32.2). Bacteria and respiratory viruses cause the majority of CAP with a minority of cases caused by fungi, such as the endemic mycoses. Geographic variations affect the spectrum and proportion of causative agents. A significant proportion of cases may be polymicrobial, most commonly bacteria in combination with either atypical bacteria or respiratory viruses. Most cases are treated without identification of a specific cause, especially in the outpatient setting.

Streptococcus pneumoniae is the most commonly identified pathogen in all treatment settings, followed by atypical bacterial agents, *Haemophilus influenzae*, and respiratory viruses. *Staphylococcus aureus* causes only 1% to 3% of cases of CAP, but is associated with significant morbidity and mortality, especially in younger adults. There are no unique clinical features of any pathogen that allow a specific identification by history alone. Human immunodeficiency virus (HIV) disease should be a diagnostic consideration in most patients hospitalized with CAP.

Laboratory studies (Tables 32.3 and 32.4) may be useful in diagnosis and management. The extent of the evaluation should depend on the severity of illness and the likelihood that test results will influence therapy. Diagnostic studies are usually unnecessary for patients treated on an outpatient basis because empiric antimicrobial choices adequately treat most common etiologies. Hospitalized patients should have, at a minimum, routine laboratory studies including a complete blood count with differential, a chest radiograph, and arterial blood gases. Blood cultures are diagnostic in up to 14% of patients hospitalized for CAP. They are most useful in patients with severe CAP (Table 32.4). The Gram stain and culture of expectorated sputum is most useful in patients with severe CAP (Table 32.4).

Table 32.2 Relevant clinical history related to specific pathogens

Anaerobes (oral)	Alcoholism, aspiration, lung abscess, recent dental work, endobronchial obstruction
Bordetella pertussis	Cough ≥2 weeks with whoop or vomiting after cough
Burkholderia cepacia	Bronchiectasis
Chlamydia pneumoniae	COPD, smokers, biphasic illness
Chlamydoia psittaci	Bird exposure
Coccidioides immitis	Travel to Southwest United States
Coronaviruses (SARS and MERS)	Travel to or residence in East Asia or the Middle East or with outbreak in other countries
Coxiella burnettii	Farm animal or pregnant cat exposure, hepatosplenomegaly
Francisella tularensis	Exposure to wild mammals, esp. rabbits and ticks in endemic areas
Haemophilus influenzae	COPD, smokers, HIV, postinfluenza
Hantavirus pulmonary syndrome	Pulmonary edema, hemoconcentration, thrombocytopenia esp. after travel to Southwest United States
Histoplasma capsulatum	Bat or bird droppings, cave exploration
Influenza	Seasonal outbreak. Travel to or residence in Asia: avian influenza
Klebsiella pneumoniae	Alcoholics
Legionella species	Hotel or cruise ship
Moraxella catarrhalis	COPD, smokers
Mycobacterium tuberculosis	Alcoholics, HIV, elderly, injection drug use
Mycoplasma pneumoniae	Prominent cough, hyperreactive airways, hemolytic anemia
Pneumocystis jirovecii	HIV, chronic corticosteroid use
Pseudomonas aeruginosa	COPD, bronchiectasis
Staphylococcus aureus	Postinfluenza, endobronchial obstruction, injection drug use
Streptococcus pneumoniae	Most common through all age groups, alcoholics, postinfluenza

Bacillus anthracis (anthrax), *Yersinia pestis* (plague), and *Francisella tularensis* (tularemia) would be the most likely bacterial bioterrorism agents to cause pneumonia.

Abbreviations: COPD = chronic obstructive pulmonary disease; SARS = severe acute respiratory syndrome; MERS = Middle East respiratory syndrome; HIV = human immunodeficiency virus.

Adapted from Infectious Diseases Society of America and American Thoracic Society Consensus Guidelines 2007.

Table 32.3 Routine studies useful in the diagnosis and management of patients hospitalized with community-acquired pneumonia

Chest radiograph (posterior and lateral)
Arterial blood gas values (for hospitalized patients. Pulse oximetry should be obtained for patients judged suitable for outpatient therapy.)
Complete blood count with differential
Chemistry panel, including electrolytes, glucose, blood urea nitrogen, and creatinine
Aminotransferases
Blood culture (2 sets drawn 10 minutes or more apart) Not necessary for all patients. See Table 32.4.
Pleural fluid stain, culture, leukocyte count with differential, pH
Sputum studies (for pneumonia unresponsive to usual antibiotics, see Table 32.4): Acid-fast stain and culture Fungal stains and culture *Legionella* spp. culture Immunofluorescent antibody, Gomori's methenamine silver, or Giemsa stain for *Pneumocystis jirovecii* (*carinii*) A Gram stain (from an appropriately obtained specimen, examined by an expert within 2 h of collection before the patient has received antibiotics)
Urinary antigen *Streptococcus pneumoniae* *Legionella* spp.
Serology (for patients with appropriate epidemiologic history) HIV serology *Legionella* spp. *Francisella tularensis* *Mycoplasma pneumoniae* *Chlamydia (pneumoniae and psittaci)* spp. *Coxiella burnetii*

Abbreviation: HIV = human immunodeficiency virus.

The sputum specimen should be grossly purulent, obtained by deep cough (or tracheal aspirate), and processed in less than 2 hours. Minimum criteria for a specimen suitable for culture are fewer than 10 squamous epithelial cells or more than 25 polymorphonuclear neutrophils (PMNs) per low-power field. Sputum studies can be diagnostic for *Legionella*, mycobacteria, fungi, and *Pneumocystis jirovecii* (Table 32.3). Molecular diagnostic tests such as polymerase chain reaction amplification assays may be performed on nasopharyngeal or lower respiratory tract specimens for many pathogens including *S. pneumoniae, Mycoplasma pneumoniae, Chlamydia pneumoniae, Bordetella pertussis*, and respiratory viruses. A parapneumonic pleural effusion is a common complication of pneumonia, and cultures obtained by thoracentesis will often give a positive result. The incidence of pleural effusion with pneumonia depends on the etiologic agent, accompanying ~95% of *Streptococcus pyogenes* infections but only 10% of *S. pneumoniae* infections. Sampling of the lower respiratory tract via bronchoalveolar lavage, bronchoscopic protected specimen brushings, or quantitative endotracheal aspirates may be useful in nonresolving pneumonia. Transthoracic needle aspiration and lung biopsy should only be considered in severely ill patients not responding to therapy for whom less invasive techniques are nondiagnostic.

Urinary antigen tests (UAT) may be useful in *Legionella* spp. and *S. pneumoniae* infections. Both tests have a greater than 90% specificity. The *S. pneumoniae* UAT may yield a diagnosis even after starting antibiotics. The *Legionella* UAT detects only serogroup I, which causes most cases of community-acquired Legionnaires' disease in the United States. Serologic studies may aid in the confirmation of atypical bacterial causes of CAP but rarely in antibiotic choice. A 4-fold rise in serologic titer, which often takes several weeks, is necessary for confirmation. Cross-reactivity among some organisms lessens the specificity of serology. A definitive microbial cause is identified in only a minority of patients even after extensive testing.

RECOMMENDATION FOR EMPIRIC SELECTION OF ANTIMICROBIAL AGENTS

Delay in antibiotic therapy for CAP increases morbidity and mortality. Empiric selection of antimicrobials is necessary in most cases. Selection of appropriate antibiotics is facilitated by categorizing patients by age and severity of illness, comorbidities, and epidemiologic factors. Some microbes cause disease in all ages and types of patients; others are common only in patients with certain comorbidities (Tables 32.5 to 32.8).

Among patients with mild pneumonia not requiring hospitalization (Table 32.5), *S. pneumoniae* is the most common bacterial pathogen. The atypical pneumonias (*M. pneumoniae* and *C. pneumoniae*) are common and are generally benign, with systemic complaints often more prominent than respiratory ones. Fever, headache, and myalgia are common. Leukocytosis is rare, and chest infiltrates consist primarily of segmental lower lobe or hilar infiltrates. *M. pneumoniae* is more common among patients younger than 30 years of age, but is recognized with increasing frequency in older persons. *M. pneumoniae* is characterized by a prominent cough, often occurs in

Table 32.4 Clinical indications for more extensive diagnostic testing

Indication	Blood culture	Sputum culture[a]	*Legionella* UAT	Pneumococcal UAT
ICU admission	X	X	X	X
Failure of outpatient antibiotic therapy		X	X	X
Cavitary infiltrates	X	X[b]		
Leukopenia	X			X
Active alcohol use	X	X	X	X
Chronic severe liver disease	X			X
Severe obstructive/structural lung disease		X		
Asplenia (anatomic or functional)	X			X
Recent travel (within 2 weeks)			X	
Positive *Legionella* UAT result		X[c]	NA	
Positive pneumococcal UAT result	X	X		NA
Pleural effusion	X	X	X	X

Abbreviations: NA = not applicable; UAT = urinary antigen test.
[a] A Gram stain should be obtained as well.
[b] Fungal, tuberculosis, and bacterial cultures.
[c] Special media for *Legionella.*
Adapted from Table 5, IDSA/ATS Consensus Guidelines 2007.

Table 32.5 Guidelines for empiric antibiotic therapy for community-acquired pneumonia in outpatients younger than 50 years with no comorbid illness

Common pathogens
Streptococcus pneumoniae
Mycoplasma pneumoniae
Chlamydia pneumoniae
Respiratory viruses
Antibiotics
Macrolide[a] Azithromycin, 500 mg PO day 1, then 250 mg daily Clarithromycin, 250 mg PO BID
If macrolide intolerant: Doxycycline 100 mg PO BID

[a] If >25% *S. pneumoniae* macrolide resistant (minimal inhibitory concentration [MIC] ≥16 μg/mL) in a community: levofloxacin 750 mg PO daily, or moxifloxacin 400 mg PO daily.

slowly evolving epidemics, and can precipitate reactive airway disease, especially in children. *C. pneumoniae* is a common cause of mild, often biphasic illness, initially with upper respiratory symptoms and pharyngitis with development of pneumonia 2 or 3 weeks later. Reinfection is common. Macrolides such as azithromycin and clarithromycin are the drugs of choice for treating outpatient pneumonia in low-risk patients. However, mycoplasma resistance to macrolides is a growing problem, particularly in Asia. Doxycycline can be used for those who are macrolide intolerant.

Patients who are older than 50 or have comorbid illnesses (Table 32.6) are more likely to require hospitalization. Some can be managed as outpatients but will require close follow-up, preferably within 3 days. Gram-negative organisms, such as *Haemophilus influenzae* and *Moraxella catarrhalis*, are more common, particularly in persons who smoke or have chronic obstructive pulmonary disease (COPD). A respiratory fluoroquinolone, such as levofloxacin or moxifloxacin, is an acceptable choice for these patients, unless they have received a fluoroquinolone in the previous 3 months or are allergic to them, in which case a macrolide plus a β-lactam should be given.

Patients hospitalized with pneumonia of moderate severity require empiric therapy to cover the organisms listed in Table 32.7. The first antibiotic dose should be given in the emergency department.

Empiric antimicrobial therapy for hospitalized patients should include either a respiratory fluoroquinolone alone or a macrolide combined with a β-lactam. If fluoroquinolones have been used in the previous 3 months, the latter regimen is preferred. Ertapenem is as efficacious as ceftriaxone but has not been extensively studied. It is useful when a broader-spectrum agent is necessary to cover anaerobes and gram-negative

Table 32.6 Guidelines for empiric antibiotic therapy for community-acquired pneumonia in patients older than 50 years or with comorbid illness not requiring hospitalization

Common pathogens
Streptococcus pneumoniae
Legionella spp.
Haemophilus influenzae
Moraxella catarrhalis
Other gram-negative bacilli
Respiratory viruses
Antibiotics
Fluoroquinolone as a single agent Levofloxacin 750 mg PO daily Moxifloxacin 400 mg PO daily
or
Macrolide[a] Azithromycin, 500 mg PO day 1, then 250 mg daily Clarithromycin, 250 mg BID
and
β-lactam Amoxicillin 1 g 3 times daily Amoxicillin-clavulanate 2 g BID Ceftriaxone, cefpodoxime, cefuroxime

[a] Doxycyline 100 mg BID may be substituted in macrolide-intolerant patients.

Table 32.7 Guidelines for empiric antibiotic therapy for community-acquired pneumonia in patients requiring hospitalization (not intensive care)

Common pathogens
Streptococcus pneumoniae
Mycoplasma pneumoniae
Chlamydia pneumoniae
Haemophilus influenzae
Legionella spp.
Aspiration
Respiratory viruses
Antibiotics
Fluoroquinolone[a] Levofloxacin 750 mg IV/PO daily Moxifloxacin 400 mg IV/PO daily
or
Macrolide[b] Azithromycin, 500 mg PO day 1, then 250 daily Clarithromycin, 250 mg BID
and
β-lactam Cefotaxime, ceftriaxone, ampicillin, ertapenem

[a] Second regimen should be substituted if fluoroquinolones have been used in the previous 3 months.
[b] Doxycyline 100 mg BID may be substituted in macrolide-intolerant patients.

organisms, but is not active against *Pseudomonas aeruginosa*. Ceftaroline, the first cephalosporin with methicillin-resistant *S. aureus* (MRSA) activity, is noninferior to ceftriaxone for CAP requiring hospitalization. Tigecycline, a glycylcycline with MRSA and anaerobic activity, is noninferior to levofloxacin in hospitalized patients with CAP. Neither ceftaroline nor tigecycline has activity against *Pseudomonas*. Given the efficacy and safety of current antibiotics for CAP, the use of these newer agents should be limited to specific circumstances when standard antibiotics are not appropriate. When the etiologic agent and its sensitivity are known, the antibiotic regimen should be as narrow and as cost-effective as possible.

Severe pneumonia causes increased mortality, ranging from 50% to 70% in some studies, especially during the first 7 days. Severe pneumonia manifests as hypoxia, tachypnea, multilobe involvement or consolidation, and signs of septic shock. These patients should receive ICU care. Organisms listed in Table 32.8 may cause more severe disease, although the severity of the pneumonia and ultimate outcome is more a function of the immune response of the host. Initial antimicrobial therapy should include either a macrolide or fluoroquinolone plus a β-lactam. Several retrospective studies indicate that the combination of a β-lactam plus macrolide may result in better outcomes especially in cases of severe CAP, although current guidelines do not include the obligatory addition of macrolides in this setting. Persons requiring ICU monitoring should have blood cultures drawn and sputum studies for Gram stain and culture. Empiric antibiotic choices should take into account organisms on the Gram stain. Gram-positive cocci in clusters suggests *S. aureus,* which is most often seen as a complication of influenza. MRSA is commonly found in the community and, if associated with the Panton-Valentine leukocidin toxin, can produce severe necrotizing pneumonia. For persons admitted to the ICU with severe pneumonia and clusters of gram-positive cocci in the sputum or cavitary lesions in the lung, initial therapy should include either vancomycin or linezolid. If vancomycin is used, strong consideration should be given to the addition of clindamycin. Linezolid and clindamycin have been shown in vitro to decrease bacterial toxin production.

Table 32.8 Guidelines for empiric antibiotic therapy for community-acquired pneumonia in patients requiring intensive care hospitalization

Common pathogens
Streptococcus pneumoniae
Legionella spp.
Staphylococcus aureus[a]
Haemophilus influenzae
Pseudomonas aeruginosa
Enterobacteriacae spp.
Gram-negative bacilli
Aspiration
Respiratory viruses
Antibiotics[a]
β-lactam[b] Ceftriaxone, cefotaxime, or ampicillin–sulbactam
and
Azithromycin or respiratory fluoroquinolone

[a] If *S. aureus* infection is suspected, either vancomycin or linezolid should be added to above regimen.

[b] If *P. aeruginosa* is a likely organism, an antipseudomonal β-lactam (piperacillin–tazobactam, cefepime, imipenem, or meropenem) should be substituted for the β-lactams listed above. Either ciprofloxacin or levofloxacin should accompany the antipseudomonal β-lactam or the combination of an aminoglycoside with azithromycin.

When a patient admitted to the ICU has severe structural defects of the lung (COPD or bronchiectasis) and gram-negative organisms in the sputum, initial antibiotics should have antipseudomonal activity (see Table 32.8).

Although rare, tularemic pneumonia should be considered in patients with exposure to wild mammals, especially rabbits, and ticks. Intravenous gentamicin should be given when tularemic pneumonia is considered. *Coxiella burnetii* causes an atypical pneumonia often accompanied by hepatosplenomegaly. It is endemic in many hot, dry areas. The most common reservoirs are sheep, goats, cattle, and ticks. Tetracycline or doxycycline is the recommended therapy. *Chlamydia psittaci* is an atypical pneumonia that should be considered in patients with exposure to birds, especially parrots. Splenomegaly and an atypical pneumonia suggests psittacosis, which is treated with tetracycline or doxycycline. *Mycobacterium tuberculosis* should be considered early when pneumonia does not respond to usual antibiotics. Endemic fungal infections, such as blastomycosis, histoplasmosis, cryptococcosis, and coccidioidomycosis, may also present as a CAP.

Viruses are responsible for up to one-third of the cases of CAP. Influenza A and B viruses are common worldwide and cause yearly seasonal epidemics. Influenza A viruses can also cause pandemics such as that caused by the 2009 novel H1N1 virus. Influenza can cause a primary viral pneumonia or predispose to secondary bacterial pneumonia, especially due to *S. aureus* or *S. pneumoniae*. Avian influenza virus infections such as H5N1 and H7N9, while limited in number, are important due to the very high case-fatality rates (~50%), typically due to overwhelming pneumonia. Other viruses associated with CAP include parainfluenza, rhinoviruses, adenoviruses, and coronaviruses. Human metapneumovirus (hMPV) most commonly occurs in late winter or early spring in young children and adults over the age of 65 years, with symptoms ranging from mild disease to severe pneumonia. hMPV may cause exacerbations of asthma. Human bocavirus and parechovirus types 1, 2, and 3 cause lower respiratory tract infection in children. Respiratory syncytial virus (RSV) can cause CAP in adults, particularly those who are immunocompromised. Two novel human coronaviruses (CoV) have been implicated in severe respiratory infection. Severe acute respiratory syndrome (SARS) caused by the SARS CoV, was first identified in 2002 in China and Southeastern Asia, resulting in over 8000 infections worldwide with a 10% case-fatality rate, before the last cases were seen in the summer of 2003. In 2012, a severe respiratory illness with a high case-fatality rate was identified in Saudi Arabia and Jordan. This Middle Eastern respiratory syndrome (MERS) is due to a novel coronavirus, MERS-CoV. As of August 2013, over 100 cases with a case-fatality rate of 50% had been identified in the Middle East, Tunisia, and Europe. Treatment for all these viruses, except for influenza, is supportive. The neuraminidase inhibitors, oseltamivir and zanamivir, decrease the duration of illness and may reduce complications seen with influenza and the spread of influenza to other patients. They should be given within the first 48 hours of symptom onset; however, patients requiring hospitalization or at high risk for complications from influenza including pregnant women, persons with immunocompromise, or persons with underlying chronic medical illnesses should be treated even if they present beyond 48 hours of symptom duration. The adamantanes, amantidine and rimantidine are not recommended to treat influenza due to widespread resistance.

THERAPEUTIC RESPONSE

Antibiotic choices should generally not be altered during the first few days of therapy unless there is marked deterioration or cultures indicate the need for a change. Usually 48 to 72 hours are required for significant clinical improvement. Fever usually lasts 2 to 4 days but may last longer, especially if bacteremia occurs. The white blood cell count generally returns toward normal after 4 days, and blood cultures become negative 24 to 48 hours after starting treatment. Duration of therapy should be individualized according to the infecting organism, response to treatment, and the overall health of the patient. Antibiotic therapy for 7 to 10 days is generally sufficient. Patients should receive a minimum of 5 days of antibiotics for CAP. Because of its long tissue half-life, azithromycin may be given for a shorter duration. Patients with pneumonia caused by *S. pneumoniae* should usually receive antibiotics for 72 hours after the resolution of fever. Bacteremic patients will require a 10- to 14-day course of treatment. Immunocompromised patients may require longer courses. When the patient is hemodynamically stable, improving clinically, and tolerating oral intake, transition to oral antimicrobials should be considered. It is not necessary that the patient be afebrile, but the fever curve should be trending down.

Resolution of abnormal radiographic findings lags behind clinical improvement and is slower in elderly patients, smokers, and those with comorbidities or multilobe involvement. Multiple chest radiographs in the hospital are unnecessary except for intubated patents and those with clinical deterioration. Patients who are older than 40 years of age or are smokers should be followed until complete radiographic resolution of the infiltrate is demonstrated with follow-up chest radiographs obtained between 7 and 12 weeks after completion of therapy. If abnormalities have not resolved or greatly improved, the possibility of an occult neoplasm should be considered.

There are a number of reasons for failure in the treatment of CAP. The serum level of the chosen antibiotics may not be high enough. Some antibiotics, such as the aminoglycosides, may not achieve high enough concentrations in the lung tissue. The etiologic agent may be resistant to the antibiotics, or less likely, resistance may develop during therapy. Initial improvement followed by recurrent fever may be due to the development of thrombophlebitis, empyema, lung abscess, or drug fever. Lack of clinical improvement should raise suspicion for alternative etiologies, such as viruses, mycobacteria, fungi, or parasites. Choice of antibiotic, dosage, and route of administration should be re-evaluated in this setting. Clinicians must always keep in mind the possibility of noninfectious mimics of pneumonia, such as pulmonary infarction, organizing pneumonia, carcinoma, pulmonary edema, atelectasis, sarcoidosis, hypersensitivity pneumonitis, and drug-induced pulmonary disease.

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33. Nosocomial pneumonia

Burke A. Cunha

INTRODUCTION

Nosocomial pneumonia (NP) may be defined as pneumonia that occurs after 5 or more days in hospital. NP is synonymous with hospital-acquired pneumonia (HAP). The subset of NP/HAP patients on ventilators are referred to as ventilator-associated pneumonias (VAP). NP occurring early, i.e., less than 5 days after admission, actually represents incubating community-acquired pneumonia (CAP) that has become clinically manifest early after hospital admission. For this reason, the respiratory pathogens causing "early NP" are the usual CAP pathogens, e.g., *Streptococcus pneumoniae*. With true NP (≥5 days after admission), the respiratory pathogens acquired in hospital are aerobic gram-negative bacilli (GNB). The most important, but not the most common, NP pathogen is *Pseudomonas aeruginosa*; some other GNB are also important NP pathogens, e.g., *Klebsiella pneumoniae* (Table 33.1).

In this chapter, the term NP is used rather than designation of the clinically meaningless healthcare-associated pneumonia (HCAP). Nursing home-acquired pneumonias (NHAP) are not the same as NP. First, the pathogens differ. NHAP pathogens are the same as CAP pathogens, e.g., *S. pneumoniae, Haemophilus influenzae*. Even though the respiratory secretion and urine/feces of nursing home/chronic care facility residents may be colonized by "hospital organisms," e.g., GNB, these organisms are not NHAP pathogens, i.e., they do not cause NHAP. Pathogens aside, the NHAP mean length of stay (LOS) is ~ 7 days, which is the same LOS (~ 7 days) as for hospitalized CAP. This is in marked contrast to the NP LOS (~ 14 days). For these reasons, it is clinically important to differentiate NHAP from NP and not combine them as HCAP.

Table 33.1 Clinical diagnosis of nosocomial pneumonia[a]

Appearance of new pulmonary infiltrates after 5 or more days in hospital with: • Otherwise unexplained new fever (>102°F) • Otherwise unexplained leukocytosis (± left shift) • Otherwise unexplained pulmonary infiltrates (*consistent* with bacterial pneumonia)[b]

[a] Definition does *not* include positive respiratory secretion cultures in ventilated patients.
Positive blood cultures (excluding blood culture skin contaminants, e.g., methicillin-sensitive *Staphylococcus aureus* [MSSA], methicillin-resistant *S. aureus* [MRSA]) or
secondary to extrapulmonary infections, e.g., central venous catheter infection, *P. aeruginosa*, *K. pneumoniae*, *Enterobacter* spp., *Acinetobacter baumannii*.

[b] See Table 33.2 (Mimics of nosocomial pneumonia).

MIMICS OF NOSOCOMIAL PNEUMONIA

Because the definition of NP is based on epidemiologic rather than pathologic criteria, there are many noninfectious disorders that fit the epidemiologic definition of NP. In intensive care unit (ICU) patients, there are many mimics of NP with fever, leukocytosis, hypoxemia, and pulmonary infiltrates on chest x-ray (CXR). Many of these mimics of NP have pulmonary infiltrates but are disorders unassociated with fever/leukocytosis. In such patients with mimics of NP, the fever/leukocytosis are due to unrelated extrapulmonary processes, e.g., drug fever, phlebitis, cerebrovascular accidents, myocardial infarction, gastrointestinal bleed, adrenal insufficiency. Patients with acute respiratory distress syndrome (ARDS) often have fever/leukocytosis, hypoxemia, and pulmonary infiltrates that are unrelated to NP but rather are due to drug-induced pancreatitis mimicking NP. Other mimics of NP may have fever. In such cases, the diagnosis is usually suggested by associated extrapulmonary signs/symptoms, e.g., systemic lupus erythematosis (SLE) with pneumonitis. Before fever, leukocytosis, hypoxemia, and pulmonary infiltrates are ascribed to NP, the clinician should carefully rule out the many mimics of NP based on nonpulmonary findings from the history, physical examination, and relevant laboratory tests (Table 33.2). In

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Table 33.2 Radiographic mimics of nosocomial pneumonia[a]

Fever *plus* leukocytosis plus CXR infiltrates *plus* positive respiratory secretion cultures ≠ NP	
• Bronchiolitis obliterans organizing pneumonia (BOOP)[a]	• Aspiration (chemical)[a]
• Sarcoidosis[a]	• Phantom tumor (localized CHF)[a]
• SLE pneumonitis	• Bronchogenic carcinoma[a]
• Rheumatoid lung[a]	• Metastatic carcinoma[a]
• Pulmonary infarcts	• Lymphoma
• Goodpasture's syndrome	• Radiation pneumonitis[a]
• Wegener's granulomatosis	• Lung contusion
• Acute respiratory distress syndrome (ARDS)	• Pulmonary hemorrhage
• Drug-induced pulmonary disease	• Mucus plug[a]
• Noncardiogenic (neurogenic) pulmonary edema[a]	
• Cardiogenic pulmonary edema (LVF)[a]	

NP = nosocomial pneumonia; SLE = systemic lupus erythematosus; LVF = left ventricular failure; CHF = congestive heart failure.

[a] The disorders listed may mimic NP and many are afebrile disorders and may be associated with leukocytosis/left shift. Fever may be present with disorders listed, not typically afebrile infection, but search should prompt for a nonpulmonary cause of the fever. ARDS is in the ICU and commonly due to acute pancreatitis (drug induced) and the patient is febrile secondary to pancreatitis not ARDS.

Diagnosis of NP should not be based on "guilt by association."

Similarly, positive respiratory secretion's culture should be considered as colonization, not NP, until proven otherwise. Other clues to the clinical nonsignificance of positive respiratory secretion cultures are growth of non-NP pathogens, *Stenotrophomonas maltophilia, Burkholderia cepacia*, or colonizing pathogens, e.g., *Enterobacter* spp., *S. aureus, Citrobacter* spp., or multiple organisms, pathogens that are significant only if in a cluster/outbreak, e.g., *Acinetobacter* spp.

Adapted from: Cunha BA, ed. *Pneumonia Essentials*, 3rd edn. Sudbury, MA: Jones & Bartlett; 2007.

ventilated patients, mimics of NP may also have positive respiratory secretion cultures. All too often, the clinical diagnosis of NP is based on "guilt by association," e.g., fever/leukocytosis, hypoxemia, infiltrates on CXR, and positive respiratory secretion cultures.

Since a definitive diagnosis of NP is problematic, i.e., lung biopsy, some degree of overtreatment is unavoidable. If mimics of NP are excluded and the presumed diagnosis is NP, empiric monotherapy should be directed against the most important NP pathogens, e.g., *P. aeruginosa*, and not based on respiratory secretion cultures.

RESPIRATORY SECRETION COLONIZATION VERSUS INFECTION

In intubated patients, respiratory secretions rapidly become colonized by nosocomial GNB. Nosocomial GNB colonization in the ICU occurs as a function of time. Antimicrobial therapy, if not chosen carefully, may not only promote colonization of respiratory secretions with GNB, but also colonization with *Staphylococcus aureus*, i.e., methicillin-sensitive *S. aureus* (MSSA) or methicillin-resistant *S. aureus* (MRSA). The common GNB colonizers of respiratory secretions, e.g., *Enterobacter* spp., *Citrobacter freundii, Burkholderia cepacia, Stenotrophomonas maltophilia*, are relatively avirulent and rarely, if ever, cause NP. Until proven otherwise, if these organisms are cultured from respiratory secretions of ventilated patients they should be considered as "colonizers" and not treated with antibiotics (Table 33.1). Respiratory secretions of ventilated patients are also commonly colonized by bona fide NP pathogens, e.g., *P. aeruginosa, K. pneumoniae, Serratia marcescens*. In contrast, *Acinetobacter baumannii* is a common colonizer of respiratory secretions, but is rarely a cause of sporadic NP. Unless part of an outbreak/cluster, respiratory secretion cultures positive for *A. baumannii* should be regarded as colonization and the cause of NP until proven otherwise. Similarly, nosocomial Legionnaires' disease occurs in clusters/outbreaks and only rarely occurs as sporadic NP. Gram-positive cocci, e.g., enterococci, or *S. aureus* (either MSSA/MRSA), are common colonizers of respiratory secretions of ventilated patients receiving certain broad-spectrum antibiotics, e.g., ciprofloxacin, imipenem, ceftazidime. However, group D streptococci rarely, if ever, cause NP. In intubated patients with presumed NP organisms cultured from respiratory secretion are often considered a cause of NP and are covered/treated. There is little/no relationship between respiratory secretion cultures and distal lung parenchymal NP pathogens. The clinical and pathologic features of *S. aureus* (MSSA/MRSA) CAP have well-described clinical parameters to evaluate potential MSSA/MRSA NP. *S. aureus* (MSSA/MRSA) CAP (virtually always associated with influenza or influenza-like illness) patients are critically ill, cyanotic, and have a fulminant necrotizing/hemorrhagic pneumonia with rapid cavitation in < 72 hours (like *P. aeruginosa* NP). This is in contrast to the intubated patient with MSSA/MRSA cultured from respiratory secretions, without the clinical/radiologic characteristics of a necrotizing/hemorrhagic pneumonia. Unless the patient has MSSA/MRSA tracheobronchitis, MSSA/MRSA in respiratory secretions represents colonization

Table 33.3 Nosocomial pathogens and respiratory secretion colonizers

Nosocomial pneumonias: respiratory pathogens	Respiratory secretions: common colonizers
Common pathogens	**Common colonizers**
Pseudomonas aeruginosa	*Staphylococcus aureus* (MSSA/MRSA)
Klebsiella pneumoniae	*Pseudomonas aeruginosa*
Uncommon	*Acinetobacter baumannii*
Serratia marcescens	*Enterobacter* spp.
Escherichia coli	*Stenotrophomonas* (*Xanthomonas*) *maltophilia*
Rare	*Burkholderia* (*Pseudomonas*) *cepacia*
Acinetobacter baumannii[a]	*Citrobacter freundii*
Legionella spp.[a]	

[a] Nosocomial pneumonias due to these organisms are virtually always part of a cluster/outbreak.

Abbreviations: MRSA = methicillin-resistant *Staphylococcus aureus;* MSSA = methicillin-susceptible *Staphylococcus aureus.*

and not MSSA/MRSA NP. Furthermore, adding MSSA/MRSA coverage in the empiric treatment of NP has no effect on outcomes (Table 33.3).

Without invasive diagnostic tests, e.g., lung biopsy, the definitive diagnosis of NP remains elusive. The epidemiologic diagnosis of NP is based on fever/leukocytosis, hypoxemia, and new-onset pulmonary infiltrates compatible with bacterial pneumonia. Obviously, there are many noninfectious mimics of NP with the same clinical presentations. *P. aeruginosa* and *S. aureus* in particular have readily recognizable clinical presentations, e.g., fulminant necrotizing/hemorrhagic pneumonias. When either of these two organisms is responsible for pneumonia, e.g., CAP due to *S. aureus* (+ influenza) or NP due to *P. aeruginosa,* such patients acutely deteriorate clinically with high spiking fevers accompanied by cyanosis and on chest x-ray (CXR) rapid cavitation ($\leq$ 72 hours) after infiltrate appearance. Fulminant necrotizing/hemorrhagic pneumonia due to either *P. aeruginosa* NP or *S. aureus* (CAP + influenza) is frequently fatal. The clinical presentation of *P. aeruginosa* NP or *S. aureus* CAP (+ influenza) is distinctive and reflects the underlying lung pathology. The epidemiologic definition of NP is, but should not be, based on nonspecific clinical findings and respiratory secretion cultures. In intubated ICU patients in the United States with presumed NP respiratory secretion cultures are positive (>25%) for MSSA/MRSA. If MSSA/MRSA were actual pathogens in >25% of NP, this would be readily apparent in very high mortality/autopsy findings, which is not the case. MSSA/MRSA remains a rare cause of NP. In a ventilated patient if either MSSA/MRSA or *P. aeruginosa* are cultured from respiratory secretions and the patient's clinical status has not dramatically deteriorated and there is no cyanosis and no rapid cavitation ($\leq$ 72 hours) on CXR then the pathogens represent colonization and not NP due to either of these pathogens. However, both *P. aeruginosa* or *S. aureus* may cause tracheobronchitis (purulent respiratory secretions with a negative CXR), which should be treated to preserve respiratory function.

OPTIMAL EMPIRIC MONOTHERAPY FOR NOSOCOMIAL PNEUMONIA

Until there are better methods to accurately diagnose NP, some overtreatment is understandable and clinically prudent. Because some overtreatment is unavoidable due to difficulties in diagnosis, clinicians use antibiotics as selectively as possible to empirically treat presumed NP. In ventilated patients optimal empiric monotherapy should have a high degree of anti-*P. aeruginosa* activity, e.g., meropenem, cefepime. In addition to an appropriate spectrum for NP, e.g., anti-*P. aeruginosa*, the antibiotic selected should have a "low resistance potential" to prevent the emergence of multidrug-resistant (MDR) GNBs as well as not promoting selection of *S. aureus* in respiratory secretions. The antibiotics often used in the therapy of NP that are most likely to result in the emergence of MDR GNBs, are ceftazidime, imipenem, and ciprofloxacin. In addition, ceftazidime and ciprofloxacin are likely to select out MSSA/MRSA in respiratory secretions. Further proof of the unimportance of including MRSA coverage in NP empiric therapy is that MRSA coverage does not improve outcomes. MRSA coverage is not necessary for the empiric therapy of NP (Tables 33.4 and 33.5).

For NP well-selected monotherapy is optimal and double drug therapy offers no advantage. When antibiotics had relatively little *P. aeruginosa* activity double drug therapy was used. Because currently available antibiotics have a high degree of anti-*P. aeruginosa* activity, optimal empiric monotherapy is effective. In bona fide *P. aeruginosa* NP, double drug therapy is preferred.

If MDR *K. pneumoniae* or MDR *P. aeruginosa* strains are the cause of NP, meropenem remains useful against most non-metallo β-lactamase-producing GNBs. For meropenem-resistant

Table 33.4 Nosocomial pneumonia: selection of antibiotic empiric therapy

Key factors in empiric antibiotic selection for NP

1. High degree of activity against *Pseudomonas aeruginosa* (and other GNB NP pathogens). MSSA/MRSA coverage unnecessary.
2. Penetrates lung parenchyma in therapeutic concentrations
3. "Low resistance" potential (avoid ciprofloxacin, ceftazidime, imipenem)
   Carefully selected antibiotics
   - Do not increase **prevalence** of MSSA/MRSA
   - Do not increase **prevalence** of VRE
   - Do not increase **potential** for *Clostridium difficile* diarrhea/colitis
4. Good safety profile

Unimportant factors in NP antibiotic selection for NP

1. MSSA/MRSA coverage
2. Penetration into epithelial cells, alveolar macrophages (except for *Legionella* spp.)

Abbreviations: NP = nosocomial pneumonia; GNB = gram-negative bacteria; MSSA = methicillin-susceptible *Staphylococcus aureus*, MRSA = methicillin-resistant *Staphylococcus aureus*; VRE = vancomycin-resistant enterococci.

Table 33.5 Empiric therapy of nosocomial pneumonia

Gram-negative nosocomial pneumonia
Preferred empiric therapy[a]
Nosocomial pneumonia (Preferred therapy coverage directed primarily against *P. aeruginosa*, MRSA coverage unnecessary) Meropenem 1 g (IV) q8h × 2 weeks Levofloxacin 750 mg (IV) q24h × 2 weeks Cefepime 2 g (IV) q8h ± amikacin 1 g (IV) q24h × 2 weeks[b]
Alternative therapy
Piperacillin/tazobactam 4.5 g (IV) q6h *plus* amikacin 1 g (IV) q24h × 2 weeks
Specific therapy
MDR *Klebsiella pneumoniae*
Tigecycline 200–400 mg (IV) × 1 dose, then 100–200 mg (IV) q24h × 2 weeks Colistin 1.7 mg/kg (IV) q8h × 2 weeks ± rifampin 600 mg (IV) q24h × 2 weeks Polymyxin B 1.25 mg/kg (IV) q12h × 2 weeks
MDR *Acinetobacter baumannii*
Tigecycline 200–400 mg (IV) × 1 dose, then 100–200 mg (IV) q24h × 2 weeks Ampicillin/sulbactam 3 g (IV) q6h × 2 weeks Colistin 1.7 mg/kg (IV) q8h ± rifampin 600 mg (IV) q24h × 2 weeks Polymyxin B 1.25 mg/kg (IV) q12h × 2 weeks
MDR *Pseudomonas aeruginosa*
Colistin 1.7 mg/kg (IV) q8h ± rifampin 600 mg (IV) q24h × 2 weeks Polymyxin B 1.25 mg/kg (IV) q12h × 2 weeks

Abbreviation: MDR = multidrug resistant.

[a] Doses are for adults with normal renal function.

[b] Note therapy of NP with piperacillin–tazobactam requires a higher than usual dose plus a second drug, e.g., amikacin. Do not use piperacillin–tazobactam at the usual dose 3.375 mg (IV) q6h or as monotherapy for NP.

Adapted from: Cunha BA, ed. *Antibiotic Essentials*, 12th edn. Sudbury, MA: Jones & Bartlett; 2013.

strains, effective antimicrobial therapy is relatively limited, e.g., colistin.

NOSOCOMIAL PNEUMONIA UNRESPONSIVE TO APPROPRIATE ANTIBIOTIC THERAPY

Empiric therapy of NP is usually given for 1 to 2 weeks. After 2 weeks of therapy, lack of CXR improvement suggests an alternate diagnosis rather than ineffective antimicrobial therapy or the development of antibiotic resistance.

After 2 weeks of optimal anti-*P. aeruginosa* NP therapy, ventilated patients with fever, leukocytosis, hypoxemia, and persistent pulmonary infiltrates on CXR may have herpes simplex virus-1 (HSV-1) NP. In a patient without pre-existing cardiopulmonary disease, otherwise unexplained "failure to wean" off a ventilator after 2 weeks of appropriate antimicrobial therapy for NP should suggest the possibility of HSV-1 NP. HSV-1 NP is an underrecognized clinical entity. If HSV-1 NP is suspected, diagnostic bronchoscopy should be performed. Herpetic vesicles in the oropharynx/airways are indicative of NP severity rather than lower respiratory tract infection, i.e., HSV-1 NP. HSV-1 cultured from respiratory secretions suggests colonization, not infection. Bronchoalveolar lavage (BAL) fluid should be obtained for cytologic diagnosis. Viral cytopathic effects in distal respiratory epithelial cells are diagnostic of active infection (not viral colonization/reactivation). Cowdry type A inclusion bodies (CPEs) in respiratory epithelial cells from BAL specimens are diagnostic of HSV-1 NP. If HSV-1 CPEs are present in BAL specimens, empiric therapy with acyclovir should be initiated (Table 33.6). Rapid improvement in oxygenation, e.g., decreased FiO_2/decreased A-a gradient follows after 3 to 5 days of acyclovir therapy. Patients can then be weaned off the ventilator over the next several days.

Importantly, cytomegalovirus (CMV) in normal hosts, unlike HSV-1, is not a common cause of NP. The diagnosis of CMV NP is based on demonstrating CMV CPEs in BAL cellular specimens. Elevated CMV IgM titers/positive CMV PCR are not diagnostic of CMV NP. CMV PCR positivity reflects CMV reactivation in peripheral white blood cells, not infection in the lungs or elsewhere.

Table 33.6 Nosocomial HSV-1 pneumonia

Symptoms
"Failure to wean" off respirator (in patients *without pre-existing lung disease*)
In immunocompetent hosts

Signs
Low-grade fevers
Unexplained hypoxemia (*with normal/near normal chest x-ray*)
CXR unchanged after 2 weeks of optimal NP antibiotic therapy

Laboratory tests
Leukocytosis (± left shift)
Otherwise unexplained ↓ pO_2 or ↑ A-a gradient (>30)
HSV serology: unhelpful
Diagnostic bronchoscopy:
HSV vesicles:
usually no HSV vesicles in respiratory passages
If present, HSV vesicles in respiratory tract (reflective of HSV severity/reactivation) not HSV NP
Viral culture:
± HSV-1 virus cultured from respiratory secretions (Dx of colonization *not* infection)
Cytology:
HVS-1 intranuclear inclusion bodies (Cowdry type A). CPEs are Dx of infection not colonization/reactivation.

Empiric therapy
Acyclovir 10 mg/kg (IV) q8h × 7–10 days
(Results in clinical improvement in 3–5 days) (↓ FiO_2, ↓ A-a gradient)

Adapted from: Cunha BA, ed. *Pneumonia Essentials*, 3rd edn. Sudbury, MA: Jones & Bartlett; 2007.

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34. Aspiration pneumonia

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INTRODUCTION

Aspiration is the introduction of oropharyngeal or gastric contents into the respiratory tract. Three major syndromes may develop as a consequence of aspiration: chemical pneumonitis, bronchial obstruction secondary to aspiration of particulate matter, and bacterial aspiration pneumonia. Less commonly, interstitial lung disease occurs in persons with chronic aspiration. Which of these consequences emerges is determined by the amount and nature of the aspirated material as well as by the integrity of host defense mechanisms.

The term *aspiration pneumonia* refers to the infectious consequences of introduction of relatively large volumes of oral material into the lower airways (macroaspiration). Although healthy persons frequently aspirate small volumes of pharyngeal secretions during sleep, the development of pneumonia after such microaspiration is normally prevented by mechanical (e.g., cough and mucociliary transport) and immunologic responses. Pneumonia arises when these host defenses are not able to limit bacterial proliferation either because of microaspiration of highly virulent pathogens to which the host lacks specific immunity (e.g., *Streptococcus pneumoniae* or enteric gram-negative bacteria) or because of macroaspiration of large quantities of organisms that may not necessarily be highly virulent.

Aspiration may be clinically obvious, as when acute pulmonary complications follow inhalation of vomited gastric contents. Such acute chemical pneumonitis, representing damage to lung parenchyma by highly acidic gastric contents, is often referred to as Mendelson's syndrome. On the other extreme, so-called silent aspiration, as occurs in persons with neurologic impairment who lack cough responses, is often followed by the indolent onset of infectious pneumonia consequent to contamination of the lower airways by low virulence mixtures of aerobic and anaerobic microorganisms from the oropharynx. It must be kept in mind, however, that chemical pneumonitis may result in the later development of aspiration pneumonia.

RISK FACTORS

Several factors increase the risk of aspiration pneumonia. First is disturbance of the normal oropharyngeal or gastric flora. The presence of gingivitis, dental plaque, and decayed teeth combined with poor oral hygiene or decreased salivary flow (e.g., due to tube feedings or anticholinergic medications) increases the predisposition to developing pneumonia following an aspiration event by increasing the quantity of relatively low virulence bacteria that colonize the oropharynx. Similarly, decreased gastric acidity (e.g., due to proton pump inhibitor use), enteral feeding, gastroparesis, or small-bowel obstruction increases colonization of gastric contents by pathogenic microorganisms, i.e., enteric gram-negative bacilli such as *Escherichia coli* and *Klebsiella pneumoniae*. Finally, alcoholism, malnutrition, diabetes, and other severe comorbidities or prior antimicrobial therapy lead to replacement of normal oral flora by more virulent microorganisms such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *K. pneumoniae* and thus also increase the risk of pneumonia following an aspiration event.

For self-evident reasons, conditions that impair cough and other normal mechanical oropharyngeal reflexes that prevent aspiration increase the risk of aspiration pneumonia. These include cerebrovascular and other neurologic diseases, alcoholism, drug abuse, general anesthesia, seizures, disorders of the gastrointestinal tract, and uncontrolled postoperative pain (see Table 34.1). In addition, pulmonary clearance defects at the mucociliary level (e.g., secondary to tobacco smoking or influenza), and impairment of normal humoral and cellular host defenses, particularly those conditions that decrease

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Table 34.1 Risk factors for aspiration

Altered level of consciousness
General anesthesia
Narcotic and sedative drugs
Drug overdose and ethanol toxicity
Metabolic encephalopathies (electrolyte imbalances, liver failure, uremia, sepsis)
Hypoxia and hypercapnia
Central nervous system (CNS) infections
Dementia
Abnormal glottic closure
Anesthetic induction or postanesthetic recovery
Postextubation
Structural lesions of the CNS (tumors, cerebrovascular accident, head trauma)
Seizures
Infection (e.g., diphtheria, pharyngeal abscess)
Gastroesophageal dysfunction
Alkaline gastric pH
Gastrointestinal tract dysmotility
Esophagitis (infectious, postradiation)
Hiatal hernia
Scleroderma
Esophageal motility disorders (achalasia, megaesophagus)
Tracheoesophageal fistula
Ascites (increased intra-abdominal pressure)
Intestinal obstruction or ileus
Diabetes (functional gastric outlet obstruction)
Neuromuscular diseases
Guillain–Barré syndrome
Botulism
Muscular dystrophy
Parkinson's disease
Polymyositis
Amyotrophic lateral sclerosis
Multiple sclerosis
Myasthenia gravis
Poliomyelitis
Tardive dyskinesia
Mechanical factors
Nasogastric or enteral feeding tubes
Upper endoscopy
Emergency and routine airway manipulation
Surgery or trauma to the neck and pharynx
Tumors of the upper airway
Tracheostomy
Endotracheal tube
Zenker's diverticulum
Other factors
Obesity
Pregnancy

immunoglobulin production (e.g., various hematologic malignancies) or result in severe neutropenia, also increase the risk of developing pneumonia after aspiration.

CLINICAL EPIDEMIOLOGY

In 2010 there were approximately 190 000 inpatient admissions in the United States for which the principal diagnosis was food/vomit (or aspiration) pneumonitis (ICD-9 507.0). These hospitalizations accounted for more than 19 000 inpatient deaths with a total medical care cost of 2.7 billion dollars. Another 370 000 persons received a secondary diagnosis of aspiration pneumonitis. Swallowing disorders due to neurologic diseases affect 300 000 to 600 000 people each year in the United States. Nearly 40% of stroke patients with dysphagia aspirate and develop pneumonia. Overall, aspiration pneumonitis accounts for approximately 0.5% of all hospitalizations, 3% to 4% of inpatient mortality, and 5% to 23% of all cases of community-acquired pneumonia.

More than 70% of cases of aspiration pneumonia are in persons older than 65 years of age. As a corollary, aspiration pneumonia is the second most frequent principal cause of hospitalizations among United States Medicare patients. Among nursing home patients, aspiration pneumonia accounts for up to 30% of cases of pneumonia, occurs at a rate three times that of age-matched patients in the community, and markedly increases the risk of death. Among such patients, difficulty swallowing food, use of tube feedings, requiring assistance with feeding, delirium, and use of sedative medications are the most frequent risk factors for aspiration pneumonia. While the debilitated elderly are at particularly high risk, prior silent aspiration is also common in apparently healthy elderly patients with community-acquired pneumonia.

Aspiration complicates the course of approximately 10% of persons admitted to hospitals for overdosage with sedative or hypnotic agents and 0.05% to 0.8% of persons receiving general anesthesia for surgical procedures. Patient characteristics independently associated with an increased risk of aspiration following general anesthesia include male sex, nonwhite race, age of >60 years, dementia, chronic obstructive pulmonary disease, renal disease, malignancy, moderate to severe liver disease, and emergency surgery.

CLINICAL COURSE AND DIAGNOSIS

Aspiration of gastric contents results in acute inflammation of the major airways and lung parenchyma with maximal hypoxemia within 10 minutes of aspiration. Local injury results in complement activation as well as release of tumor

necrosis factor-α, interleukin-8, and other proinflammatory cytokines that in turn are primarily responsible for the acute nonobstructive complications of chemical aspiration. The severity of lung injury is greatest when the pH is less than 2.5, but severe pulmonary injury does occur at higher pH.

Acute symptoms and signs of chemical pneumonitis include respiratory distress, fever, cough, reflex bronchospasm, leukocytosis, and pulmonary infiltrates. Life-threatening hypoxemia may develop as a consequence of atelectasis, pulmonary capillary leak, and direct alveolar damage. These findings are easily attributable to chemical pneumonitis if they follow witnessed vomiting and aspiration of gastric acidic contents. If the event is not witnessed, detection of the gastric enzyme pepsin in a tracheal aspirate may serve as a marker for gastric aspiration pneumonitis.

Many patients with chemical pneumonitis improve without any specific antimicrobial therapy. Other patients develop progressive clinical symptoms and worsening radiographic findings for several days after an aspiration event. Such progression indicates the emergence of the acute respiratory distress syndrome and/or bacterial pneumonia. Alternatively, patients may initially improve for several days but then worsen with the onset of recurrent symptoms and signs indicative of secondary bacterial pneumonia.

Differentiation of aspiration pneumonia from progressive chemical pneumonitis is often challenging as there is frequent overlap between these two syndromes. This distinction is important given the desirability of avoiding unnecessary antibiotic use, especially as pneumonia fails to develop in approximately half of all aspiration events. Furthermore, given the differences in microbial etiology of aspiration pneumonia versus community-acquired pneumonia, it is important to consider aspiration in persons with pneumonia who have the risk factors listed in Table 34.1 even if an aspiration event has not been witnessed.

The clinical presentation of aspiration pneumonia is much less dramatic than that of chemical pneumonitis. Many episodes of aspiration pneumonia, especially those involving normal oral flora (i.e., mixed aerobic/anaerobic infections), result from silent aspiration. Clinical characteristics include fever, alteration of general well-being, and respiratory symptoms such as productive cough, dyspnea, and pleuritic pain. In elderly patients with aspiration pneumonia, the early signs and symptoms of pulmonary infection may be muted and overshadowed by nonspecific complaints such as general weakness, decreased appetite, altered mental status, or decompensation of underlying diseases. These patients may have an indolent disease and not develop fever, malaise, weight loss, and cough for 1 to 2 weeks or more after aspiration. This is an especially common presentation for patients who present with mixed aerobic/anaerobic lung abscesses or empyemas after an aspiration event.

Neither routine nor specialized laboratory tests, e.g., C-reactive protein, soluble triggering receptor expressed on myeloid cells (TREM-1), lipid-laden macrophage, and serum procalcitonin distinguish between aspiration pneumonitis and aspiration pneumonia. The role of procalcitonin and amylase in bronchoalveolar lavage remains to be established.

Radiographic evaluation is necessary to establish the diagnosis of pneumonia as there is no combination of historical data, physical findings, or laboratory results that reliably confirms the diagnosis. Limitations of chest radiography for the diagnosis of pneumonia include poor specificity in patients with the acute respiratory distress syndrome and decreased sensitivity in persons with previous structural lung disease, very early infection, severe dehydration, or profound granulocytopenia. Otherwise, the failure to detect an infiltrate essentially rules out the diagnosis of pneumonia. Although spiral computed tomography (CT) of the chest provides a more sensitive means of detecting infiltrates than chest radiography, such infiltrates may not actually represent pneumonia. Esophagography and CT are especially useful in the evaluation of aspiration disease related to tracheoesophageal or tracheopulmonary fistula.

Radiologic findings do not distinguish between chemical pneumonitis and aspiration pneumonia, save for the fact that radiologic abnormalities typically have a more rapid onset with chemical pneumonitis. However, when compared with other causes of pneumonia, pneumonia complicating aspiration more often involves the posterior segment of the right upper lobe, the superior segment of the right lower lobe, or both, as well as the corresponding segments in the left lung. Manifestations of severe, mixed aerobic/anaerobic infection include necrotizing pneumonia, lung abscess, and empyema (Figures 34.1–34.4). Foreign-body aspiration typically occurs in children and manifests as obstructive lobar or segmental overinflation or atelectasis.

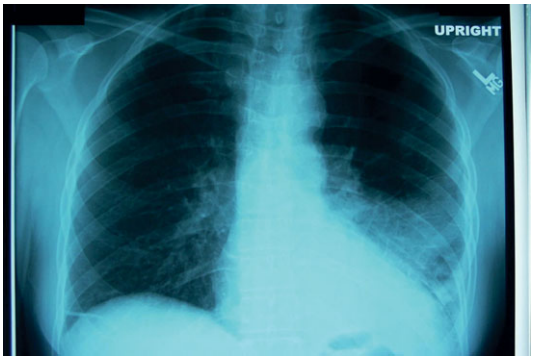

Figure 34.1 *K. pneumoniae* infection causing left lower lobe pneumonia in a 47-year-old woman who aspirated during a period of depressed consciousness due to alcohol intoxication.

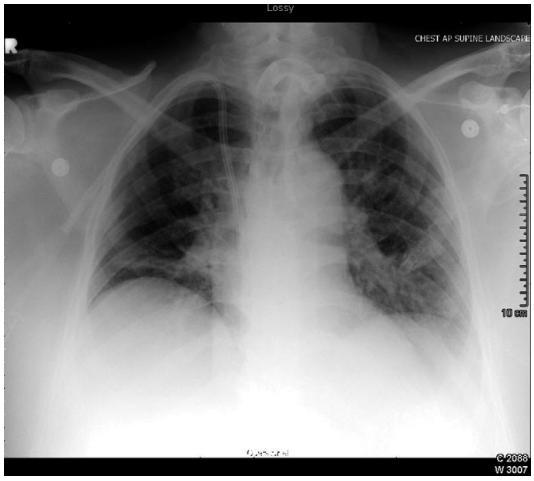

Figure 34.2 Bilateral lower lobe pneumonia due to *P. aeruginosa* in a dialysis-dependent nursing home patient following an episode of vomiting.

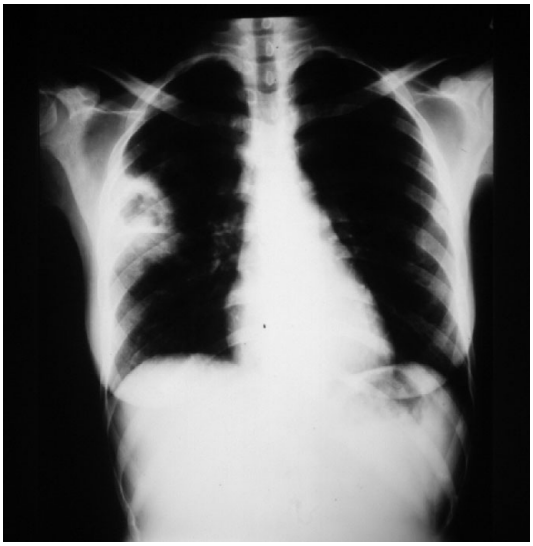

Figure 34.3 Mixed aerobic/anaerobic lung abscess following aspiration.

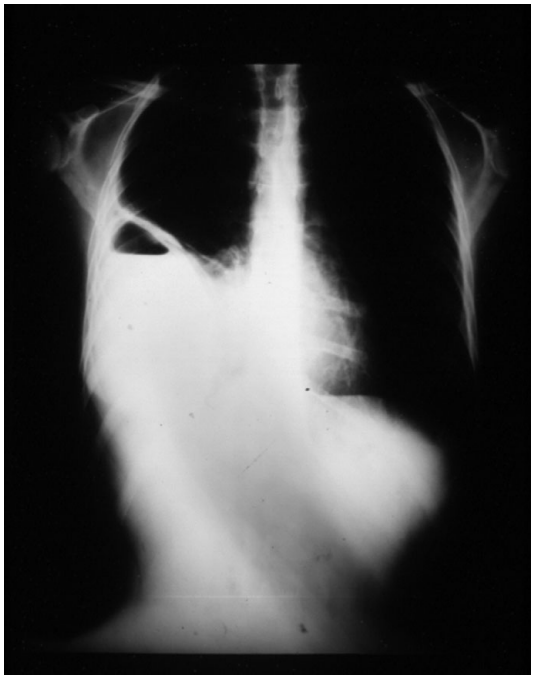

Figure 34.4 Mixed aerobic/anaerobic empyema following aspiration.

An extensive, patchy bronchopneumonic pattern may be observed in patients following massive aspiration of gastric contents.

Although the utility of sputum examination is much debated, pleural fluid (if present) and two sets of blood cultures should be obtained and efforts to obtain sputum should be pursued before initiation of antimicrobial therapy in hospitalized patients with aspiration pneumonia. Sputum samples must be carefully collected, transported, and processed to optimize the recovery of common aerobic bacterial pathogens such as *S. pneumoniae*. Because anaerobic cultures are not performed for sputum specimens, the presence of mixed bacterial flora on the sputum Gram stain is used to suggest the presence of polymicrobial infection with mixed aerobic/anaerobic oropharyngeal flora. Inspection of the sputum Gram stain is also necessary to ensure that the materials being cultured are not unduly contaminated by saliva. Bronchoscopic sampling of the lower respiratory tract (with a protected specimen brush or by bronchoalveolar lavage)

and quantitative culture are particularly useful in critically ill patients with hospital-acquired aspiration pneumonia, especially when the response to initial antimicrobial therapy is poor.

Unfortunately, despite extensive evaluation, the microbial cause of pneumonia can be identified in only 40% to 60% of hospitalized patients. However, when successful, identification of the infecting microorganism serves to verify the clinical diagnosis of infection and facilitates the use of specific therapy instead of unnecessarily broad-spectrum antimicrobial agents.

MICROBIOLOGY

The microbial etiology of aspiration pneumonia is complex and variable. The distribution of responsible pathogens differs in persons with community- versus hospital-acquired illness and varies with the presence or absence of previous antimicrobial exposure, comorbidities, or odontogenic disease.

In many studies performed during the 1970s, bacteriologic specimens were obtained by percutaneous transtracheal sampling, and rigorous laboratory methods were used to optimize the recovery of anaerobic bacteria from patients who were often in the later stages of the disease who had complications such as abscesses or empyema. Although typical causes of bacterial pneumonia such as *S. pneumoniae* were often recovered, these studies demonstrated that viridans streptococci and anaerobic organisms, including *Peptostreptococcus*, *Bacteroides, Prevotella*, and *Fusobacterium*, were the predominant pathogens in aspiration pneumonia.

Although some recent studies show a decreased prevalence of anaerobic bacteria as causes of aspiration pneumonia, the adequacy of attention to anaerobic culture techniques is often uncertain, leaving in doubt whether the true frequency of anaerobic infection has been underestimated. Well-performed studies continue to demonstrate anaerobes in up to 20% of nursing home patients with aspiration pneumonia; increased rates are found in patients with greater levels of debility. Conversely, the frequency of anaerobic infection is somewhat less in edentulous patients. In recent studies, the most frequently recovered aerobic organisms from persons with community-acquired aspiration pneumonia have been *S. pneumoniae, Haemophilus influenzae, S. aureus,* and Enterobacteriaceae (e.g., *E. coli, Klebsiella* species, and *Enterobacter* species).

Aerobic bacteria, particularly *S. aureus*, enteric gram-negative bacilli (i.e., Enterobacteriaceae), and occasionally *P. aeruginosa*, are more common causes of aspiration pneumonia in persons who develop disease while hospitalized or in a nursing home setting. At least 40% of hospital-associated pneumonias, many of which are due to aspiration, are caused by *S. aureus* and Enterobacteriaceae. Patients admitted to a respiratory or intensive care unit have the highest risk of nosocomial gram-negative bacillary pneumonia. *P. aeruginosa* is most common in persons who have received prior intensive antimicrobial therapy or who have underlying bronchiectasis or severe immunologic compromise. Polymicrobial infection is common in patients with aspiration pneumonia.

CLINICAL MANAGEMENT

Although corticosteroids have long been used in the treatment of acute chemical pneumonitis due to aspiration, this treatment cannot routinely be recommended. Prospective studies have failed to show a benefit in animal models of acid lung injury or in patients with either aspiration pneumonitis or the acute respiratory distress syndrome.

Antibiotic use is not warranted in most patients who acutely develop fever, leukocytosis, and pulmonary infiltrates following aspiration as these consequences are caused by chemical irritation and inflammation rather than due to established infection. Antibiotic use in such patients is essentially prophylactic and may facilitate colonization and infection by more resistant pathogens. However, there may be some benefit in selected populations such as persons with acute life-threatening complications of aspiration or those who have aspirated heavily colonized gastric contents (e.g., in the setting of small-bowel obstruction). Antibiotics should generally be administered to patients whose symptoms do not resolve within 48 to 72 hours or in whom new or progressive signs of pulmonary infection later emerge.

The need to select antibiotics with robust antianaerobic activity in the treatment of patients with aspiration pneumonia is controversial. Vigorous antianaerobic therapy may not offer meaningful benefit to patients with uncomplicated pneumonia, especially if therapy is not unduly delayed. However, specific antianaerobic therapy should be given to persons with necrotizing pneumonias, lung abscesses, or empyemas and

Table 34.2 Suggested empiric therapy for inpatients with aspiration pneumonia

Suspected pathogens	Preferred agents	Alternative agents
Mixed aerobic/ anaerobic flora	β-lactam plus metronidazole, β-lactam/β-lactamase inhibitor[a]	Clindamycin, moxifloxacin, ertapenem
Enterobacteriaceae	β-lactam/β-lactamase inhibitor,[a] cefepime, carbapenem[b]	Third-generation cephalosporin[c] or fluoroquinolone,[d] both +/− aminoglycoside[f]
P. aeruginosa	Antipseudomonal β-lactam[e] +/− aminoglycoside,[f] carbapenem +/− aminoglycoside[f]	Ciprofloxacin + aminoglycoside, ciprofloxacin + antipseudomonal β-lactam[f]
S. aureus	Vancomycin	Linezolid, quinupristin–dalfopristin, telavancin

Note: Therapy should be modified when the identity and susceptibility of the responsible pathogen(s) is determined.

[a] Ticarcillin–clavulanate and piperacillin/tazobactam are the preferred β-lactam/β-lactamase inhibitors for the treatment of nosocomial pneumonia due to Enterobacteriaceae. Ampicillin–sulbactam lacks adequate activity against many nosocomial enteric gram-negative bacilli.

[b] Ertapenem, imipenem, and meropenem have equivalent activity against *Enterobacter* spp. mixed aerobic/anaerobic flora. Only imipenem and meropenem have activity against *P. aeruginosa*.

[c] Third-generation cephalosporins: cefotaxime, ceftriaxone, and ceftazidime.

[d] Levofloxacin and ciprofloxacin generally have equivalent activity against *Enterobacter* spp. and *P. aeruginosa*. High resistance rates, particularly for nosocomial isolates limit the empiric usefulness of these agents in many settings.

[e] Antipseudomonal β-lactams: ceftazidime, cefepime, imipenem, meropenem, mezlocillin, piperacillin, or piperacillin–tazobactam.

[f] Addition of an aminoglycoside should be strongly considered in serious ill patients to ensure adequate breadth of antimicrobial therapy.

to persons who present with the indolent onset of aspiration pneumonia. Because of the emergence of β-lactamase-mediated resistance among anaerobes, empirical treatment for mixed aerobic/anaerobic flora requires the use of a β-lactam/β-lactamase inhibitor, clindamycin, or metronidazole combined with a penicillin, ampicillin, or an appropriate cephalosporin (Table 34.2). Because of the inevitable presence of aerobes, metronidazole monotherapy should not be given.

Considering the range of pathogens and antimicrobial resistance, initial therapy of aspiration pneumonia that develops in nursing home or hospitalized patients must be carefully selected. Although monotherapy may be reasonable for immunocompetent patients with mild to moderate diseases who are known or likely to be infected by susceptible strains of Enterobacteriaceae, broad-spectrum multidrug therapy is often necessary to ensure coverage of the likely pathogens. The choice of a particular combination must depend on the severity of infection, presence or absence of immunocompromise, and hospital-specific patterns of antimicrobial resistance and infection by specific microorganisms. Therapy should be made more specific when the pathogen(s) has been identified and susceptibilities are known.

With appropriate antimicrobial therapy, 50% of patients treated for aspiration pneumonia defervesce within 2 days of initiation of antibiotic therapy and 80% do so within 5 days. Prolonged fever is more common in patients with lung abscess or with infections by aggressive pathogens such as *P. aeruginosa*.

PREVENTION

Precautions should be taken to minimize the possibility of aspiration in hospitalized patients. Avoidance of the recumbent position and hypopharyngeal suctioning prevent aspiration among patients who are intubated. Guidelines from the American College of Chest Physicians and the American Gastroenterology Association provide specific recommendations regarding the evaluation of patients who are at risk for aspiration due to dysphagia. These guidelines recommend a multidisciplinary approach to patient evaluation. Patients with documented aspiration during swallowing studies have a 4- to 10-fold increased risk of pneumonia.

Placement of gastrostomy or post-pyloric tubes in persons with dysphagia is not superior to the use of a nasogastric tube for the prevention of aspiration or pneumonia. Lack of benefit is likely related to ongoing aspiration of oral secretions and continued aspiration of gastric contents in persons fed by gastrostomy or post-pyloric tubes. Nonetheless, decreased local irritation, fewer mechanical problems, and improved nutrition justify the use of gastrostomy tubes in many patients. When used, the residual volume of tube feedings in the stomach should be monitored,

and tube feedings should be held if the residual volume exceeds 50 mL.

The use of acid-suppressive medications (both proton pump inhibitors and histamine-2 blockers) is associated with a modest increase in the risk of pneumonia, including aspiration pneumonia. Potential mechanisms for this effect include increases in the colonization of the stomach with pathogenic microorganisms and direct impairment of neutrophil function. Minimizing the use of these medications may reduce the risk of aspiration pneumonia. Conversely, the use of angiotensin-converting enzyme inhibitors may reduce aspiration pneumonia by improving swallow and cough reflexes.

Good periodontal care and oral antiseptic decontamination with chlorhexidine decreases the burden of pathogenic bacteria in oral secretions and thereby may prevent aspiration pneumonia. In contrast, prophylactic antibiotic use is not recommended for patients in whom aspiration is suspected or witnessed.

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35. Lung abscess

Lisa L. Dever

Lung abscess is a chronic or subacute lung infection initiated by the aspiration of contaminated oropharyngeal secretions. The result is an indolent, necrotizing infection in a segmental distribution limited by the pleura. Except for infections with unusual organisms such as *Actinomyces*, the process does not cross interlobar fissures, and pleural effusion is uncommon. The resultant cavity is usually solitary, with a thick, fibrous reaction at its periphery. So defined, lung abscess is almost always associated with anaerobic bacteria, although the majority of infections are polymicrobial with microaerophilic and aerobic bacteria present.

In contrast, necrotizing pneumonia is an acute, often fulminant, infection characterized by irregular destruction of alveolar walls and therefore multiple cavities. This infection spreads rapidly through lung tissue, frequently crossing interlobar fissures, and is often associated with pleural effusion and empyema. The duration of illness before recognition is usually only a few days. Causative organisms include *Staphylococcus aureus, Streptococcus pyogenes, Klebsiella pneumoniae, Pseudomonas aeruginosa*, and, less commonly, other gram-negative bacilli, *Legionella* species, *Nocardia* species, and fungi.

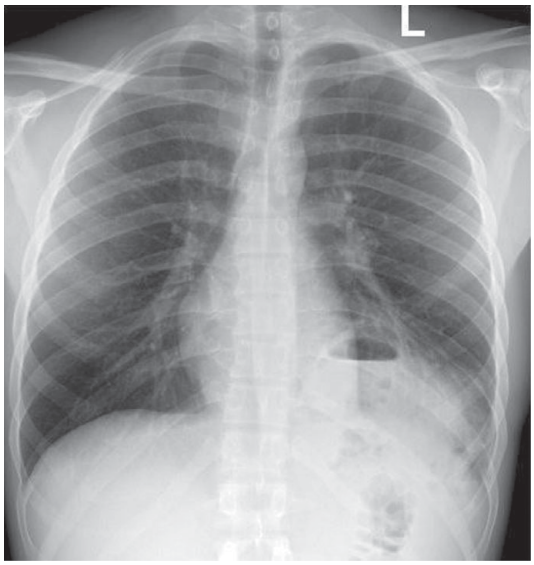

Figure 35.1 Chest radiograph showing a large cavitating lung abscess with air–fluid level in the left lower lobe.

DIAGNOSIS

The focus of this discussion will be the diagnosis and therapy of anaerobic lung abscess. Diagnosis can usually be made from the clinical presentation and chest radiograph findings. Many patients have conditions such as seizure disorders, neuromuscular diseases, alcoholism, or other causes of impaired consciousness that predispose them to aspiration of oropharyngeal secretions. Additionally, patients with impaired local and systemic host defenses are at greater risk. Gingival disease and poor dental hygiene, which promote higher concentrations of anaerobic organisms in the mouth, are common. Patients usually give a several-week history of fever and cough; putrid sputum occurs in less than 50% of patients. Hemoptysis may also occur. With chronic infection, patients will often experience weight loss and anemia, mimicking malignancy. Chest radiographs show consolidation in a segmental or lobar distribution with central cavitation, and air–fluid levels are often present (Figure 35.1). Chest tomography can further define the extent and location of the abscess (Figure 35.2). The lung segments most commonly involved are those that are dependent when the person is supine (i.e., posterior segments of the upper lobes and superior segments of the lower lobes).

The etiologic diagnosis of lung abscess is hampered by contamination of specimens by the normal anaerobic flora of the mouth, prior antimicrobial therapy, and difficulties inherent in culturing and identifying anaerobic bacteria. Although the Gram stain of sputum may be

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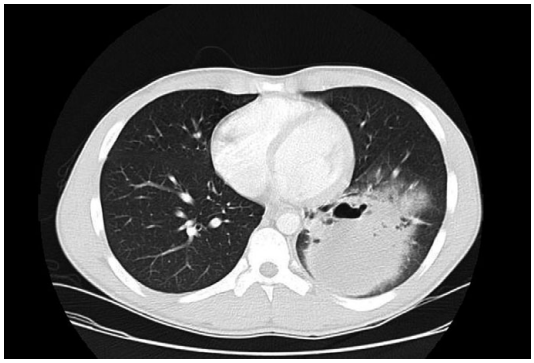

Figure 35.2 Computed tomography scan of the chest further defines the location and extent of the abscess cavity measuring 12 × 9 cm.

helpful in suggesting an etiologic diagnosis, routine sputum cultures are of no value because all contain anaerobic organisms. Techniques that have been used to obtain uncontaminated lower-airway specimens for anaerobic cultures include transtracheal needle aspiration, transthoracic needle aspiration, and open lung biopsy. Using these techniques, early investigators demonstrated anaerobic bacteria in virtually all untreated patients. These invasive techniques are seldom warranted in the clinical management of patients today. Quantitative cultures of bronchoalveolar lavage or other bronchoscopically obtained lower-airway specimens, such as those obtained with a protected specimen brush, may prove useful in the occasional patient suspected of having lung abscess, but are not needed in most. Transthoracic fine-needle aspiration guided by either ultrasound or computed tomography (CT) has been used increasingly for diagnostic purposes. Although generally safe in experienced hands, serious complications such as pneumothorax and bacterial contamination can result and greatly prolong the recovery period.

Anaerobic organisms most commonly recovered from lung abscesses are listed in Table 35.1. Multiple anaerobic organisms are commonly present along with aerobic or microaerophilic organisms. The viridans streptococci, particularly the *Streptococcus milleri* group, appear to be significant pathogens. *K. pneumoniae* was the most common pathogen in a retrospective review of 90 cases of community-acquired lung abscess from Taiwan. *K. pneumoniae* was recovered from 30 patients (33%), compared to 28 patients with anaerobic organisms. There are likely several explanations for these findings, including prior antibiotic therapy and geographic location. Other than determination of β-lactamase production, susceptibility testing of anaerobic organisms is usually not required.

Table 35.1 Anaerobes most commonly isolated in lung abscess

Organism
Gram-negative bacilli
Pigmented *Prevotella* spp.
Pigmented *Porphyromonas* spp.
Nonpigmented *Prevotella* spp.
Bacteroides fragilis group
Fusobacterium nucleatum
Fusobacterium spp.
Gram-positive cocci
Peptostreptococcus spp.
Peptococcus spp.
Gram-positive bacilli
Clostridium perfringens
Clostridium spp.
Propionibacterium acnes
Actinomyces spp.

Table 35.2 Intravenous antibiotic therapy of anaerobic lung abscess[a]

Antibiotic	Intravenous dosage	Frequency
Clindamycin	600 mg	q8h
Penicillin G plus metronidazole	2–3 million U 500 mg	q4h q6h
Alternative regimens with broader-spectrum activity[b]		
Ampicillin–sulbactam	3 g	q6h
Ticarcillin–clavulanate	3.1 g	q6h
Piperacillin–tazobactam	3.375 g	q6h
Cefoxitin	2 g	q6h
Ertapenem	1 g	q24h
Imipenem	500 mg	q6h
Meropenem	1 g	q8h
Moxifloxacin	400 mg	q24h

[a] All dosages are for adults with normal renal function.
[b] Includes activity against gram-negative aerobic bacilli.

THERAPY

Most lung abscesses are treated empirically. Table 35.2 provides therapeutic options for intravenous treatment of lung abscess. Selection of agents should be guided by the spectrum of pathogens suspected or isolated from appropriate collected specimens. Historically, penicillin has been the antibiotic of choice because of its good in vitro activity against most anaerobic and

microaerophilic bacteria present in the oral cavity. Two randomized clinical trials found that clindamycin is superior to penicillin, with time to resolution of symptoms and failure rate significantly lower in clindamycin-treated patients. Failure of penicillin therapy was associated with the isolation of penicillin-resistant *Bacteroides* species in one of these studies. Although increasing resistance of anaerobes and gram-positive bacteria to clindamycin has been reported, it is still preferred over penicillin for treatment of lung abscess when anaerobes or microaerophilic streptococci are likely to be predominant pathogens.

Although the combination of metronidazole and penicillin has been used successfully for the treatment of anaerobic pulmonary infections for decades, it should not be used if staphylococci or aerobic gram-negative bacilli may be part of the infectious process. Metronidazole has excellent bactericidal activity against virtually all gram-negative anaerobes but lacks activity against microaerophilic streptococci, as well as *Actinomyces* species, and should not be used as a single drug agent in the treatment of lung abscess.

A number of other agents have good in vitro activity against anaerobic organisms, including β-lactamase producers, and may pose less risk for the development of *Clostridium difficile*-associated disease than clindamycin. These agents include second-generation cephalosporins, carbapenems, β-lactam/β-lactamase inhibitor combination drugs, and newer fluoroquinolones. In addition, these drugs are attractive for the treatment of lung abscess because of their activity against many of the aerobes that may be present in mixed infections. Ampicillin–sulbactam was found to be as effective as clindamycin with or without an added cephalosporin in the treatment of aspiration and lung abscess in a prospective trial. Drugs that have little or no anaerobic activity should not be used in the treatment of lung abscess. These include aminoglycosides, aztreonam, and the older fluoroquinolones, levofloxacin and ciprofloxacin. Although a number of newer antimicrobials have a suitable spectrum of activity in vitro, it is unlikely that any will ever prove to be more efficacious than current therapy in prospective clinical trials. This is because of the difficulties inherent in conducting trials in this condition – no single institution sees large numbers of patients with lung abscess, it is difficult to isolate anaerobic organisms from uncontaminated respiratory specimens for accurate diagnosis and susceptibility testing, and the patients' response to treatment varies widely but is often slow, which can lead to the erroneous conclusion of treatment failure if that decision is made too early.

Table 35.3 Oral antibiotic therapy of anaerobic lung abscess

Antibiotic	Dosage (mg)	Frequency
Clindamycin	300	QID
Penicillin G plus	750	QID
Metronidazole	500	QID
Amoxicillin/clavulanate	875	BID
Moxifloxacin	400	Daily

Note: All dosages are for adults with normal renal function.

Duration of therapy

The duration of therapy for lung abscesses must be individualized, but extended therapy is usually required. Parenteral therapy is recommended initially in seriously ill patients and should be continued until the patient is afebrile and clinically improving. A prolonged course of oral antibiotics follows initial parenteral therapy. Less severely ill patients can be treated effectively with oral antibiotics alone. Options for oral therapy are provided in Table 35.3. Therapy should be continued until there is complete resolution or at least stabilization of chest radiograph lesions – this may require 6 to 8 weeks of therapy. Relapses may occur when therapy has been discontinued before resolution of chest radiograph findings, even when patients are clinically asymptomatic.

Other therapy

The majority of patients with lung abscesses respond to appropriate antimicrobial therapy and spontaneous drainage of the abscess through the tracheobronchial tree. Bronchoscopy may be required in those who have unchanged or increasing air–fluid levels and who remain septic after 3 to 4 days of antibiotic therapy. However, it rarely results in direct drainage of the abscess cavity and may lead to spillage of purulent material into the airways. In patients failing to respond to medical therapy, and in those with large abscess cavities (>6 to 8 cm diameter), drainage may be accomplished percutaneously, endoscopically, or surgically. Percutaneous catheter drainage, guided by CT or ultrasound, is the approach that has gained the most popularity in recent

years. Although there are no controlled trials evaluating the role of this procedure in the treatment of lung abscess, a review of the literature suggests that in appropriately selected patients this approach is safe and effective. The safety of this approach, however, depends critically on the degree of synthesis of the two pleural surfaces. If the visceral pleura has not been firmly adhered to the chest wall, a pyopneumothorax results, often with bronchopleural fistula – a true disaster that is to be avoided. Successful drainage through pigtail catheters placed directly in abscess cavities using a flexible bronchoscope, in some instances with use of a laser to perforate the abscess cavity, has been described. It must be remembered that the gross appearance of the bronchial orifice and the results of cytologic examinations may falsely suggest the presence of an underlying malignancy because of intense and long-lived inflammation. However, lung abscesses in adults older than 50 years of age are frequently associated with carcinoma of the lung, either because of cavitation of the neoplasm or cavitation behind a proximal bronchial obstruction. Such patients should be followed to resolution with great care. Thoracotomy or video-assisted thorascopic surgery for resection of lung abscess (most commonly a lobectomy), is required in fewer than 15% of patients. Surgery is generally reserved for patients who have failed medical therapy and other attempts at drainage and may have additional complications such as empyema, bronchopleural fistula, or suspicion of malignancy.

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36. Empyema and bronchopleural fistula

Charlotte E. Bolton and Dennis J. Shale

Infection of the pleural space leading to empyema formation, and the importance of clearing infection and pus from this space, has been recognized since ancient times. Historically, empyema was associated with pneumococcal pneumonia, with *Streptococcus pneumoniae* causing up to 70% of pleural space infections. With effective antibiotic treatment for community-acquired pneumonia, the incidence of empyema due to pneumococcus has decreased and the spectrum of causative organisms has widened, with *S. pneumoniae*, *Streptococcus Milleri* group, and *Staphylococcus aureus* now accounting for up to approximately 65% and an increasing isolation rate for anaerobes and gram-negative organisms. However, parapneumonic effusions occur in 30% to 60% of pneumonia cases, and, when empyema occurs, it is associated with an overall mortality of 20% with a further 20% requiring surgical intervention. Importantly, a reported increase has occurred in recent times with the young and elderly at the greatest risk of empyema.

Parapneumonic effusions are classified as simple or uncomplicated, complicated, and empyema, based on the appearance and biochemical characteristics of aspirated fluid, which supports the clinical impression of a continuum of disease (Table 36.1).

This classification also has clinical utility in that, during the early acute phase, with free flowing fluid, treatment is simpler than in the more chronic fibropurulent stage associated with multiple loculations and the need for greater interventional therapy. Empyema may be defined as the presence of organisms and numerous host defense cells, neutrophils, in the pleural fluid, or, more narrowly, as pus apparent to the naked eye. Bronchopleural fistula (BPF) may be caused by an empyema or may be associated with empyema formation following surgery, penetrating lung injuries, or a lung abscess.

ETIOLOGY

Empyema occurs most commonly in association with bacterial pneumonia, either in a community- or hospital-acquired setting. In a study in 434 pleural infections in the United Kingdom using standard culture and nucleic acid amplification techniques a causative organism was identified in 74%. Of the 336 isolates in the community-acquired setting 52% were of the genus *Streptococcus*, approximately 20% were anaerobes, 10% were staphylococcal, and 10% were gram-negative organisms. In the hospital-acquired infections (60 isolates) *Staphylococcus* was the major genus

Table 36.1 Classification of parapneumonic effusions and empyema

	Appearance	Biochemistry and bacteriology	Risk category for poor outcome
Simple/uncomplicated parapneumonic	Clear fluid	pH >7.2 LDH ≤1000 IU/L Glucose >3.3 mmol/L Negative Gram smear or culture	1 and 2 Very low or low
Complicated parapneumonic	Clear fluid or turbid	pH ≤7.2 LDH >1000 IU/L Glucose ≤3.3 mmol/L Positive Gram smear or culture likely	3 Moderate
Empyema	Frank pus	Positive Gram smear or culture likely Biochemistry unnecessary	4 High

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isolated (35%) of which 71% were methicillin-resistant forms; 23% were gram-negative organisms; 18% were *Streptococcus*; and 8% were anaerobes. Other organisms isolated included *Actinomyces* spp., *Enterococcus* spp., and *Mycobacterium tuberculosis*. This large study supports smaller studies suggesting the spectrum of organisms in pleural infections differs from that in pneumonia. Local events such as thoracic surgery, rupture of the esophagus, hepatic or subphrenic abscesses, and all penetrating injuries may introduce organisms, especially gram-negative or anaerobic organisms, into the pleural space. Ameba may enter the pleural space from an amebic abscess in the liver. Tuberculous empyema is a modest problem in the developed world, but is still seen in reactivation of tuberculosis in the elderly. However, in developing countries, with rapid urbanization, continued population increase, and greater levels of human immunodeficiency virus infection, there is an increasing incidence of tuberculous empyema. Pleural space infections may cause a BPF or may occur secondary to a BPF. Lung resection surgery remains the major cause of BPF, occurring in 3% to 5% of these operations.

CLINICAL FEATURES

There are no specific clinical features to differentiate simple from uncomplicated parapneumonic effusions. The main features are fever, chest pain, sputum production, appropriate physical signs of an effusion, and peripheral blood leukocytosis. Progression to an empyema is usually indicated clinically by the persistence or recurrence of fever and features of systemic upset with a lack of resolution of physical signs, because differentiation of consolidation from a small- to medium-volume effusion may not be possible. Other physical features include dyspnea with large effusions, rapid-onset finger clubbing, lethargy, and marked weight loss. Purulent sputum may indicate the development of a BPF. However, more insidious onset may occur with the presentation occurring over weeks to months after the original pneumonia or injury.

INVESTIGATIONS

A chest radiograph usually shows collection of fluid, although a localized, loculated collection may resemble an intrapulmonary mass. Differentiation between these possibilities may be resolved by the addition of a lateral chest radiograph to the standard posteroanterior film or by ultrasound or computed tomographic (CT) scanning. Ultrasonography is superior to CT in identifying septations in a loculated collection and also defines pleural thickening. Increasingly bedside ultrasound is used to guide a percutaneous diagnostic aspiration, increasing the diagnostic yield and patient safety. However, it is occasionally difficult to distinguish between empyema with a BPF and a lung abscess. In this setting, the use of CT scanning may guide both investigation and management approaches.

Aspirated material should be collected under anaerobic conditions and a portion submitted for anaerobic culture and a sample in a blood culture bottle can increase the anaerobic yield. Routine bacterial and mycobacterial culture should be undertaken with cytologic examination. If appropriate, fungi and parasites should be sought. Other investigations including pH, glucose concentration, and lactate dehydrogenase (LDH) activity of the fluid may be of use if there is little evidence of purulence to the naked eye. A meta-analysis of pleural fluid biochemistry, based on user characteristics, demonstrated that pH, especially $\leq$7.2, was a guide to the need for tube drainage and that glucose or LDH determination conferred no extra benefit; however, if pH assessment is unavailable, a glucose $\leq$60 mg/dL (3.3 mmol/L) is an alternative guide. Pleural fluid pH is measured in nonpurulent samples taken into a heparinized syringe and determined in a blood gas analyzer. There is no need to determine the pH of purulent samples. Litmus paper assessment is not an alternative. It should be remembered that lidocaine can lower the pH of samples and hence the sampling syringe should not be contaminated by this.

Generally, percutaneous pleural biopsy is not helpful and potentially harmful, although the diagnosis of tuberculosis is often made only from such material.

The literature on the value of individual investigations in guiding management is very limited. The American College of Chest Physicians (ACCP) analysis of risk of a poor outcome is based on pooled data, a small number of randomized controlled trials, and expert consensus but provides a framework to guide management of treatment (Table 36.1).

THERAPY

There has been a paucity of evidence on which to base therapeutic decisions, which reflects the

Table 36.2 Management options for pleural space infection

Therapeutic option	Comment
Observation and antibiotics	Acceptable option for small-volume category 1 or 2 low-risk collections
Therapeutic thoracentesis	Repeated treatment used in complicated effusions and empyema. Small studies suggest benefits, but no comparison with tube drainage
Tube thoracostomy	Most commonly used drainage method. Combined with antibiotics can improve clinical and radiologic status in 24–36 hours
Fibrinolysis	Probably not of value in most complicated effusions. Can be used in patients unfit for required surgical intervention
Medical or surgical thoracoscopy	Allows complete drainage and inspection of the pleural space. Small studies suggest leads to more rapid resolution of effusion
Decortication	Allows removal of all pus, tissue debris, and connective tissue. Is major surgery and requires the patient to be fit for surgery. Appropriately used, will reduce management period. Not for routine management of residual pleural thickening
Open drainage	An alternative option to decortication for patients unfit for surgery, but leads to a prolonged recovery period

wide breadth of the condition in terms of clinical feature and pathology. However, the recent ACCP and the British Thoracic Society (BTS) UK guidelines have both reviewed evidence and graded it to develop management recommendations. These documents represent current good practice, but both emphasize the need for more robust studies in the area of the management of pleural space infections.

Management options are summarized in Table 36.2 with summary notes. All patients with a pleural effusion in the presence of sepsis or pneumonia require diagnostic aspiration. Patients with parapneumonic effusion or empyema require antibiotics, usually, commenced empirically and subsequently guided by culture results. Many will have received antibiotics already, and negative cultures do not indicate cessation of antimicrobial therapy.

Small or insignificant effusions, the maximal thickness of which is $\leq$10 mm on ultrasound scanning or decubitus radiograph, simple or uncomplicated (category 1), may not need thoracentesis and are unlikely to need tube drainage. However, if the volume increases up to 50% hemithorax, simple or uncomplicated (category 2), or a positive Gram stain or culture is reported, further thoracentesis is recommended, though in a very small effusion such results are often false positives. In these categories the risk of a poor outcome is low, and they equate to the former simple or uncomplicated parapneumonic effusions.

Larger effusions occupying more than 50% hemithorax with evidence of loculation or parietal pleural thickening or with a pH $\leq$7.2 or evidence of infection in the pleural space (category 3) require closed tube drainage and carry a moderately high risk of a poor outcome. Generally, such drainage is effective, though negative low-pressure high-volume suction may be needed if flow is slow and will hasten the obliteration of the pleural space. In the past large-bore tubes were recommended for drainage, but more recently narrow-bore tubes placed with imaging guidance have been shown to be just as effective and to be better tolerated by patients. Tube drainage is contraindicated in patients with a neoplasm causing airway obstruction, which is the only indication for bronchoscopy in empyema. Full characterization of this category, which corresponds to the complicated parapneumonic effusions in other classifications, requires more extensive investigation to develop an appropriate management plan (Table 36.2). Effective antibiotic choice and closed tube drainage should lead to radiologic and clinical improvement within 24 to 36 hours. Failure to respond requires further investigation, including imaging to assess tube position, any residual collection, or the formation of loculation, and should include either ultrasound or contrast-enhanced CT scanning as loculation and parietal pleural thickening are indicators of a poor outcome. A slow response to lack of improvement will allow an empyema to form and may require surgical intervention, while increasing the risk of prolonged morbidity and a higher mortality.

The presence of pus defines an empyema (category 4), which carries a high risk of a poor outcome and requires closed tube drainage and antibiotic treatment. Frequently in empyema, the chest tube can become blocked, requiring saline flushes to maintain patency. As many infections will be of mixed organisms, antibiotic coverage for both anaerobic and nonanaerobic organisms is required. Surgical options are likely to be needed in this group. It requires a cautious and balanced decision so that surgery is not contemplated too late, a widely reported problem, when the patient's condition may reduce the chance of a satisfactory outcome. Medical or

surgical thoracoscopy has been reported to reduce the time to recovery and to be as effective as formal surgical intervention, but the design of comparisons is inadequate to make firm recommendations other than that surgical options should be pursued if there is evidence of continuing sepsis and a collection after 7 days of antibiotic treatment and drainage.

Decortication aims to remove pus and fibrous tissue lining the pleural cavity but is a major surgical procedure and is unsuitable for debilitated patients, who should be considered for fibrinolytic therapy or open drainage. Decortication has the benefit of a quicker resolution of the empyema over methods of open drainage, which have a median healing period of 6 to 12 months. In general, decortication is not needed for residual pleural thickening from the successful management of categories 3 or 4, unless it persists for longer than 6 months or where there is extensive pleural thickening or respiratory symptoms secondary to restrictive effects.

The evidence for using fibrinolytic agents has been inconclusive due to small, often open, studies. A recent double-blind study in 454 patients with complicated pleural infection and at category 3 or 4 risk compared streptokinase with placebo, with all other treatment options as per routine. The primary end point of death or surgical drainage at 3 months was no different between treatment groups, $p = 0.43$. Similarly, secondary end points of death rate, requirement for surgery, radiographic outcome, and length of hospital stay were also no different between the streptokinase or placebo groups, whereas serious adverse events were increased in the streptokinase group, relative risk 2.49 (95% confidence interval 0.98–6.36). Important contraindications include BPF, coagulation disorders, and allergy.

Currently fibrinolytic therapy is not recommended for routine care of infected pleural effusions but remains an option for the patient unfit for surgery or in the absence of free flowing pus. Treatment with streptokinase 250 000 international units twice daily for 3 days or urokinase 100 000 international units daily for 3 days has been recommended. The latter is less likely to produce allergic side effects. Early clinical studies comparing the use of streptodornase (DNase) with tissue plasminogen activator and in combination in complicated parapneumonic effusions and empyema suggest this combination is effective and reduces the need for surgery and the length of hospital stay.

Table 36.3 Management of bronchopleural fistula (BPF)

Small BPF
Some may close spontaneously:
Without empyema
Transbronchoscopic fibrin glue
Transbronchoscopic tissue glue
Transbronchoscopic vascular occlusion coils/Amplatzer devices
Transbronchoscopic laser/tetracycline/gel foam
Thoracoscopic sealing
With empyema
Antibiotic/tube drainage and attempted closure of BPF
Large BPF
Typically associated with empyema:
Surgical options include decortication or open drainage of empyema and occlusion of the BPF by direct closure or well-vascularized muscle or omental flaps

This classification of empyema has the value of matching a spectrum of clinical status to a plan of escalating therapeutic options but remains only a guide based on limited evidence. Patients may move in either direction along this spectrum, so careful and repeated assessment of the patient's status is required, particularly soon after a therapeutic intervention is made, to ensure a continuing appropriate management response.

The aim with BPF, whether in the setting of trauma, neoplasm, or empyema, is to deal with the air leak and any new or residual empyema. Air in the pleural cavity indicates the presence of a BPF and need for tube drainage. The air leak may be dealt with either by surgical or by non-surgical intervention, largely depending on the size and duration of the BPF (Table 36.3).

Pleural space infections demand major management decisions of physicians. There are various approaches to the patient with empyema and BPF, and the heterogeneity of the response means that the management of this problem should be individualized to the patient. There is considerable literature relating to such problems, but most studies until recently have been too small to demonstrate clear beneficial options.

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PART VI

Clinical syndromes: heart and blood vessels

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37. Endocarditis of natural and prosthetic valves: treatment and prophylaxis

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DEFINITION AND PATHOGENESIS

The term *infective endocarditis* (IE) denotes an infection of the endothelial surface of the heart. This is usually a valvular surface, but nonvalvular extracardiac endothelium can also be infected. Previously, IE was classified as acute or subacute, depending on the severity of clinical presentation; however, now classification and therefore therapeutic decisions are based on the bacteriology and the valvular tissue involved, that is, native valve versus prosthetic valve.

Structural abnormalities that cause turbulent blood flow across a high to low pressure gradient denude epithelium from surfaces impacted on by the turbulence; such damaged areas (most commonly valvular surfaces) are predisposed to platelet and fibrin deposition and eventually to the formation of sterile vegetation, also known as nonbacterial thrombotic endocarditis (NBTE). When transient bacteremia occurs after injury to mucosal surfaces in the oropharynx, genitourinary tract, or gastrointestinal tract, organisms can become fixed onto the NBTE, where they adhere firmly, multiply, and stimulate further deposition of platelets and fibrin. The infected site is sustained by inaccessibility of the organisms to host defenses. Complications may arise through local bacterial spread or through embolization of fragments of the vegetation. The endovascular location of the lesions causes multiorgan bacterial seeding as well as organ damage through immune complex deposition.

NATIVE VALVE ENDOCARDITIS

In most cases of native valve endocarditis (NVE), there is an identifiable predisposing cardiac lesion. Mitral valve prolapse is now the most commonly identified underlying cardiac abnormality in patients with IE in the United States. The risk of IE is estimated to be five to eight times greater than that of individuals with a normal mitral valve. Men with mitral valve prolapse are at considerably greater risk than women, although the frequency of mitral valve prolapse is three times greater in women than in men. Rheumatic heart disease is still the most common underlying heart condition for bacterial endocarditis in developing countries. Other recognized predisposing cardiac lesions are ventricular septal defects, subaortic and valvular aortic stenosis, tetralogy of Fallot, coarctation of the aorta, Marfan syndrome, and pulmonary stenosis, but not uncomplicated atrial septal defects.

Although the overall incidence of IE, 1.7 to 6.2 cases per 100 000 person-years, has remained relatively stable over time, since the late 1960s the epidemiologic features of IE have changed in the developed world as a result of increasing longevity and the introduction of more invasive procedures within the healthcare system. The steady increase in the median age (47 to 69 years compared to 30 to 40 years in pre-antibiotic era) has given rise to degenerative valvular diseases (calcified aortic stenosis, calcified mitral valve annulus, and mitral valve prolapse) and increased exposure to healthcare-associated infections. *Staphylococcus aureus* has surpassed viridans group streptococci as the leading cause of IE. In data published from the International Collaboration of Endocarditis-Prospective Cohort Study (ICE-PCS) *S. aureus* was the most commonly identifiable pathogen among the 1779 cases of definitive IE (31.4%). *S. aureus* IE remains the most aggressive form of native valve infection; patients have a higher mortality rate and are more likely to experience an embolic and/or a central nervous system (CNS) event (Figures 37.1–37.3). Enterococci (10% of cases of native valve IE) present an enhanced risk to elderly men and young women with genitourinary disease. In recent years, both enterococci and staphylococci have become major pathogens in infections originating from intravascular catheters. Occasionally, almost all species of bacteria can cause IE. Fastidious oropharyngeal

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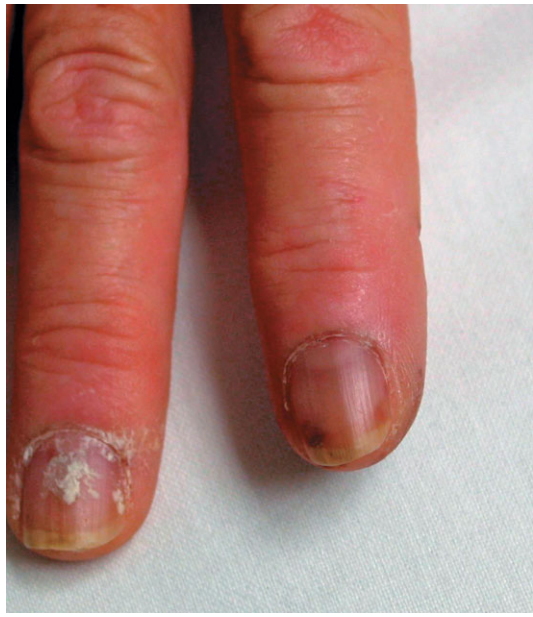

Figure 37.1 Splinter hemorrhage of nails in patient with *Staphylococcus aureus* infective endocarditis.

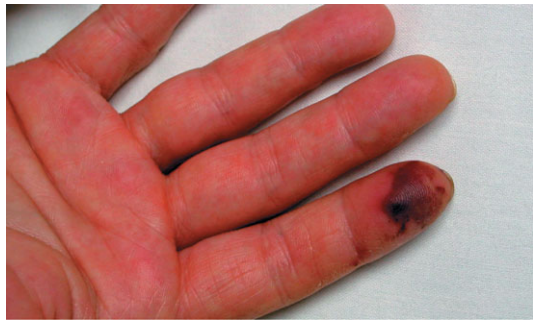

Figure 37.3 Embolic lesions in a patient with *Staphylococcus aureus* infective endocarditis.

organisms such as the HACEK group cause 10% of community-acquired IE. Fungi rarely cause IE on a native valve (2%) except in intravenous drug abusers (13%).

PROSTHETIC VALVE ENDOCARDITIS

The overall incidence of prosthetic valve endocarditis (PVE) is 1% to 4% during the first 12 months following valve surgery. The causative organisms differ in early and late PVE. Infection within 60 days of valve insertion is considered to be early PVE and is usually caused by *Staphylococcus epidermidis* (25% to 30%) or *S. aureus* (15% to 20%). In a prospective study of patients with prosthetic valves and *S. aureus* bacteremia conducted

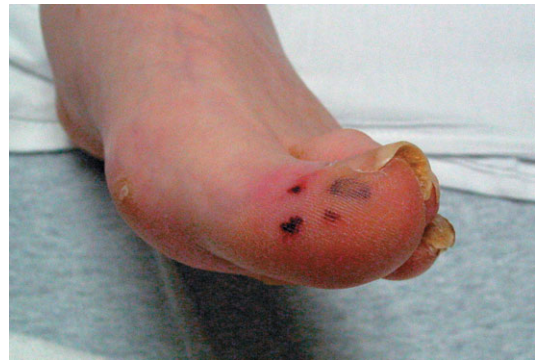

Figure 37.2 Embolic lesions in a patient with *Staphylococcus aureus* infective endocarditis.

at Duke University Medical Center, 26 of 51 patients (51%) developed PVE. The risk of endocarditis in this study was independent of the type of valve (mechanical vs. bioprosthetic), location (mitral vs. aortic), or onset of bacteremia after prosthetic valve implantation. The remaining cases of PVE are caused by gram-negative aerobic organisms, enterococci, diphtheroids, and streptococci. Fungal endocarditis may develop in patients with prolonged hospitalization with indwelling central venous catheters and long-term antibiotic use. Organisms that cause late PVE closely resemble those of NVE, although staphylococci remain predominant.

NOSOCOMIAL ENDOCARDITIS

IE can occur as a complication of nosocomial bacteremia. Since the mid 1980s, the increased use of intravascular devices and invasive diagnostic procedures, with their consequent complications, has increased the risk of healthcare-associated endocarditis. Colonized intravascular catheters now account for up to two-thirds of healthcare-associated IE. *S. aureus*, including methicillin-resistant *S. aureus* (MRSA), *S. epidermidis*, enterococcus, and *Candida* species are the predominant pathogens.

The Infectious Disease Society of America has updated the catheter-related bloodstream infection (CRBSI) guidelines, with key recommendations regarding *S. aureus* BSI (Table 37.1). *S. aureus* in blood should rarely, if ever, be considered a contaminant and a low threshold should be maintained regarding suspicion of IE in this setting.

Long-term catheters should be removed in the setting of endocarditis. Transesophageal echocardiography (TEE) should be performed (at least 5–7 days after the onset of bacteremia or fungemia) for

Table 37.1 CRBSI with *S. aureus*

Catheter removal recommended
Long-term catheters should be removed from patients with CRBSI associated with any of the following conditions: endocarditis, severe sepsis, bloodstream infection that continues despite more than 72 hours of appropriate antimicrobial therapy, suppurative thrombophlebitis, or infections due to *S. aureus, Pseudomonas aeruginosa,* fungi, or mycobacteria
***S. aureus* specific recommendations**
In addition to catheter removal, patients should receive 4–6 weeks of antimicrobial therapy, or a minimum of 14 days of therapy if they meet the following criteria: the patient is not diabetic or immunosuppressed; if the infected catheter is removed; if the patient has no prosthetic intravascular device (e.g., pacemaker or recently placed vascular graft); if there is no evidence of endocarditis or suppurative thrombophlebitis on TEE and ultrasound, respectively; if fever and bacteremia resolve within 72 h after initiation of appropriate antimicrobial therapy; and if there is no evidence of metastatic infection on physical examination and sign or symptom-directed diagnostic tests

patients with CRBSI who have a prosthetic heart valve, pacemaker, or implantable defibrillator.

INFECTIVE ENDOCARDITIS IN THE INTRAVENOUS DRUG ABUSER

Endocarditis in intravenous drug abusers (IVDAs) involves mainly normal valves. Only 20% of the patients have an underlying valvular abnormality when IE is diagnosed. Infection is believed to result from the deposition of bacteria on valves that have sustained microscopic injury through bombardment with drug-associated contaminants injected intravenously. The tricuspid valve is predominantly involved in IVDAs, but aortic and mitral valves may also be damaged. Although *S. aureus* is known to be the most common causative organism in patients with IE associated with IVDAs, a variety of microorganisms and fungi, including unusual and fastidious organisms (e.g., the HACEK group) and gram-negative organisms (e.g., *Pseudomonas* species from water sources used), are not uncommon in IVDAs, particularly in the patients who are not meticulous in their injection practices. Polymicrobial infections may also be seen. Because of the higher incidence of right-sided lesions and the generally younger age of the affected group, prognosis for recovery in treated IVDAs' IE is better than in the general population. However, valvular damage sustained in the course of the infection confers an extremely high risk of recurrent IE in those patients who continue to use intravenous drugs.

DIAGNOSIS OF INFECTIVE ENDOCARDITIS

Definitive diagnosis of IE requires documentation of sustained bacteremia with a microorganism typical for endocarditis in a patient with an underlying valvular cardiac lesion or by direct demonstration of the pathogen by culture or histopathology of the vegetation or an embolus. The Duke criteria, in use since 1994 to diagnose IE clinically, were primarily developed to facilitate epidemiologic and clinical research. The Duke criteria incorporate echocardiographic findings and IVDA as an important epidemiologic risk factor into the previously formulated Von Reyn criteria for IE and expanded their sensitivity and specificity. Patients with suspected endocarditis were stratified in three categories: definite, possible, and rejected cases. Although its high sensitivity was confirmed by several subsequent studies, some problems emerged with the original criteria with the broad classification of cases as "possible," the increased relative risk of endocarditis with *S. aureus* bacteremia, the widespread use of TEE for diagnosis (Figures 37.4 and 37.5), and the classification of culture-negative endocarditis. Modifications of the Duke criteria were proposed in 2000 (Table 37.2) because they have been used as a clinical guide for the diagnosis of IE.

THERAPY

A vegetation consists of microorganisms in high density (10^8 organisms/g of tissue) and in a reduced metabolic state inside an acellular lesion with impaired host defenses. Eradication of IE is thus almost totally dependent on the efficacy of the antimicrobial therapy. To achieve this end, certain principles of therapy are critical:

1. Parenteral antibiotics are usually required to provide a predictably high serum antibiotic level and thus to optimize penetration of the antibiotic into tissue.
2. Bactericidal rather than bacteriostatic antibiotics should be used to compensate for impaired host defenses in the vegetation.
3. Prolonged therapy is required for complete eradication of microorganisms.

In a patient with suspected IE but in whom culture results are not available, empiric antimicrobial therapy should be directed against staphylococci, streptococci, and enterococci unless epidemiologic data point at alternative etiologies. Nafcillin or oxacillin, 2 g IV every 4 hours, and gentamicin, 1 mg/kg IV every 8 hours,

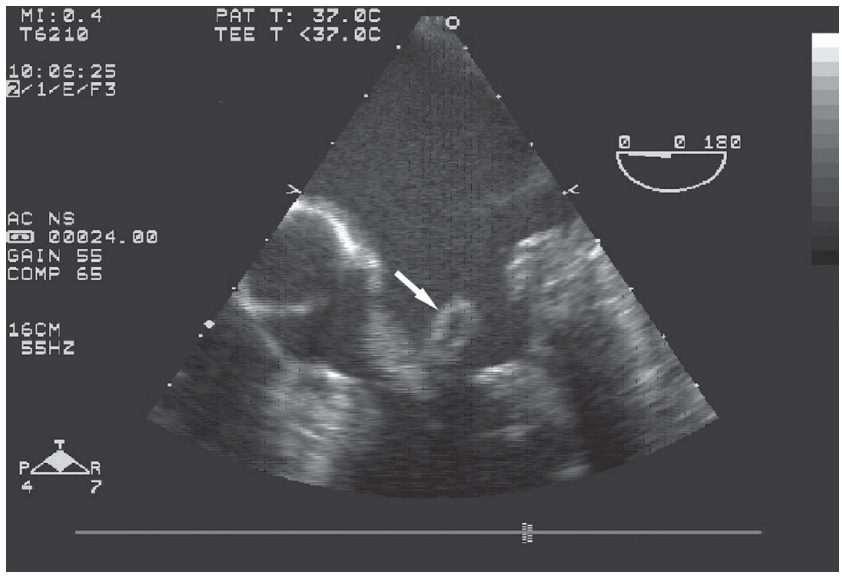

Figure 37.4 Transesophageal echocardiogram of a patient with *Haemophilus parainfluenzae* infective endocarditis showing large vegetation in mitral valve chordae apparatus (*arrow*).

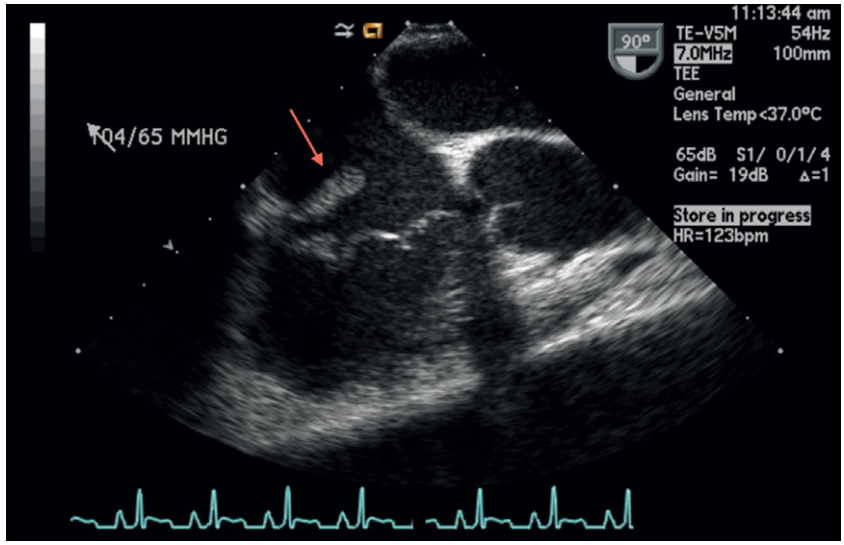

Figure 37.5 Transesophageal echocardiogram of an intravenous drug user with a large vegetation on the tricuspid valve (*arrow*).

may be used as initial therapy. Vancomycin, 15 mg/kg every 12 hours, should be used if the patient is allergic to penicillin. Vancomycin should also be the drug of choice in suspected nosocomial endocarditis because of the high incidence of MRSA and coagulase-negative *S. epidermidis* (CoNS) in such a setting.

Viridans streptococci and *Streptococcus bovis*

Antibiotic selection of the therapy of streptococcal endocarditis is based on the minimal inhibitory concentration (MIC) of the isolated organism to penicillin (Table 37.3). Viridans streptococci and *S. bovis* are generally highly susceptible to penicillin (MIC $\leq$0.12 μg/mL) and can be treated with aqueous penicillin G or ceftriaxone for 4 weeks. The addition of gentamicin can shorten therapy to 2 weeks, but such therapy should be reserved for patients with normal renal function and uncomplicated (i.e., short duration, minimal distal disease) endocarditis. The same regimen applies to the therapy of streptococcal PVE, but the duration of treatment is prolonged to 6 weeks. For streptococci with moderate resistance to penicillin (MIC

Table 37.2 Modified Duke criteria for diagnosis of infective endocarditis

Definitive infective endocarditis	
Pathologic criteria Microorganism demonstrated by culture or histology of vegetation or emboli or intracardiac abscess Histopathologically proven at autopsy or surgery	
Clinical criteria 2 major; 1 major and 3 minor criteria; or 5 minor criteria	
Possible infective endocarditis	
1 major and 1 minor or 3 minor criteria[a]	
Rejected	
Alternative diagnosis, resolution of syndrome with ≤4 days of antibiotic; no histopathologic evidence with ≤4 days of antibiotic therapy; does not meet criteria for "possible" IE.	
Major criteria	**Minor criteria**
Positive blood cultures Typical microorganism for IE from 2 separate blood cultures, as follows: Viridans streptococci, *Streptococci bovis*, HACEK group, *Staphylococcus aureus*[a], or community-acquired enterococci with no primary focus Persistently positive blood cultures with microorganism consistent with IE: At least 2 positive blood cultures drawn 12 h apart All of 3 or a majority of 4 or more separate blood cultures: first and last sample at least 1 h apart Single blood culture positive for *Coxiella burnetii* or positive serology: antiphase 1 IgG ab titer 1:800[a] Endocardial involvement by showing vegetation; or abscess; or new prosthetic valve dehiscence; or *de novo* valvular regurgitation in echocardiogram. TEE recommended for prosthetic valve, "possible IE" cases, or complicated IE with intracardiac abscess[a]	Predisposing heart condition or intravenous drug use Fever (38°C) Vascular phenomena Immunologic phenomena Positive blood cultures but short of major criteria or serologic evidence of infection; excludes single positive blood cultures with coagulase-negative staphylococci and organism consistent with IE Echocardiogram consistent with IE but short of major criteria was eliminated[a]

Abbreviations: TEE = transesophageal echocardiogram; IE = infective endocarditis; IgG = immunoglobulin G; ab = antibody.
[a] Modifications from the original Duke Criteria

0.12–≤0.5 μg/mL), the addition of gentamicin for the first 2 weeks is always recommended to prevent relapse. IE caused by highly penicillin-resistant viridans streptococci (MIC 0.5 μg/mL) and newly named *Abiotrophia defectiva* and *Granulicatella* species (formally known as nutritionally variant streptococci) are difficult to treat and should be treated with the same regimen as recommended for enterococcal endocarditis. Vancomycin is an option only for penicillin-allergic patients.

Staphylococci

Most strains of *S. aureus* are resistant to penicillin by virtue of β-lactamase production. Therapy is based on antistaphylococcal penicillins (i.e., nafcillin, oxacillin) or first-generation cephalosporins (i.e., cefazolin) administered for 6 weeks (Table 37.4). The addition of gentamicin to nafcillin enhances the rate of killing of bacteria and the sterilization of blood, but no advantage results from longer than 3- to 5-day use, whereas toxicity increases. Currently its use is optional. Vancomycin should be used only in cases of serious β-lactam allergy (immunoglobulin E [IgE]-mediated hypersensitivity) or if a methicillin-resistant isolate is suspected or documented; otherwise high-dose cefazolin (6 g/24 h IV in three equally divided doses) can be substituted for nafcillin for a less frequent dosing regimen. Increasing rates in methicillin-resistant strains in both hospital and community obligates the use of vancomycin as empiric antibiotic therapy. Following a recent non-inferiority trial, daptomycin (6 mg/kg intravenously daily) was approved for treatment of *S. aureus* bacteremia and right-sided endocarditis caused by methicillin-susceptible *S. aureus* (MSSA) or MRSA. In a patient with uncomplicated right-sided *S. aureus* endocarditis (only tricuspid valve involved) resulting from IVDA, 2 weeks of intravenous nafcillin with gentamicin for 2 weeks may be adequate therapy. These findings do not extrapolate to treatment with vancomycin. Ceftaroline, a new antistaphylococcal antibiotic, lacks clinical data to warrant use at this time.

Table 37.3 Antibiotic therapy for streptococcal endocarditis

Viridans streptococci or *S. bovis* MIC ≤0.12 μg/mL	Viridans streptococci or *S. bovis* MIC 0.12 μg/mL to ≤0.5 μg/mL	Viridans streptococci or *S. bovis* MIC 0.5 μg/mL
Native valve		
PCN G, 12–18 mU/24 h IV 4 wk or Ceftriaxone, 2 g/24 h IV/IM 4 wk	PCN G, 24 mU/24 h IV 4 wk or Ceftriaxone, 2 g2/4 h IV/IM 4 wk plus	PNC G, 18–30 mU/24 h IV 4–6 wk or Ampicillin, 12 g/24 h IV 4–6 wk plus
PCN G, 12–18 mU/24 h IV 2 wk or Ceftriaxone, 2 g/24 h IV/IM 2 wk plus Gentamicin, 1 mg/kg q8h IV/IM for the first 2 wk	Gentamicin 1mg/kg IV/IM q8h for the first 2 wk	Gentamicin, 1 mg/kg q8h IV/IM 4–6 wk
Prosthetic valve		
PCN G, 24 mU/24 h IV 6 wk or Ceftriaxone, 2 g/24 h IV/IM 4 wk with or without Gentamicin 1 mg/kg IV/IM q8h for the first 2 wk[a]	PCN G, 24 mU/24 h IV 6 wk or Ceftriaxone, 2 g/24 h IV/IM 6 wk plus Gentamicin 1 mg/kg IV/IM q8h for 6 wk	PCN G, 24 mU/24 h IV 6 wk or Ceftriaxone, 2 g/24 h IV/IM 6 wk plus Gentamicin 1mg/kg IV/IM q8h for 6 wk
If patient is allergic to PCN		
Vancomycin, 30 mg/kg q24h IV divided in 2 doses, no more than 2 g/24 h unless concentration inappropriately low 4 wk	Vancomycin, 30 mg/kg q24h IV divided in 2 doses, no more than 2 g/24 h unless concentration inappropriately low 6 wk	Vancomycin, 30 mg/kg q24h IV divided in 2 doses, no more than 2 g/24 h unless concentration inappropriately low 6 wk plus Gentamicin, 1 mg/kg q8h IV/IM 4–6 wk

Abbreviations: MIC = minimal inhibitory concentration; PCN = penicillin.

[a] Combination therapy has not demonstrated superior cure rates compared to monotherapy

Table 37.4 Antibiotic therapy for staphylococcal endocarditis

S. aureus or coagulase-negative staphylococcus native valves	*S. aureus* or coagulase-negative staphylococcus prosthetic valves
Methicillin sensitive	
Nafcillin, 12 g q24h IV 6 wk plus (optional) Gentamicin, 1 mg/kg q8h IV 3–5 days or Cefazolin, 6 g q24h IV 6 wk plus (optional) Gentamicin, 1 mg/kg q8h IV 3–5 days	Nafcillin, 12 g q24h IV ≥6 wk plus Rifampin, 300 mg PO q8h ≥6 wk plus Gentamicin, 1 mg/kg q8h IV first 2 wk
Methicillin-resistant or PCN allergic	
Vancomycin, 30 mg/kg q24h IV divided in 2 doses, no more than 2 g/24 h unless concentration inappropriately low 6 wk	Vancomycin, 30 mg/kg q24h IV divided in 2 doses ≥6 wk plus Rifampin, 300 mg PO q8h ≥6 wk plus Gentamicin, 1 mg/kg q8h IV first 2 wk
Daptomycin, 6 mg/kg q24 IV 4–6 wk (for right-sided endocarditis only).	

In PVE, the most common causative agents are *S. aureus* and coagulase-negative *S. epidermidis* (see Table 37.4). Both species are commonly resistant to β-lactam antibiotics; thus, until sensitivity to methicillin can be confirmed, vancomycin should be used as the primary therapy of endocarditis. Bacteriologic failures are common, and surgical valve replacement may be necessary.

Enterococci and vancomycin-resistant enterococcus

Enterococci are intrinsically resistant to the bactericidal effect of penicillin or vancomycin. Therefore, for the treatment of endocarditis, the addition of aminoglycoside is needed to promote bactericidal effect. Cephalosporins are inactive against enterococci and cannot substitute for penicillin in this setting. Emergence of enterococci highly resistant to penicillin, aminoglycosides, and vancomycin has seriously compromised the efficacy of available treatment; therefore, all enterococcal isolates in cases of suspected IE should be subjected to in vitro sensitivity testing.

Table 37.5 Antibiotic therapy for enterococcal and PCN-resistant strain streptococcal endocarditis

Enterococci and PCN-resistant strain streptococci, native valves or prosthetic valves[a]	
Penicillin sensitive	
PNC G, 18–30 mU/24 h IV plus gentamicin, 1 mg/kg q8h IV 4–6 wk or Ampicillin, 12 g q24h IV, plus gentamicin, 1 mg/kg IV q8h 4–6 wk	
Penicillin resistant or PCN allergic (β-lactamase-producing strain)	
Ampicillin–sulbactam, 12 g q24h IV 6 wk, plus gentamicin, 1 mg/kg IV q8h 6 wk or Vancomycin, 30 mg/kg q24h IV divided in 2 doses 6 wk, plus gentamicin[b], 1 mg/kg q8h IV 6 wk	
Enterococci PCN- and vancomycin-resistant, native valves or prosthetic valves	
E. faecium	***E. faecalis***
Linezolid, 600 mg IV/PO q12h ≥ 8 wk or Quinupristin–dalfopristin 22.5 mg/kg 24 h divided in 3 doses ≥8 wk	Imipenem–cilastatin, 2 g q24h IV ≥8 wk, plus ampicillin 12 g q24h IV ≥8 wk or Ceftriaxone, 2 g q24h IV/IM ≥8 wk, plus ampicillin 12 g q24 h IV ≥8 wk

Abbreviation: PCN = penicillin.

[a] Prosthetic valve or intracardiac material; recommended therapy for 6 weeks.

[b] Substitute gentamicin with streptomycin, 15 mg/kg q24h IV/IM divided in 2 doses 4–6 wk, whenever enterococci are gentamicin-resistant but streptomycin-sensitive

Treatment of NVE from community-acquired enterococcus (i.e., one relatively sensitive to penicillin and susceptible to synergistic killing with aminoglycosides) is 4 to 6 weeks of penicillin or vancomycin plus gentamicin (Table 37.5). Patients with prosthetic valve infection should have therapy prolonged for a minimum of 6 weeks. When enterococcal strains are gentamicin-resistant, streptomycin should be used as alternative combination therapy whenever susceptible, although recent studies suggest that a combination of ampicillin (12 g per 24 hours) with ceftriaxone (2 g twice daily) may be effective in IE due to *Enterococcus faecalis*, in strains both susceptible to and highly resistant to gentamicin. In patients who cannot tolerate the potential side effects of an aminoglycoside, this may be a reasonable second-line choice of therapy; however, further prospective trials would be beneficial to fully support this combination. For enterococci highly resistant to ampicillin and highly resistant to aminoglycosides, treatment is based on vancomycin alone. The relapse rate may increase substantially.

Vancomycin-resistant enterococcus (VRE) now accounts for 15% of infections in critical care units. *Enterococcus faecium* is much more commonly vancomycin resistant than *E. faecalis*. Occasional cases of VRE endocarditis have been reported. Few therapeutic options are available for the treatment of multiply resistant enterococci, thus there is no standard regimen for VRE endocarditis. From compassionate use data, linezolid resulted in a cure rate of 77% in VRE IE. Clinical success rates for treatment of vancomycin-resistant *E. faecium* (VREF) infections with quinupristin–dalfopristin (Synercid) are as high as 73%, although data are extremely limited with regard to VREF endocarditis. As mentioned above, double β-lactam combination therapies have a synergistic bactericidal activity in vitro and in vivo for *E. faecalis*; these combinations have been used to treat high-level aminoglycoside-resistant strains and some cases of multidrug-resistant *E. faecalis* endocarditis (Table 37.5).

Figure 37.6 presents an algorithm for managing enterococcal endocarditis.

Other treatment considerations

Gram-negative organisms of the HACEK group grow slowly on standard culture medium and while most will grow within 6 days, some may require 2 weeks of incubation. β-lactamase-producing HACEK organisms have emerged; therefore, ampicillin can no longer be recommended. At this time, third- or fourth-generation cephalosporins or ampicillin–sulbactam should be the regimen of choice. Fluoroquinolones (ciprofloxacin, levofloxacin, gatifloxacin, or moxifloxacin) could be used as an alternative regimen in patients who cannot tolerate β-lactam therapy (Table 37.6).

Most streptococci other than viridans or enterococci (i.e., pneumococcus, group A to G streptococci) remain susceptible to penicillin, but empiric therapy must allow for possible resistance. Although pneumococcal endocarditis is rare (≤1%), its aggressive fulminant course and the increasing incidence of penicillin and cephalosporin resistance have mandated vancomycin with or without ceftriaxone as the empiric regimen. Nongroup A strains of streptococci may need gentamicin in addition to penicillin to ensure synergistic killing. Enterobacteriaceae and *Pseudomonas aeruginosa* are uncommon causes of endocarditis. Therapy should be determined by in vitro susceptibility testing. Adequacy of the regimen may require monitoring via serum bactericidal activity.

Treatment of PVE is generally longer than NVE. If infection occurs within a year after surgery, empiric therapy should particularly target *S. epidermidis* and *S. aureus*. Combination triple

Table 37.6 Antibiotic therapy for endocarditis caused by HACEK[a] microorganisms

Native and prosthetic valve
Ceftriaxone 2 g/24 h IV/IM 4 wk or Ampicillin–sulbactam 12 g/24 h IV 4 wk or Ciprofloxacin 1 g/24 h PO or 400 mg q12h IV 4 wk (need close monitoring)

[a] *Haemophilus parainfluenzae, H. influenzae, H. aphrophilus, H. paraphrophilus, A. actinomycetemcomitans, C. hominis, E. corrodens, K. kingae*, and *K. denitrificans*.

therapy is recommended (Table 37.4); animal models demonstrate rapid sterilization of vegetations with the addition of rifampin. Thus, when PVE is clinically suspected, the combination of vancomycin, gentamicin, and rifampin should be initiated empirically. For staphylococcal infection, nafcillin or oxacillin should be substituted for vancomycin if susceptibility results allow. If the pathogen is resistant to all available aminoglycosides, a fluoroquinolone may be used as an alternative. Duration of aminoglycoside use is similar to recommendations for infection of native valves.

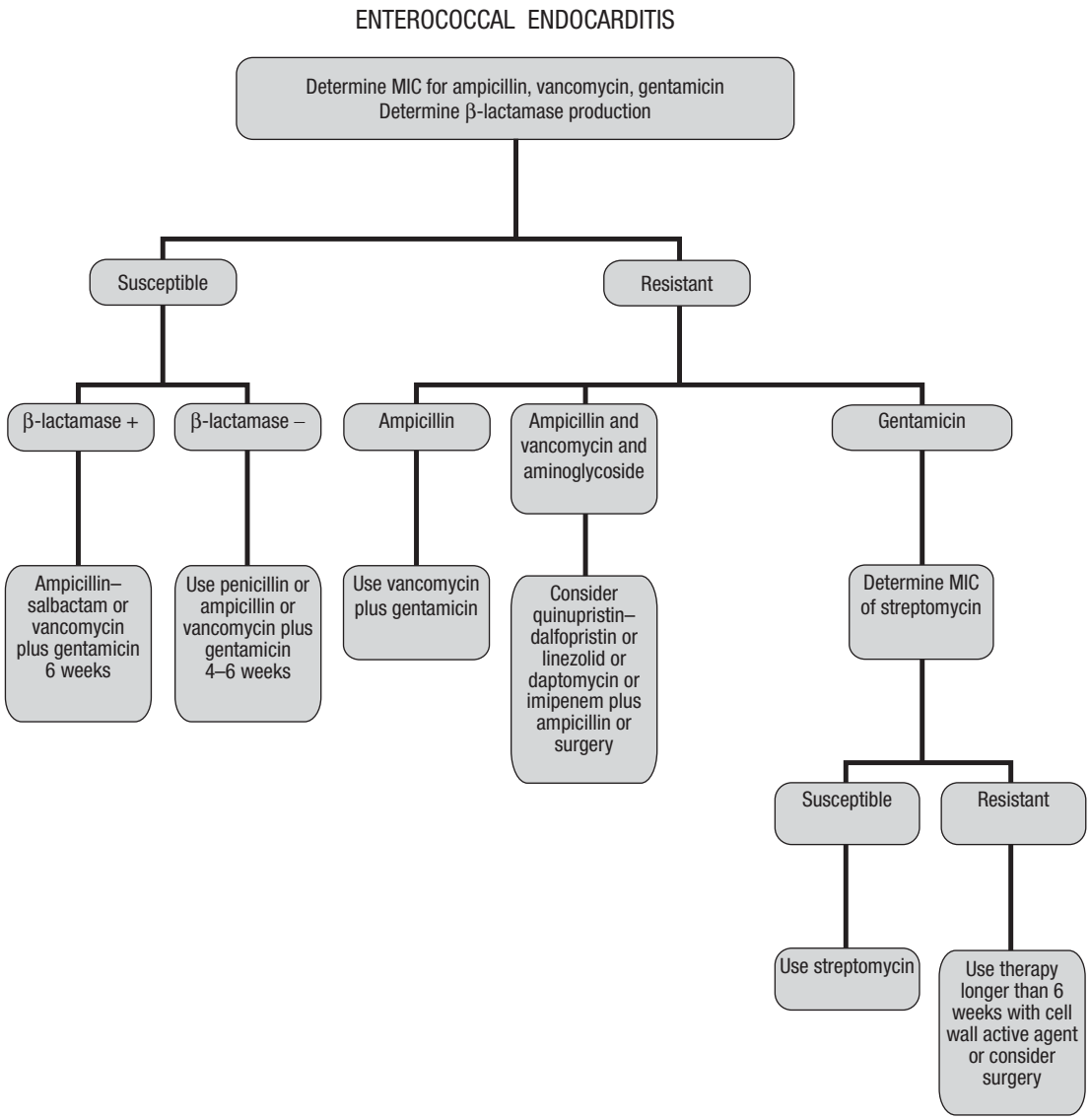

Figure 37.6 Algorithm for the treatment of enterococcal endocarditis.

Table 37.7 Antibiotic therapy for culture-negative endocarditis

Native valve	Prosthetic valve
Ampicillin–sulbactam 12 g/24h IV 4–6 wk plus Gentamicin 1 mg/kg IV/IM q8h for 4–6 wk or Vancomycin 30 mg/kg q24h IV divided in 2 doses 4–6 wk plus Gentamicin 1 mg/kg IV/IM q8h for 4–6 wk plus Ciprofloxacin 1 g/24h PO or 400 mg q12h IV 4–6 wk	**Early infection (≤1 yr)** Vancomycin 30 mg/kg q24h IV divided in 2 doses 6 wk plus Gentamicin 1 mg/kg IV/IM q8h 2 wk plus Cefepime 2 g q8h IV 6 wk plus Rifampin 300 mg q8h PO/IV 6 wk
If *Bartonella* suspected, Ceftriaxone, 2 g/24 h IV/IM 6 wk plus gentamicin 1 mg/kg IV/IM q8h 2 wk with or without Doxycycline 100 mg PO/IV q12h 6 wk	

Table 37.8 Cardiac conditions warranting endocarditis prophylaxis

Prophylaxis recommended
Prosthetic heart valves Previous history of endocarditis Certain congenital heart conditions, including • unrepaired or incompletely repaired cyanotic congenital heart disease, including those with palliative shunts and conduits • a completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure • any repaired congenital heart defect with residual defect at the site or adjacent to the site of a prosthetic patch or a prosthetic device Valvular disease in cardiac transplant recipients
Prophylaxis no longer recommended
Mitral valve prolapse Rheumatic heart disease Bicuspid valve disease Calcified aortic stenosis Congenital heart conditions such as ventricular septal defect, atrial septal defect, and hypertrophic cardiomyopathy.

Due to higher mortality and valvular complications of PVE, especially when due to *S. aureus*, surgery is more frequently considered than in native valve infection.

Fungal endocarditis is poorly responsive even to the gold-standard treatment (amphotericin B for ≥6 weeks). Surgical valve replacement is usually necessary. In patients with hemodynamically stable valves and candida or aspergillus infections susceptible to imidazoles, long-term suppression with fluconazole (*Candida albicans*) or itraconazole (*Aspergillus* species) may be the preferred therapeutic choice. In PVE, valve replacement is usually mandatory regardless of the fungal organism.

Culture-negative endocarditis (CNE) remains an important category of IE. Infectious etiologies of culture-negative endocarditis include fastidious species such as *Bartonella* species, HACEK organisms, and other less common bacterial and fungal organisms. Traditionally, serologies have been the diagnostic modality of choice in CNE, but recent molecular advances (16S ribosomal RNA PCR) and epidemiology may also be helpful (Table 37.7).

Oral regimens have not had a significant role in the treatment of endocarditis because adequate antibiotic serum levels could not be achieved. With newer agents such as the quinolones, the serum concentration after oral administration is equivalent to that seen with parenteral dosing. These agents have been used for the oral treatment of highly susceptible gram-negative pathogens. Also, a 4-week oral regimen of ciprofloxacin plus rifampin has been used to treat uncomplicated right-sided endocarditis in IVDAs. Close monitoring of patients is mandatory.

PROPHYLAXIS

The American Heart Association's (AHA) most recent guideline in April 2007 made substantial changes in recommending preventive antibiotics. Most individuals will no longer need prophylactic antibiotics before dental procedures to prevent IE. This recommendation is based on recent evidence that suggests that the risks of prophylactic antibiotics outweigh the benefits for most patients. Multiple studies show that the risk of developing IE is very low, with 1 in 114 000 adults in the United States with prosthetic valves developing IE and 1 in 142 000 adults with rheumatic heart disease developing disease after dental procedures.

Data also suggest that endocarditis is much more likely to result from random bacteremias associated with daily activities than from dental, gastrointestinal, or genitourinary instrumentation; currently, there is no compelling evidence to link endocarditis risk with bacteremia from invasive and dental procedures. The new guidelines consider only cardiac conditions with the highest risk of adverse outcome from endocarditis for which prophylaxis should be recommended (Table 37.8). The procedures are limited to dental and invasive respiratory procedures and surgery of infected soft tissues (Table 37.9).

The antibiotic regimens are listed in Table 37.10.

Table 37.9 Procedures warranting endocarditis prophylaxis

Prophylaxis recommended
All dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa
Tonsillectomy and/or adenoidectomy
Invasive respiratory procedures to treat infection
Surgical procedures involving infected skin and soft tissues
Prophylaxis not recommended
Injection of local intraoral anesthetic through noninfected tissue
Taking dental radiograph
Placement of removable prosthodontic or orthodontic appliances
Adjustment of orthodontic appliances
Placement of orthodontic brackets
Shedding of deciduous teeth
Bleeding from trauma to the lips or oral mucosa
Endotracheal intubation
Bronchoscopy without biopsy
Tympanectomy tube insertion
Transesophageal echocardiogram
Gastrointestinal or genitourinary procedures
Vaginal delivery or vaginal hysterectomy
Cesarean section
Dilatation and curettage
Ear and body piercing
Tattooing

SURGICAL INDICATIONS IN THE MANAGEMENT OF INFECTIVE ENDOCARDITIS

In certain cases of IE, surgery is associated with improved patient outcomes. Some of these indications are strongly supported by evidence. Other indications are more relative and have conflicting evidence, but expert opinion often favors surgical intervention (Table 37.11). Congestive heart failure resulting from acute aortic insufficiency remains the major indication for immediate valve replacement because of the unacceptable high mortality rate in medically treated patients. Nonresponse to antimicrobial therapy may mandate valve removal if no alternative source for the continued bacteremia or fungemia is found. Fungal endocarditis on a prosthetic valve almost always requires valve replacement. With aggressive preoperative and postoperative antibiotic therapy, valve replacement with a mechanical prosthesis during active IE is a safe procedure. The risk of relapse of endocarditis in a newly implanted prosthetic valve is minimal. Several recent studies have shown mortality benefit both in the combination of medical and surgical treatment and in early versus later surgical treatment in NVE patients with indications for surgical intervention; this remains a controversial area.

Table 37.10 AHA-recommended prophylactic regimens

Single dose 30–60 minutes before procedure
Oral Amoxicillin 2 g
Unable to take oral medications Ampicillin 2 g IV/IM or cefazolin/ceftriaxone* 1 g IV/IM
Allergic to penicillin Clindamycin 600 mg or azithromycin/clarithromycin 500 mg or cephalexine 2 g
Allergic to penicillin and unable to take oral medications Clindamycin 600 mg IV or cefazolin/ceftriaxone* 1 g IV/IM

* Use only if non-IgE-mediated allergic reaction.

Table 37.11 Indications for surgical intervention in native and prosthetic valve infective endocarditis

Surgery usually recommended	Surgery to be considered
Congestive heart failure from acute aortic insufficiency	Large (10 mm) anterior mitral leaflet vegetation
Infective endocarditis caused by organism that may respond poorly to antimicrobial therapy (e.g., fungal or *Brucella* spp.)	Increase in vegetation size despite adequate treatment (after 4 weeks of antibiotic)
Persistent bacteremia after 1 week of adequate antibiotic therapy	Periannular extension on infection or myocardial abscesses
More than one embolic event occurring within the first 2 weeks of antibiotic therapy	IE caused by resistant enterococci species when effective bactericidal therapy is not available
Presence of echocardiography finding consistent with local cardiac complications such as valve dehiscence, large perivalvular abscess, rupture, or perforation of a valve	Uncontrolled infection caused by highly antibiotic-resistant pathogens despite optimal therapy (enterococci or gram-negative bacilli)
Staphylococcus aureus prosthetic valve endocarditis complicated by perivalvular abscess or dehiscence (reduces mortality rates)	
PVE or left-sided IE caused by gram-negative bacteria such as *Serratia marcescens*, *Pseudomonas* spp.	

Treatment duration after surgery depends on culture data from the operating room; if operating room cultures are sterile, the antibiotic duration does not change. If operating room cultures are still positive, antibiotic therapy is considered to start at the time of surgery and should continue to completion on guidelines for the particular organism and NVE versus PVE. Patients who have

NVE and undergo surgery and receive a prosthetic valve are treated for NVE, not for PVE.

Local cardiac complications of IE may require surgical intervention. TEE may detect valvular dehiscence, rupture, fistula, perforation, perivalvular extension of abscess, a large abscess, or a large vegetation (10 mm) on an anterior mitral valve leaflet. Because large vegetations tend to embolize, valve replacement or vegetectomy may be indicated in a patient with suspected or documented recurrent CNS or large vessel emboli. The incidence of stroke from embolic events in patients receiving appropriate antimicrobial therapy in a recent European study was 4.82/1000 patient days in the first week of therapy and fell to 1.71/1000 patient days in the second week.

Anticoagulation during IE is a considerable risk for intracerebral hemorrhage. Anticoagulation is not recommended as a therapeutic option; however, maintenance anticoagulation in a patient with a prosthetic valve should be continued regardless of the diagnosis of endocarditis because of the risk of mechanical thrombosis. It may be prudent to monitor these patients on 2 weeks of heparin therapy by current guideline recommendations.

SUGGESTED READING

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38. Acute pericarditis

Richard A. Martinello and Michael Cappello

INTRODUCTION

The pericardium serves to protect the heart from physiologic changes in intracardiac pressure related to respiration and postural change, and it may also augment the mechanical function of the cardiac chambers. The pericardium is composed of a visceral layer that directly adheres to the epicardium and a parietal layer separated by 10 to 35 mL of serous fluid.

EPIDEMIOLOGY AND ETIOLOGIC AGENTS

Both infectious and noninfectious processes have been identified as causes of pericarditis (inflammation of the pericardium). Most cases are due to viral pathogens, are self-limited, and the specific pathogen remains unidentified. Purulent pericarditis due to bacterial or fungal pathogens is less common and the incidence is much lower than during the pre-antibiotic era. In one recent series, pericarditis was diagnosed in 5% of adults presenting for emergency care due to chest pain that was not associated with myocardial infarction. Most episodes of pericarditis occur in the spring and summer coincident with the peak prevalence of enteroviruses. During the winter months, influenza virus is a frequent cause of pericarditis, whereas pericarditis due to bacterial or atypical pathogens occurs throughout the year. There are no clinical features which allow the differentiation between viral and idiopathic causes of acute pericarditis.

In areas of the world where the incidence of infection with *Mycobacterium tuberculosis* remains high, tuberculosis is responsible for more than 50% of cases of acute pericarditis. Tuberculosis should be considered in persons who have spent significant time in endemic countries, including international adoptees, immigrants, and refugees. Patients with human immunodeficiency virus (HIV) are more likely to experience nonpulmonary manifestations of tuberculosis, such as pericarditis, and have been shown to experience higher rates of mortality due to tuberculous pericarditis than their non-HIV counterparts.

Pericarditis may also develop following cardiothoracic surgery. This may be due to a bacterial surgical site infection or postpericardiotomy syndrome, a noninfectious inflammatory condition that generally develops days to 6 months following cardiac surgery. In immunocompromised hosts, the range of potential pathogens that can cause pericarditis is quite broad and includes viruses, bacteria, fungi/yeasts, and parasites (Table 38.1) Acute pericarditis can also be due to noninfectious causes (Table 38.2).

PATHOGENESIS

Microbial pathogens may gain entry into the pericardial space by direct extension from the chest (e.g., in the context of pneumonia or mediastinitis), through direct extension from the heart itself (e.g., endocarditis), through hematogenous or lymphatic spread (bacteremia or viremia), or via direct inoculation (e.g., surgery, trauma). The presence of an adjacent or otherwise concurrent infection, as well as a history of recent surgery or trauma, may provide significant clues to specific pathogens. For example, purulent pericarditis due to *N. meningitidis* has been diagnosed in patients with concurrent bacterial meningitis. In a review of 162 children with purulent pericarditis, all but 10 patients had at least one additional site of infection, suggesting that isolated cardiac disease occurs infrequently in those with purulent pericarditis. In cases where either *S. aureus* or *H. influenzae* type B was the responsible pathogen, pneumonia, osteomyelitis, and cellulitis were the most frequently identified additional sites of infection. Tuberculous pericarditis, however, usually occurs in the absence of identifiable pulmonary disease, suggesting that the pathogenesis involves the spread of mycobacteria from adjacent mediastinal lymph nodes into the pericardium.

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Table 38.1 Infectious causes of acute pericarditis

Viruses
Coxsackievirus A
Coxsackievirus B[a]
Echoviruses
Middle East respiratory syndrome-coronavirus
Mumps virus
Influenza viruses
Cytomegalovirus
Herpes simplex virus
Hepatitis B virus
Measles virus
Adenovirus
Human immunodeficiency virus
Varicella virus
Bacteria
Burkholderia pseudomallei
Staphylococcus aureus [a]
Streptococcus pneumoniae [a]
Haemophilus influenzae [a]
Neisseria meningitidis [a]
Streptococcus pyogenes
α-Hemolytic streptococci
Klebsiella spp.
Pseudomonas aeruginosa
Escherichia coli
Salmonella spp.
Shewanella algae
Anaerobes
Listeria monocytogenes
Neisseria gonorrhoeae
Coxiella burnettii
Actinomyces spp.
Nocardia spp.
Mycoplasma pneumoniae
Mycobacteria
Mycobacterium tuberculosis
Mycobacterium avium complex
Fungi
Histoplasma capsulatum
Blastomyces dermatitidis
Candida spp.
Aspergillus spp.
Cryptococcus neoformans
Coccidioidomycosis
Parasites
Toxoplasma gondii
Entamoeba histolytica
Toxocara canis
Schistosomes
Wuchereria bancrofti

[a] Most common causes of acute bacterial or viral pericarditis in North America.

Table 38.2 Major noninfectious causes of acute pericarditis

Collagen vascular diseases
Systemic lupus erythematosus
Rheumatoid arthritis
Scleroderma
Rheumatic fever
Drugs
Procainamide
Hydralazine
Myocardial injury
Acute myocardial infarction
Chest trauma (penetrating or blunt)
Postpericardiotomy syndrome
Sarcoidosis
Familial Mediterranean fever
Uremia
Neoplasia
Primary
Metastic
Irradiation

The inflammatory response in the pericardial space leads to extravasation of additional pericardial fluid, polymorphonuclear white blood cells, and monocytes. During bacterial or fungal pericarditis, the inflammatory process may be sufficient to lead to loculation and fibrosis. Significant fibrosis may lead to constrictive pericarditis, which is manifest by signs and symptoms associated with compromised ventricular filling. The rapid accumulation of exudative fluid, as is often seen in purulent pericarditis, frequently leads to hemodynamic changes. Cardiac tamponade occurs when increased fluid within the pericardial space prevents adequate right atrial filling and leads to reduced stroke volume, low output cardiac failure, and shock. If the accumulation of pericardial fluid occurs more slowly, as is common with viral pericarditis, large amounts may be present without hemodynamic effect.

SYMPTOMS AND CLINICAL MANIFESTATIONS

Chest pain is the most common presenting symptom of acute pericarditis. Due to the relationship between the phrenic nerve and pericardium, pain resulting from inflammation of the pericardium may be retrosternal with radiation to the shoulder and neck or may localize between the scapulae. Often, the pain is worsened by swallowing or deep inspiration or is positional and worsened when the patient is supine but lessened by

leaning forward while sitting. Dyspnea is also a common presenting symptom. If pericarditis has resulted from contiguous spread of bacteria or fungi from an adjoining structure, the signs and symptoms of the primary infectious process may predominate. Purulent pericarditis due to a bacterial pathogen tends to be more acute and severe in nature, whereas viral pericarditis is typically of lesser severity. Symptoms of tuberculous pericarditis tend to be insidious in presentation.

In infants, the presenting signs and symptoms of pericarditis may be nonspecific and include fever, tachycardia, and irritability. Older children may complain of chest and/or abdominal discomfort. A study by Carmichael *et al.* in 1951 showed that more than half of patients diagnosed with "nonspecific" pericarditis of presumed viral origin described a respiratory illness preceding the diagnosis of pericarditis by 2 to 3 weeks.

On physical exam, nearly all patients with pericarditis, regardless of cause, will have tachycardia. Those with bacterial pericarditis are also likely to have fever and tachypnea, as well as possible evidence of at least one additional site of infection (e.g., pneumonia, surgical site infection, osteomyelitis, etc.). Perhaps the most characteristic physical finding in acute pericarditis is the presence of a friction rub on cardiac auscultation. The rub may be confused with a high-pitched murmur, particularly when it is only present in systole. Pericardial friction rubs may have as many as three components, which correspond with atrial systole, ventricular systole, and rapid ventricular filling during early diastole. A rub may be best appreciated with the patient leaning forward or in the knee-chest position. Although more than one component of a pericardial rub may be present, all three components were noted in less than 50% of patients in one case series.

The presence of a pulsus paradoxus or jugular venous distension suggests the possibility of cardiac tamponade, which may require emergent intervention. This is most frequently seen in the presence of a large or rapidly accumulating pericardial effusion but can also result from constrictive disease due to long-standing pericarditis with fibrosis.

DIAGNOSIS

An acutely enlarged cardiac silhouette on chest radiograph, particularly in the absence of increased pulmonary vascularity, suggests the presence of pericardial effusion. However, there may be no radiographic abnormalities detected in patients with small, but rapidly accumulating, effusions, as well as in those with constrictive disease.

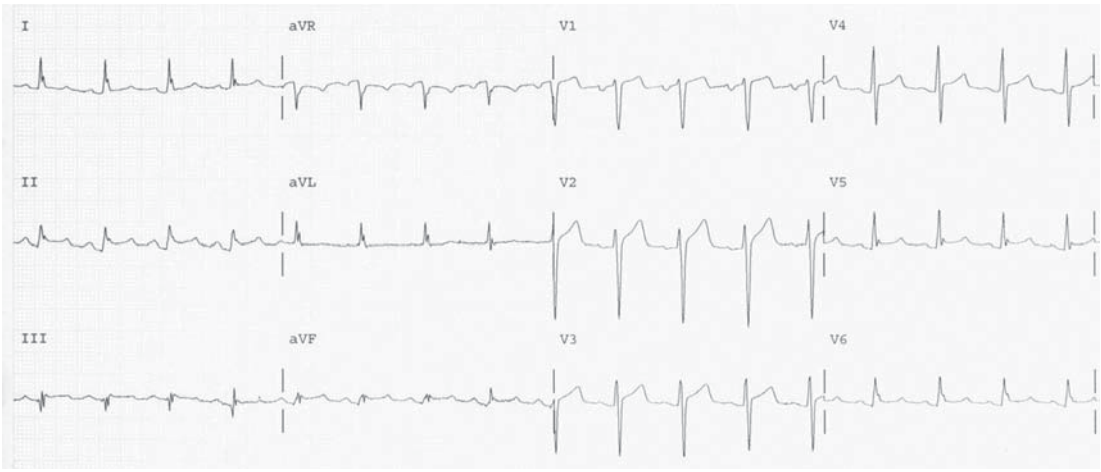
Although the pericardium is not involved in the electrical activity of the heart, pericarditis is associated with classic electrocardiographic changes, which are likely due to concomitant inflammatory changes in the epicardium and outer myocardium. Electrocardiographic changes may be present in 50% of patients with acute pericarditis, and the specific changes evolve over time. Elevation or depression of the ST and/or depression of the PR segments may occur early in the disease process (Figure 38.1). Over subsequent days, the ST segment returns to baseline. Late ECG changes in pericarditis may include flat or inverted T waves. These ECG changes can be differentiated from those due to myocardial infarction as it is uncommon for T-wave inversions to be detected until the ST segment changes resolve. Large pericardial effusions may result in reduced voltage or electrical alternans due to beat-to-beat variation in the position of the heart within the pericardial fluid.

Echocardiography is the diagnostic study of choice for detecting excess pericardial fluid and is recommended for all patients in whom pericarditis is suspected. In patients with poststernotomy pericarditis, computed tomography (CT) scan and magnetic resonance imaging (MRI) are both extremely useful for identifying mediastinal fluid collections and potential abscesses.

Pericardiocentesis is the most specific means of determining the etiology of pericarditis, though the overall diagnostic yield may be low. Drainage of pericardial fluid should be performed when there is evidence for cardiac tamponade or a suspicion of tuberculous, neoplastic, or purulent pericarditis. The fluid should be transported quickly to the microbiology laboratory for Gram, acid-fast, and silver stains, as well as culture for bacteria (aerobic and anaerobic), fungi, mycobacteria, and viruses, as indicated. Pericardial fluid should also be analyzed for cell count and differential, glucose, total protein, red blood cell count, and cytology may be considered. When tuberculous pericarditis is suspected, biopsy of the pericardium for histology increases the diagnostic yield, and an adenosine deaminase level should be measured in the pericardial fluid.

For patients in whom a viral etiology is suspected, swabs from the nasopharynx, throat, and rectum may be obtained for culture or polymerase chain reaction (PCR) as these sites are more likely

(A)



(B)

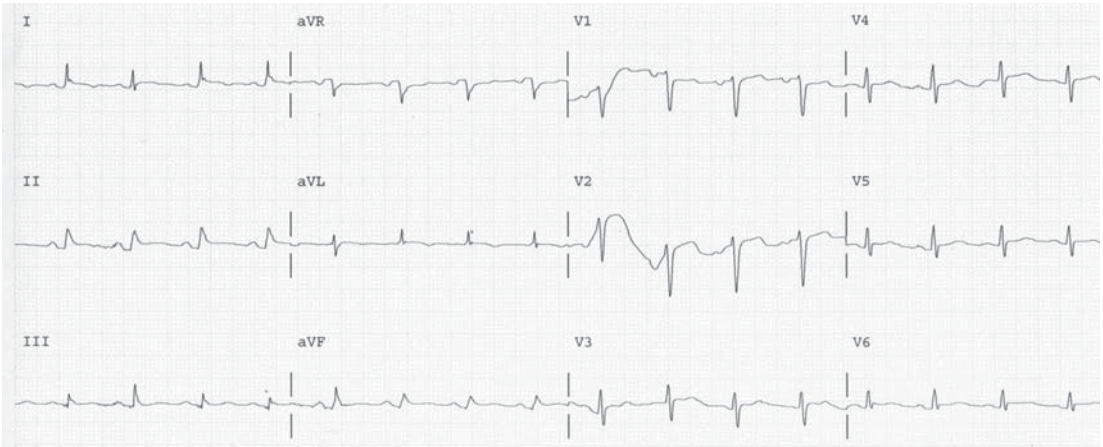


Figure 38.1 (A) Electrocardiogram (ECG) in acute pericarditis. ST segment elevation is noted with an upward concave appearance in all leads except I, aVR, and aVL. PR segment depression is noted in I, II, III, aVF, and the precordial leads (courtesy of Dr. Thuy Le). (B) ECG from the same patient as in A, but 3 days later. Note that PR segment depression persists in II, III, and aVF. Some ST elevation persists but has markedly diminished compared with the initial ECG (courtesy of Dr. Thuy Le).

to yield a positive culture for enterovirus than the pericardial fluid itself. However, extensive testing to identify the etiology of viral pericarditis has not been found, in general, to be clinically useful. In the setting of pneumonia, sputum or tracheal aspirates can be cultured for bacteria, and diagnostic studies for influenza A or B virus should be obtained. Acute and convalescent antibody titers may be measured for the common enterovirus serotypes and other pathogens.

In patients with purulent pericarditis, blood cultures are frequently positive. These patients should be carefully evaluated for other infectious processes, including pneumonia, osteomyelitis, and meningitis. A positive bacterial culture from one of these alternative sites is strongly suggestive of the identity of the pericardial pathogen.

The diagnosis of tuberculous pericarditis can be particularly challenging. Although a study by Strang *et al.* found cultures of pericardial fluid to be positive in 75% of suspected cases, results may not be available for weeks. In this setting, pericardial biopsy may yield a more rapid diagnosis of *M. tuberculosis* infection, particularly if the characteristic granulomatous changes are present. Cigielski *et al.* have recently shown that a PCR-based assay was nearly as sensitive as culture (81% vs. 93%) for detecting *M. tuberculosis* in

pericardial biopsy specimens. The obvious advantage to PCR is the speed with which results can be obtained, although false-positive results may occur more frequently than with culture.

TREATMENT

Urgent drainage of pericardial fluid should be considered in any patient with a possible diagnosis of purulent pericarditis or if hemodynamic compromise is identified. The outcome in these patients is generally poor without drainage, even when appropriate antibiotics are administered. Likewise, purulent infections contiguous with the mediastinum should be drained. Intrapericardial fibrinolysis for persons with purulent pericarditis may prevent future complications of constrictive or persistent pericarditis.

If the Gram stain of pericardial fluid does not suggest an etiologic agent in the setting of purulent pericarditis, then empiric antibiotic coverage should be initiated while awaiting the results of cultures. The antibiotic(s) for empiric coverage should be chosen according to whether the patient has evidence for a contiguous site of infection, history of recent cardiothoracic surgery, trauma, or other relevant risk factors. In patients with community-acquired purulent pericarditis and no history of antecedent surgery or trauma, empiric treatment directed at *S. aureus* (oxacillin, nafcillin or vancomycin) and common respiratory pathogens (ceftriaxone) would be appropriate.

If a viral etiology is suspected, nonsteroidal anti-inflammatory drugs (NSAIDs) are used as first-line therapy and have been found to relieve chest discomfort in 85% to 90% of patients. Typically, ibuprofen (1600 mg to 3200 mg divided per day) is the drug of choice due to its low incidence of adverse events compared with other NSAIDs. Some experts favor the use of aspirin (650 mg to 975 mg every 6 to 8 hours) in patients who have experienced a recent myocardial infarction, as evidence from animal studies have led to concern that other NSAIDs may impair scar formation. Indomethacin should be avoided in persons with coronary artery disease as it has been shown to decrease coronary artery blood flow.

Colchicine (600 mg to 1000 mg twice daily initially, then 500 mg twice daily) has been shown to effectively decrease the incidence of primary and secondary recurrent pericarditis. Some experts recommend its use during first episodes of pericarditis if NSAIDs are unable to completely abate symptoms. Treatment with NSAIDs, with or without cholchicine, is generally continued for 4 weeks and 3 months, respectively. Markers of inflammation (i.e., ESR and CRP) may be periodically followed to assess disease progression and help guide tapering of NSAIDS, and other anti-inflammatory medications (if used). Evidence supporting the use of systemic corticosteroids is limited and there is concern that their use, especially higher doses, may be associated with greater rates of relapse; use should only be considered in persons with persistent symptoms despite full doses of NSAIDs or in persons in whom NSAIDs are contraindicated (e.g., third trimester of pregnancy).

It is recommended that patients avoid strenuous activity during the initial weeks after diagnosis of acute pericarditis, but patients may then reintroduce activities after complete resolution of symptoms.

Tuberculous pericarditis should be treated with four active antimicrobial agents until susceptibilities are known. The recommended duration of therapy for pericarditis caused by *M. tuberculosis* is 6 to 12 months, with the longer durations reserved for patients who improve more slowly. Whether corticosteroids should be used as an adjunct to antitubercular therapy remains uncertain. Trials have shown modest improvements in clinical outcomes with corticosteroid use but were generally small in size and had other limitations. Likewise, it is not clear that there is a role for routine pericardial drainage or pericardiectomy in the treatment of tuberculous pericarditis.

COMPLICATIONS

Increased intrapericardial pressure due to an accumulating effusion may result in cardiac tamponade. Tamponade should be suspected if the patient's hemodynamic status is unstable, heart sounds are diminished, jugular venous pressure is raised, or if pulsus paradoxus is present. Echocardiography may note significant variation in blood flow across the mitral and tricuspid valves with respiration and collapse of the right-sided chambers during diastole. Drainage of the pericardial effusion is essential in the setting of purulent pericarditis or in the presence of tamponade. Patients with purulent pericarditis should be treated with a combination of both antimicrobial therapy and drainage. High mortality rates have been observed for patients with purulent pericarditis who have received only medical or surgical management in isolation.

A minority of patients may experience recurrent pericarditis involving reaccumulation of the

pericardial effusion, fever, and chest pain. These episodes may relapse and remit for several years and are most commonly diagnosed in patients with prior viral pericarditis. Recurrent episodes are rarely complicated by either tamponade or constriction and are effectively treated with NSAIDs with or without cholchicine or corticosteroids. Pericardiectomy, pericardial window placement or other surgical procedures may be considered for those with the most recalcitrant signs and symptoms.

Constrictive pericarditis occurs due to the development of a thickened fibrous exudate within the pericardium, and the pericardium itself may calcify. The reduced compliance of the pericardial sac may impair diastolic filling and result in hemodynamic compromise. Constrictive pericarditis has most commonly been associated with antecedent tuberculous pericarditis, cardiac surgery, and radiation-induced pericarditis, though patients with a history of prior pericarditis of any etiology are at risk for developing constrictive disease. Constrictive pericarditis typically presents within 3 to 12 months of the initial episode, though the time interval may be days to years. Less severe cases may be managed medically by careful monitoring of the patient's fluid status, but pericardiectomy remains the definitive therapy.

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39. Myocarditis

Lori A. Blauwet

DEFINITION

Myocarditis is a rare, potentially deadly, and often underdiagnosed cause of heart failure that primarily affects children and young adults. Historically, the diagnosis of myocarditis was confirmed by analysis of endomyocardial biopsy specimens. The Dallas criteria, proposed in 1986, define myocarditis as an inflammatory cellular infiltrate of the myocardium with or without myocyte necrosis and/or degeneration of adjacent myocytes. These criteria have been criticized due to inter-reader variability in interpretation, low sensitivity due to sampling error, discrepancy with other markers of viral infection and immune activation in the myocardium and lack of prognostic value. Immunohistochemical stains that detect cellular surface antigens such as anti-CD3, anti-CD4, and anti-CD28 (T lymphocytes), anti-CD8 (macrophages), and Class I and II anti-human leukocyte antigens may have greater sensitivity than the Dallas criteria and may have prognostic value.

In patients with previously unexplained heart failure, the presence of viral genomes may indicate active infectious lymphocytic myocarditis. The most common viruses screened in patients with suspected myocarditis are parvovirus B19 (PVB19), adenovirus, enterovirus, cytomegalovirus, Epstein–Barr virus, herpes simplex virus 1 and 2, human herpesvirus 6 (HHV-6), and hepatitis C virus.

Fulminant myocarditis is described as acute onset of severe heart failure due to viral myocarditis. Cardiac sarcoidosis is a rare form of inflammatory myocarditis distinguished histologically by non-necrotizing interstitial granulomas. Idiopathic giant cell myocarditis (GCM) is another rare form of inflammatory myocarditis that is characterized histologically by multinucleated giant cells, myocyte necrosis, and a lymphocytic inflammatory infiltrate.

ETIOLOGY

Most cases of myocarditis are triggered by infection or exposure to a toxin, although some cases are thought to be due to primary immunologic abnormalities in the patient (Tables 39.1 and 39.2). Viral infection is the most common cause of myocarditis, with adenoviruses and enteroviruses historically being the most common culprits. With the development of new molecular techniques such as polymerase chain reaction (PCR) and *in situ* hybridization, PVB19 and HHV-6 are the most common viruses detected, particularly in Europe. Two or more viruses are not infrequently found during PCR examination of myocardial tissue, but it is unclear whether this represents concurrent or past viral infection. Whether geographic differences account for the varying distribution of viral species implicated in myocarditis or whether these differences in distribution are more likely due to temporal epidemiologic differences as well as differences in diagnostic procedures also remains unclear. Some studies have suggested that PVB19 is an innocent bystander, not a pathologic agent, in adult myocarditis because persistent low-level titers of PVB19 are fairly common and may not be related to myocardial injury. Whether or not quantification of PVB19 load would be helpful remains a subject of debate.

Myocarditis can be triggered by bacterial and protozoal infections. The most common non-viral pathogens which either directly infect the heart or activate inflammatory mechanisms are *Corynebacterium diphtheriae* (diphtheria), *Streptococcus A* (rheumatic fever), *Borrelia burgdorferi* (Lyme disease), and *Trypanosoma cruzi* (Chagas disease).

Numerous medications and environmental exposures can have toxic effects on the myocardium (Table 39.2).

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Table 39.1 Infectious etiologies of myocarditis

Viral
Adenovirus
Arborvirus
Chikungunya virus
Enterovirus
Echovirus
Coxsackie A
Coxsackie B
Polio
Flavivirus
Dengue
Yellow fever
Hepatitis B virus
Hepatitis C virus
Herpesviruses
Cytomegalovirus
Epstein–Barr
Herpes simplex
Human herpesvirus 6
Varicella-zoster
Human immunodeficiency virus
Influenza A and B
Mumps
Parvovirus (especially parvovirus B19)
Rabies
Respiratory syncytial virus
Rubeola
Rubella
Variola (smallpox)

Bacterial
Actinomyces
Burkholderia pseudomallei (melioidosis)
Brucella
Chlamydia (especially *C. pneumoniae* and *C. psittaci*)
Clostridium
Corynebacterium diphtheriae (diphtheria)
Francisella tularensis (tularemia)
Haemophilus influenzae
Gonococcus
Legionella pneumophila (Legionnaires' disease)
Listeria monocytogenes
Mycobacterium (tuberculosis)
Mycoplasma pneumoniae
Neisseria meningitidis
Salmonella
Staphylococcus aureus
Streptococcus A (rheumatic fever)
Streptococcus pneumoniae
Tetanus
Vibrio cholerae

Spirochetal
Borrelia burgdorferi (Lyme disease)
Borrelia recurrentis (relapsing fever)
Leptospira
Treponema pallidum (syphilis)

Rickettsial
Coxiella burnetii (Q fever)
Rickettsia prowazekii (typhus)
Rickettsia rickettsii (Rocky Mountain spotted fever)
Rickettsia tsutsugamushi (scrub typhus)

Fungal
Aspergillus
Blastomyces
Candida
Coccidioides
Cryptococcus
Histoplasma
Mucor species
Nocardia
Sporothrix schenckii

Protozoal
Balantidium
Entamoeba histolytica (amebiasis)
Leishmania
Plasmodium falciparum (malaria)
Sarcocystis
Toxoplasma gondii (toxoplasmosis)
Trichinella spiralis
Trypanosoma cruzi (Chagas disease)
Trypanosoma brucei (African sleeping sickness)

Helminthic
Ascaris
Echinococcus granulosus
Heterophyes
Paragonimus westermani
Schistosoma
Strongyloides stercoralis
Taenia solium (cysticercosis),
Toxocara canis (visceral larva migrans)
Trichinella spiralis
Wuchereria bancrofti (filariasis)

PATHOGENESIS

The pathogenesis of myocarditis in humans is not completely understood. Much of our understanding of the pathophysiology of myocarditis has been derived from murine models of enteroviral infection, particularly Coxsackievirus B3, which suggests that viral myocarditis is characterized by three stages (Figure 39.1). Stage I involves viral entry into the cardiomyocyte via endothelial cell receptors. Group B Coxsackieviruses and some adenoviruses use the Coxsackievirus-adenovirus receptor (CAR) to transport their viral genomes into myocytes. In addition to CAR, Coxsackieviruses use decay-accelerating factor (DAF) and adenoviruses use special integrins ($\alpha_{v\beta3}$ and $\alpha_{v\beta5}$) as coreceptors for viral entry. Differential binding to DAF increases viral virulence in Coxsackievirus

Table 39.2 Noninfectious etiologies of myocarditis

Toxins

Drugs

Aminophylline
Amphetamines
Anagrelide
Catecholamines
Chemotherapy agents
- **Anthracyclines**
- Cyclophosphamide
- Cytarabine
- 5-fluorouracil
- Mitomycin
- Monoclonal antibodies
- Paclitaxel
- **Tyrosine kinase inhibitors (including trastuzumab)**

Chloramphenicol
Chloroquine
Cocaine
Ephedrine
Ethanol
Interleukin-2
Methysergide
Minoxidil
Phenytoin
Zidovudine

Environmental

Arsenic
Carbon monoxide
Heavy metals (cobalt, copper, iron, lead)

Hypersensitivity reactions

Drugs

Allopurinol
Antimicrobials
- Amphotericin B
- Azithromycin
- Cephalosporins
- Chloramphenicol
- Dapsone
- Isoniazid
- Penicillins
- Streptomycin
- Stibogluconate
- Sulfonamides
- Tetracycline

Dobutamine
Gefitinib
Loop diuretics
Methyldopa
Mexiletine
Nonsteroidal anti-inflammatories
- Indomethacin
- Mesalamine

Psychiatric medications
- Benzodiazepines
- Carbamazepine
- Clozapine
- Lithium
- Phenobarbital
- Tricyclic antidepressants

Thiazide diuretics

Vaccines

- **Smallpox vaccination**
- Tetanus toxoid

Venoms

- Insects (bee, wasp)
- Spider (black widow)
- Scorpion
- Snake

Autoimmune diseases

Crohn's disease
Dermatomyositis/polymyositis
Giant cell myocarditis
Inflammatory bowel disease
Rheumatoid arthritis
Sjögren syndrome
Still's disease
Systemic lupus erythematosus
Systemic sclerosis (scleroderma)
Takayasu's arteritis
Ulcerative colitis
Wegener's granulomatosis

Systemic diseases

Celiac disease
Churg–Strauss syndrome
Collagen vascular diseases
Hypereosinophilic syndrome with eosinophilic endomyocardial disease
Kawasaki disease
Sarcoidosis

Other

Heat stroke
Hypothermia
Transplanted heart rejection
Radiation

B infections. Viral infection does not occur in the absence of CAR expression on myocytes.

Stage I also involves acute myocardial injury due to a combination of direct viral injury to the myocytes and the innate immune response, which involves upregulation of multiple inflammatory mediators, including cytokines, nitric oxide, toll-like receptors, and complement, and exposure of intracellular antigens such as cardiac myosin. Viruses that evade the innate immune response replicate, producing proteins that lead to myocyte apoptosis and necrosis. Stage II begins approximately 4 to 5 days post viral infection when the acquired immune response arises. Lasting several weeks to several months, this subacute phase is characterized by an antigen-specific response that

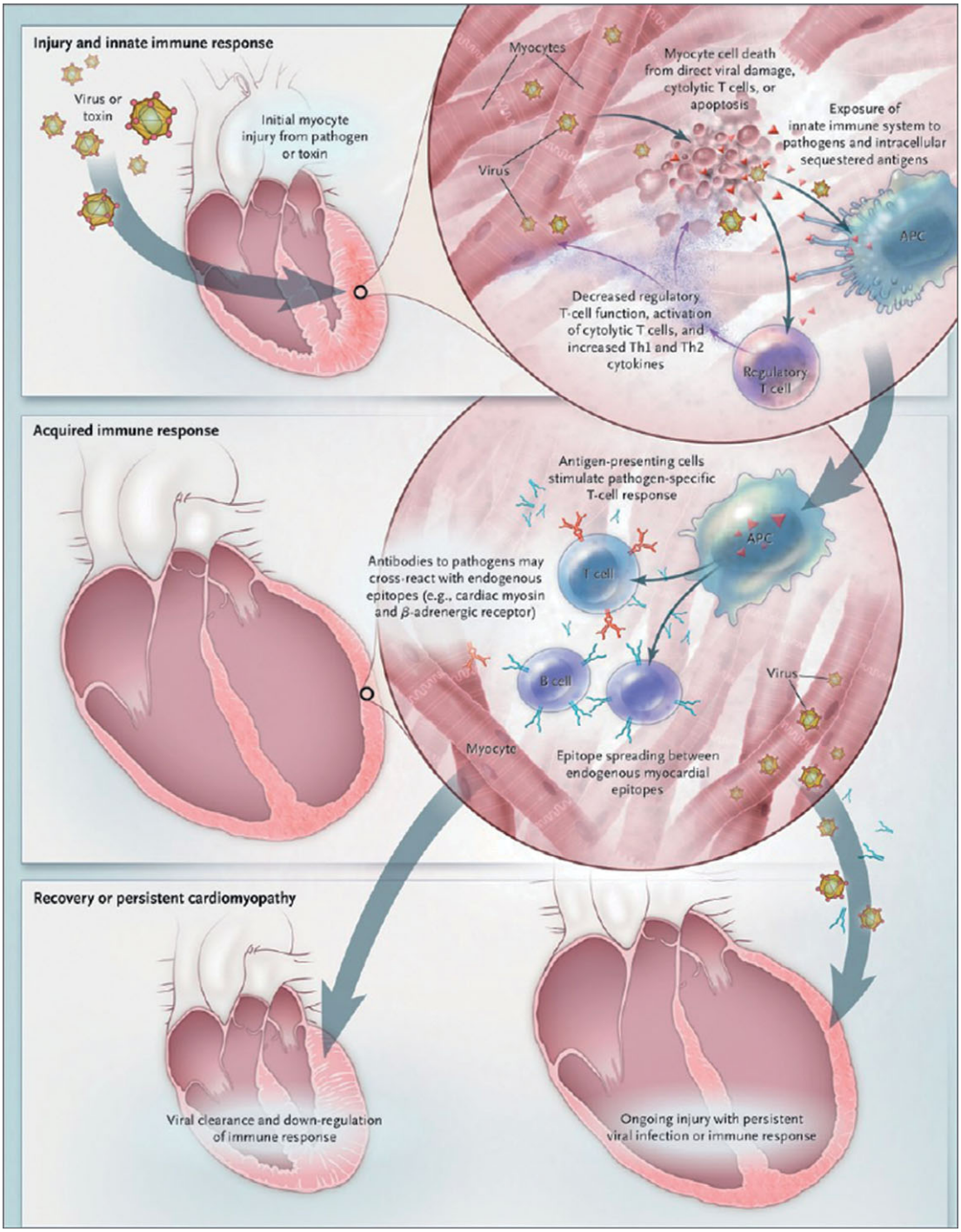

Figure 39.1 Pathogenesis of viral myocarditis
The current understanding of the pathogenesis of viral myocarditis is based on murine models. In these models, myocarditis progresses from acute injury to chronic dilated cardiomyopathy (DCM) in three distinct stages. During stage I, viral entry into cells results in direct myocardial injury, exposure of host antigens such as cardiac myosin, and activation of the innate immune system. The acquired immune response is the dominant feature in stage II, whereby activated T lymphocytes, antibodies, and autoantibodies induce significant myocardial inflammation. In most patients, stage III involves viral clearance, downregulation of the immune system, and complete myocardial recovery. In some patients, however, stage III is characterized by the persistence of viral genomes and cardiac-specific inflammation in the myocardium, leading to chronic DCM. APC = antigen-presenting cell. (From *New England Journal of Medicine*, LT Cooper, Jr, Myocarditis, vol 8, pp.1526–1538. Copyright (2009) Massachusetts Medical Society. Reprinted with permission.)

is mediated primarily by T lymphocytes. Virus-specific T-killer cells are targeted to infected cells and destroy these host cells through secretion of cytokines or perforins. B lymphocytes produce antibodies directed against viral antigens and autoantibodies directed against cardiac proteins that may augment myocardial damage.

In most patients with myocarditis, viral clearance and downregulation of the immune system occurs during stage III, resulting in complete myocardial recovery without sequelae. In some patients, however, the virus is not cleared and cardiac-specific inflammation persists, resulting in chronic myocardial damage which leads to myocardial remodeling and the development of dilated cardiomyopathy (DCM).

EPIDEMIOLOGY

Due to varying clinical presentations and infrequent utilization of endomyocardial biopsy (EMB), the diagnosis of myocarditis is often missed, making it difficult to estimate the true incidence of this disease. Autopsy studies have estimated the incidence of myocarditis to range from 0.12% to 12%, depending on the population studied. The Myocarditis Treatment Trial showed that biopsy-proven myocarditis occurred in 9.6% of adult patients with unexplained heart failure. An analysis of hospital dismissal ICD-9 codes estimated that between 0.5% and 4% of heart failure cases are due to myocarditis.

Myocarditis has a slightly greater prevalence in men compared to women. Most trials and registries have a female to male ratio of 1:1.5 to 1:1.7. This sex difference may be at least partially explained by sex hormones. Estrogenic hormones have been shown to protect against viremia and viral infectivity of cardiomyocytes while also decreasing the potentially harmful inflammatory response in female mice. Testosterone, on the other hand, has been shown to inhibit anti-inflammatory responses in male mice.

CLINICAL PRESENTATION

The clinical presentation of acute myocarditis in adults varies by clinical scenario. Typically, but not always, a viral prodrome including fever, myalgias, arthralgias, rash, and respiratory or gastrointestinal symptoms precedes the onset of acute myocarditis by several days to several weeks. Patients with myocarditis may present with chest pain, dyspnea, palpitations, fatigue, edema, syncope and/or decreased exercise tolerance. The presence of pleuritic chest pain, particularly in the setting of pericardial effusion, may indicate myopericarditis. Cardiac arrhythmias are common.

Patients with fulminant myocarditis usually present with severe heart failure symptoms that rapidly lead to cardiogenic shock, whereas patients with cardiac sarcoidosis tend to present in a more indolent manner with chronic DCM and either high-grade atrioventricular block (AVB) or new ventricular arrhythmias. Patients with GCM tend to present with acute heart failure symptoms that inexorably progress to probable early death or transplant despite guideline-directed heart failure therapy.

DIAGNOSIS

The first step in diagnosing myocarditis is to exclude more common causes of cardiac dysfunction such as atherosclerosis or valvular heart disease. There are no laboratory, electrocardiographic (ECG), or echocardiographic findings specific for myocarditis. When acute myocarditis is suspected, initial laboratory testing usually includes assessment of serum cardiac biomarkers. Troponin T, troponin I, and/or CK-MB may be elevated. Serum markers of inflammation including C-reactive protein, erythrocyte sedimentation rate, and leukocyte count are frequently elevated, but these are nonspecific. Serologic testing of suspected viral agents is not recommended, as the viruses that cause myocarditis are common and positive serology does not necessarily establish causality. Testing for noninfectious causes of heart failure including autoimmune disease, infiltrative myocardial diseases such as amyloidosis and hemochromatosis, and thyroid dysfunction may be warranted.

Most myocarditis patients have nonspecific changes on their initial ECG, including sinus tachycardia, ST-segment or T-wave abnormalities that may mimic acute myocardial infarction or acute pericarditis, AVB, and partial or complete bundle branch block. Nonsustained ventricular or supraventricular arrhythmias are fairly common. The presence of Q waves or a QRS duration of greater than 120 ms is associated with increased risk of cardiac death or heart transplantation. Chest x-ray may show cardiomegaly, pulmonary venous congestion, interstitial infiltrates and/or pleural effusions.

The most common echocardiographic findings in patients with acute myocarditis are a dilated left ventricle with reduced left ventricular ejection

Table 39.3 Myocarditis diagnostic classification

Classification	Patient presentation	Criteria	Histologic classification	Biomarker, ECG, and/or imaging findings consistent with myocarditis	Treatment
Possible sublinical acute myocarditis	Asymptomatic	One or more of the following required: • Troponin elevation • ECG findings suggestive of acute cardiac injury • Echocardiographic or cardiac MRI findings consistent with abnormal cardiac function	Absent	Present	Unknown
Probable acute myocarditis	Symptomatic	One or more of the following required: • Troponin elevation • ECG findings suggestive of acute cardiac injury • Echocardiographic or cardiac MRI findings consistent with abnormal cardiac function	Absent	Present	Per clinical syndrome
Definite myocarditis	Symptomatic or asymptomatic	Histologic or immunohistologic evidence of myocarditis	Present	Present or absent	Per clinical syndrome

fraction (LVEF). New regional wall abnormalities may be present, either in a coronary or noncoronary distribution. Decreased right ventricular function is less common than decreased left ventricular function, but is a strong predictor of poor prognosis.

Cardiac MRI has become a routine noninvasive test that may be highly sensitive and specific for diagnosing acute myocarditis, particularly when both T1- and T2-weighted images are obtained.

Histologic or immunohistologic evidence of an inflammatory infiltrate with or without myocyte necrosis on myocardial biopsy specimens remains the gold standard for the diagnosis of myocarditis. The Dallas criteria, proposed in 1986, define active myocarditis as the presence of both inflammatory cells and adjacent myocyte necrosis and borderline myocarditis as the presence of inflammatory cells without associated myocardial injury. The Marburg criteria, proposed in 1997, state that a clear-cut infiltrate of $\geq$14 leukocytes/mm^2 (quantitated by immunohistochemistry) and myocyte necrosis or degeneration must be present to diagnose acute myocarditis. Chronic myocarditis is defined as an infiltrate of $\geq$14 leukocytes/mm^2 without myocyte necrosis or degeneration. Fibrosis may or may not be present in either acute or chronic myocarditis.

Outside of a few tertiary medical centers, EMB is not routinely performed in adult patients with suspected myocarditis due to perceived risk and cost of the procedure. EMB is strongly indicated in adult patients with either of the following two clinical scenarios: (1) new unexplained heart failure symptoms of less than 2 weeks duration coupled with a normal or dilated left ventricle and hemodynamic compromise, or (2) new unexplained heart failure symptoms of 2 weeks' to 3 months' duration with a dilated left ventricle and ventricular arrhythmias, high-grade AVB, or failure to respond to guideline-directed heart failure therapy within 1 to 2 weeks. These clinical scenarios suggest the diagnosis of either necrotizing eosinophilic myocarditis (scenario 1) or GCM (scenario 1 or 2), both of which have a poor prognosis that may be modified with immunosuppressive treatment. EMB may be considered in adults who present with other clinical scenarios, including patients with (1) DCM of any duration with suspected allergic reaction and peripheral eosinophilia; (2) unexplained heart failure of any duration associated with anthracycline therapy; or (3) unexplained heart failure associated with restrictive cardiomyopathy. EMB is considered reasonable in the setting of unexplained cardiomyopathy in children, as biopsy results may help to identify those who will likely respond to medical treatment and thus decrease the need for cardiac transplantation. EMB is usually obtained transvenously from the right ventricle and carries a less than 1:1000 risk of major complications when performed by experienced operators.

A three-tiered classification for diagnosing acute myocarditis as *subclinical*, *probable*, or *definite* has recently been proposed (Table 39.3).

TREATMENT

Guideline-directed medical therapy

There are no guidelines to direct therapy for patients with subclinical acute myocarditis. If the LVEF is <40%, then it would be reasonable to consider a short course of either an angiotensin-converting enzyme inhibitor (ACE-I) or an angiotensin II receptor blocker (ARB) and possibly a beta-blocker, with regularly scheduled clinical follow-up.

Therapy for adult patients who present with heart failure symptoms and are diagnosed with probable or definite myocarditis consists of guideline-directed heart failure therapy including sodium and fluid restriction as well as treatment with diuretics and an ACE-I or an ARB. Beta-blocker therapy should be added once acute heart failure symptoms have resolved. The potential benefit of calcium channel blocker therapy in patients with viral myocarditis has not been established. Digoxin should be used with caution in patients with viral myocarditis, as administration of high-dose digoxin to mice with viral-induced myocarditis increased mortality. Non-steroidal anti-inflammatory medications should be avoided, as use of these medications in mouse models of viral myocarditis results in augmented inflammation and increased mortality. Strenuous exercise should be avoided for 6 months after acute infection, as mouse models have shown this type of activity to be deleterious. Patients who present with severe heart failure symptoms may require intravenous vasodilators or inotropes, while patients in cardiogenic shock may require mechanical circulatory support with intra-aortic balloon pumps, extracorporeal membrane oxygenation, or left ventricular/biventricular assist devices. Cardiac transplantation is reserved for patients who do not respond to guideline-directed heart failure therapy and mechanical circulatory support.

Antiviral therapy

As myocarditis is most often caused by viral infection, it would seem reasonable that elimination of viral translation, transcription, and proliferation with the use of antiviral medications, such as pleconaril or soluble CAR-Fc, that target viral attachment to host-cell receptors, virus entry, or virus uncoating would be effective in early stages of the disease, but, unfortunately, most patients present several weeks after viral infection. These agents are therefore likely providing little benefit to patients with acute viral myocarditis.

Immunosuppressive therapy

Treatment of acute viral myocarditis with immunosuppressive drugs has not shown to be beneficial in adults. Results from the Myocarditis Treatment Trial showed that myocarditis patients treated with prednisone plus either azathioprine or cyclosporine had similar changes in LVEF and transplant-free survival to patients treated with placebo. Immunosuppression in patients with GCM, cardiac sarcoidosis, necrotizing eosinophilic myocarditis, and myocarditis associated with connective tissue disorders, however, is warranted because immunosuppression has been shown to improve outcomes in patients with these disorders. Several small case–control studies have shown that immunosuppressive treatment may be effective in children with acute myocarditis, but randomized controlled trials in this regard are lacking.

The Tailored Immunosuppression in Inflammatory Cardiomyopathy (TIMIC) trial randomized 85 adult patients with chronic myocarditis without persistent viral genomes to either prednisone and azathioprine or placebo. Patients in the immunosuppression group experienced significant improvement in LVEF and quality of life, while none of the patients in the placebo group had sustained improvement in either of these outcomes, indicating that immunosuppression may be efficacious in patients with chronic myocarditis/DCM.

Immunomodulatory therapy

Small studies using intravenous immunoglobulin (IVIG) in adult myocarditis patients have shown mixed results. Interferon-alpha and interferon-beta therapy in mice with viral-induced myocarditis reduces myocyte injury, decreases inflammatory cell infiltrates, and results in elimination of cardiac viral load. A small case series of patients with chronic DCM and persistent enteroviral or adenoviral genomes in their myocardium showed that treatment with interferon-beta eliminated viral genomes and improved LVEF compared with placebo. In the Betaferon In patients with Chronic viral Cardiomyopathy (BICC) trial the Betaferon group had significantly reduced cardiac enteroviral load, increased LVEF, and decreased left ventricular volumes compared

with placebo. Whether or not these results can be extrapolated to treatment of other viruses (e.g., PVB19 or HHV-6) remains unclear.

NATURAL HISTORY AND PROGNOSIS

Natural history and prognosis in acute myocarditis varies by clinical scenario. Patients with acute lymphocytic (viral) myocarditis who present with mild symptoms and normal or near normal LVEF usually spontaneously improve without consequences, although approximately 15% of these patients may develop recurrent myocarditis. In contrast, the Myocarditis Treatment Trial revealed that symptomatic adult patients who presented with an LVEF <45% have a 1-year mortality of 20% and a 2-year mortality of 56%. The Intervention in Myocarditis and Acute Cardiomyopathy (IMAC) trial enrolled 62 patients with recent-onset heart failure due to myocarditis or idiopathic DCM and a baseline LVEF <40%, randomizing them to conventional heart failure therapy plus/minus IVIG. Overall, LVEF improved from a mean of 25% at baseline to a mean of 41% at 6 months and 42% at 12 months, regardless of treatment arm. Transplant-free survival was 92% at 1 year and 88% at 2 years. The IMAC-2 trial enrolled 373 patients with recent-onset nonischemic DCM and showed that recovery differed between sexes. Mean LVEF in men increased from 23% at baseline to 39% at 6 months, while mean LVEF in women with nonperipartum cardiomyopathy increased from 24% at baseline to 42% at 6 months. Women with peripartum cardiomyopathy had the greatest myocardial recovery, with mean LVEF increasing from 24% at baseline to 45% at 6 months. There were no deaths at 4 years.

FUTURE DIRECTIONS

Although EMB remains the gold standard for the diagnosis of myocarditis, it is an invasive test with associated risks of major complications. The development of a sensitive and specific noninvasive test is sorely needed. Prevention of myocarditis through vaccination against cardiotropic viruses such as enterovirus, adenovirus, PVB19, HHV-6, and HIV may decrease the incidence of myocarditis in the future.

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40. Mediastinitis

Ravi Karra and Keith S. Kaye

The mediastinum is the space in the thorax between the lungs; it houses the heart, great vessels, esophagus, trachea, thymus, and lymph nodes. The connective tissues of the mediastinum are continuous with the long fascial planes of the head and neck, one reason why mediastinitis was primarily a complication of pharyngeal infections until the advent of thoracic surgery. By virtue of its deep position within the thorax, the mediastinum is a relatively protected organ space. There are four major portals of entry into the mediastinum: (1) direct inoculation of the mediastinum following sternotomy (i.e., postoperative mediastinitis [POM]); (2) spread along the long fascial planes of the neck (i.e., descending mediastinitis); (3) rupture of mediastinal structures, such as the esophagus; and (4) contiguous spread of infection from adjacent thoracic structures.

POSTOPERATIVE MEDIASTINITIS

Postoperative mediastinitis (POM) is classified as an organ/space infection by Centers for Disease Control and Prevention (CDC) criteria and is a dreaded complication of median sternotomy. POM classically presents as a febrile illness with sternal wound dehiscence and purulent drainage, usually 2 to 4 weeks after sternotomy. Occasionally POM presents as a more chronic, indolent infection months to years after sternotomy. Sometimes, only superficial signs of infection are present, making POM difficult to diagnose. Frequently, a high index of clinical suspicion is required to differentiate POM from a more superficial sternal wound infection.

Pathogenesis

Infection most often occurs as the result of direct inoculation of host bacteria into the mediastinum during surgery. Bacteria that colonize the skin and oral mucosa, such as coagulase-negative *Staphylococcus* (CoNS) and *Staphylococcus aureus* are the most common causes of POM. Gram-negative bacilli, a less common cause of POM, are believed to spread to the mediastinum from the abdomen. Infrequently, pathogens such as *S. aureus* might be introduced into the mediastinum by a member of the surgical team or by contaminated operative instruments. Whether bacterial contamination develops into full-blown infection is a combination of three major factors: (1) inoculum of bacterial contamination, (2) the degree of local tissue and vascular damage, and (3) host immunity. Larger inoculum and greater perioperative tissue damage both increase the risk for infection. Decreased host immunity increases susceptibility to the development of POM, contributing to an elevated risk for mediastinitis after cardiac transplantation.

Epidemiology and outcomes

Despite advances in surgical techniques and the use of preoperative prophylactic antibiotics, rates of POM in the modern era remain around 1.0%. The high number of median sternotomies performed annually makes POM a frequently encountered problem.

Risk factors for the development of POM comprise three categories: (1) host-related factors, (2) hospital-related factors, and (3) technical or operative factors. Host-related factors include diabetes, obesity, advanced age, prior sternotomy, chronic obstructive pulmonary disease, and New York Heart Association (NYHA) class III or IV heart failure. Hospital factors include prolonged postoperative mechanical ventilation and prolonged postoperative stay in an intensive care unit. Operative factors include mobilization of an internal mammary artery, increased duration of surgery, and surgical complexity. Complex surgeries are simultaneous coronary artery bypass grafting and valve repair, "repeat" or "redo" median sternotomy, and surgical re-exploration following initial sternotomy.

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POM is associated with significant attributable morbidity and mortality. Estimates of postoperative mortality range from 11.8% to 14% in patients with POM compared to 2.7% to 5.5% in uninfected operative controls. Some series report mortality rates as high as 40%. Risk factors for mortality in the immediate postoperative period are related to the patient (advanced age and postoperative bacteremia), the hospitalization (e.g., mechanical circulatory support and prolonged postoperative mechanical ventilation), technical factors (prolonged operative duration, surgical re-exploration, blood transfusion), and the specific pathogen. POM due to methicillin-resistant *S. aureus* (MRSA) is associated with particularly adverse clinical outcomes. Patients with POM are not only at increased risk for mortality during the immediate postoperative period but also carry a two- to four-fold increased risk for death for up to 10 years following cardiothoracic surgery. Risk factors for long-term mortality in patients with POM include age >65 years, serum creatinine >2.0 mg/dL prior to surgery, infection with MRSA, delay of sternal closure more than 3 days following therapeutic debridement for POM, and failure to treat POM with effective antimicrobial agents within 7 days of therapeutic sternal debridement.

DESCENDING NECROTIZING MEDIASTINITIS

Mediastinitis arising from the migration of pathogens from head or neck infection, as opposed to direct inoculation of the mediastinum, is classified as descending necrotizing mediastinitis. Pharyngeal infections cause nearly 50% of all descending necrotizing mediastinitis. However, virtually any infection of the head and neck can spread into the mediastinum. If infections of the head and neck are treated with appropriate antimicrobial agents, descending necrotizing mediastinitis can be prevented. In the modern age of antibiotics, descending mediastinitis is becoming increasingly rare.

Pathogenesis

Spread to the mediastinum can occur via each of the three spaces of the head and neck: the pretracheal space (suppurative thyroid and tracheal infections), the perivascular space (oropharyngeal infections), and the retrovisceral space (oropharyngeal infections). Negative intrathoracic pressure during inspiration acts to draw infection into the mediastinum from these spaces. The retropharyngeal space houses the "danger" space, so named because it extends from the base of the skull all the way to the diaphragm. Spread within the retropharyngeal space is involved in the pathogenesis of approximately 70% of cases of descending mediastinitis. Infections of the perivascular space can also be complicated by thrombophlebitis of the jugular vein (Lemierre's disease) and direct extension of infection into the carotid artery. (See Chapter 10, Deep neck infections.)

Epidemiology and outcomes

The microbiology of descending necrotizing mediastinitis reflects the bacteria that usually colonize or infect the head and neck. Often, descending necrotizing mediastinitis is a polymicrobial infection involving anaerobes. Common anaerobes include *Fusobacterium*, *Prevotella*, *Vellionella*, *Peptostreptococcus*, and other oral anaerobes. *Streptococcus* spp. are common pathogens. *Actinomyces* can also cause descending mediastinitis.

Patients with descending necrotizing mediastinitis often present with fevers, signs of an underlying head and neck infection, and sometimes sepsis. However, in immunocompromised patients, obvious clinical signs and symptoms may not be readily apparent. Signs of associated neck infection can provide clues to the presence of descending mediastinitis and include trismus, pain of the oropharynx, pain on movement of the neck, dysphagia, hoarseness, stridor, and occasionally erythema of the overlying skin. Overall, the diagnosis of descending necrotizing mediastinitis requires a high degree of clinical suspicion. Early recognition and treatment is important, as this syndrome can be rapidly fatal, with an estimated mortality rate of 15% in spite of therapy.

MEDIASTINITIS ORIGINATING FROM MEDIASTINAL STRUCTURES

Mediastinitis can also occur as a result of direct spillage of bacteria from mediastinal structures. Perforation of any of the organs or vessels housed in the mediastinum, most commonly the esophagus, can lead to mediastinitis. Perforation of the esophagus can occur after heavy emesis (as in Boerhaave's syndrome); following ingestion of sharp objects; or following procedures involving the esophagus such as endoscopy, myotomy, or esophageal stenting. Mediastinitis can develop following tracheal perforation, which sometimes occurs as a complication of endotracheal intubation and bronchoscopy. Rare cases of mediastinitis have

been reported as a consequence of spread of infection from the aorta following surgical repair or central venous line placement.

In mediastinitis originating from mediastinal structures, particularly Boerhaave's syndrome, patients often present with chest pain and fever. If mediastinitis is suspected, special attention in the history should be focused on recent procedures involving the trachea or esophagus or episodes of heavy retching.

MEDIASTINITIS FROM CONTIGUOUS THORACIC INFECTIONS

If untreated, pulmonary infections due to bacteria, fungi, and *Mycobacteria* can cause secondary mediastinitis by contiguous spread. Mediastinitis caused by bacterial pathogens usually presents as an acute infection. Mediastinitis due to tuberculosis or histoplasmosis tends to have a subacute or chronic course compared to bacterial infection. These infections can lead to granulomatous mediastinitis or immune-related deposition of collagen within the mediastinum and resultant fibrosing mediastinitis.

EVALUATION OF SUSPECTED MEDIASTINITIS

It is important to obtain a history of predisposing events, such as median sternotomy, head and neck illness, or endoscopy or bronchoscopy.

Patients with mediastinitis classically present with chest pain and fever. The chest pain is sometimes pleuritic in nature. On exam, patients with mediastinitis usually display signs of severe systemic illness such as hypotension and sepsis. In some instances, patients may not present with overwhelming systemic signs and symptoms of infection. Often, a high degree of clinical suspicion is needed to differentiate POM from superficial infection.

Mediastinitis may present differently depending on the type of infection present in a given case. For example, patients with POM classically present within 3 weeks of surgery with erythema or frank purulent drainage at the sternal incision site. If the sternum is firmly depressed on either side of the incision, a sternal "click" is sometimes elicited, representing sternal instability from damage of underlying tissue planes. Unfortunately, acute signs and symptoms of POM might not be present and sometimes patients present with only mild signs of infection, such as small amounts of drainage or erythema from a median sternotomy site. In contrast, patients with descending necrotizing mediastinitis often have signs of head and neck infection, making evaluation of the head and neck a critical component of the physical exam. Sometimes, in cases of dental abscess, fluctuant masses are present at the base of the teeth. Other signs include tonsillar exudates, pharyngeal inflammation, or cervical lymphadenopathy. Neck tenderness may represent tracking of infection from the head or neck to the mediastinum. "Hamman's crunch," present in some cases of mediastinitis, refers to crunching sounds on cardiac auscultation with each heartbeat and is indicative of air in the mediastinum. Patients with mediastinitis secondary to spread of infection from adjacent organs often have signs or symptoms associated with infection of the adjacent organ space (e.g., findings of pulmonary consolidation in cases of pneumonia).

When considering mediastinitis, diagnostic evaluation includes complete blood count, white blood cell differential, blood cultures, C-reactive protein, and imaging. Chest x-ray may show a widened mediastinum (most commonly seen in cases of descending necrotizing mediastinitis). Rarely, chest x-ray might demonstrate pneumomediastinum. Chest computed tomography (CT) and magnetic resonance imaging (MRI) are the most useful radiographic tests. CT and MRI commonly demonstrate fluid in the mediastinum and pneumomediastinum. While remaining sensitive for POM, chest CT or MRI are less specific, as postoperative inflammation can be difficult to differentiate from infection or abscess.

PREVENTION AND TREATMENT OF SUSPECTED MEDIASTINITIS

Postoperative mediastinitis

In patients undergoing sternotomy, preoperative antibiotic prophylaxis is recommended. First- or second-generation cephalosporins can be administered within 60 minutes prior to surgery. In patients or institutions with high rates of MRSA or in patients with a penicillin allergy, vancomycin can be considered as part of the prophylactic regimen in combination with agents active against gram-negative bacilli. Organized programs to preoperatively decontaminate the nasopharynx and the nares of patients with chlorhexidine prior to surgery have been shown to reduce the incidence of postoperative infection, including deep sternal

infections. More recently, implementation of a program consisting of preoperative chlorhexidine baths and mupirocin treatment of the nares for patients with *S. aureus* colonization was shown to reduce rates of deep surgical site infections, including mediastinitis. Other approaches such as use of implantable antibiotic sponges at the time of surgery or vaccination against *S. aureus* have proven to be less effective.

Optimal treatment of POM involves a combination of definitive surgical debridement and appropriate antimicrobial therapy. In POM, the most common pathogens are gram-positive cocci (*Staphylococcus* spp. and *Streptococcus* spp, ~70% of cases) and gram-negative bacilli (~12% of cases). Therefore, initial antimicrobial therapy typically includes two agents: one with activity against aerobic gram-positive cocci and one with activity against aerobic gram-negative bacilli. Gram-positive coverage usually includes a β-lactam (such as nafcillin or cefazolin) or glycopeptides (such as vancomycin). At institutions where MRSA is a notable POM pathogen, vancomycin should be used for empiric gram-positive therapy. Empiric coverage for gram-negative pathogens usually involves treatment with a fluoroquinolone, aminoglycoside, or extended-spectrum cephalosporin. *Pseudomonas* is a rare pathogen in mediastinitis and, therefore, anti-pseudomonal drugs are not typically required for empiric therapy. Antimicrobial therapy should be tailored based on culture results from the sternum and/or mediastinum; and blood. Results from sternal culture specimens, ideally obtained in the operating room, are usually available within 3 to 5 days after they are submitted.

Immediate surgical debridement, including removal of sternal wires, is needed to confirm the diagnosis of mediastinitis (by demonstrating the presence of pus in the mediastinum), to obtain tissue for microbiologic culture, and to remove purulent material and devitalized or grossly infected tissue. Sternectomy, including removal of the avascular costal cartilage, usually is necessary due to concurrent sternal osteomyelitis. After initial debridement and sternectomy, various therapeutic operative approaches can be implemented. Historically, the sternum was left open and packed until granulation tissue visibly developed. However, this approach was associated with considerable morbidity and mortality, often due to superinfection of the open mediastinum. Utilization of negative pressure wound therapy (NPWT, Wound Vacs) for mediastinitis may improve outcomes. Several series demonstrate shorter hospital stays, faster time to complete sternal closure, and even decreased mortality with NPWT compared to an open sternum. The preferred approach for sternal closure following sternectomy is to use a muscle flap, usually derived from the pectoralis or omentum, with the use of fenestrated drains in the mediastinum. Closure of the sternum with a muscle flap typically occurs either immediately after sternectomy and debridement or soon afterward. Delayed closure is associated with adverse outcome. Occasionally, the sternum is closed primarily without use of a muscle flap.

Descending necrotizing mediastinitis, mediastinitis originating from mediastinal structures, and mediastinitis from contiguous thoracic infections

In descending necrotizing mediastinitis, empiric antimicrobial therapy should provide activity against gram-positive cocci, anaerobes, and gram-negative rods. When the infection is restricted to the upper mediastinum, transcervical drainage is recommended. However, when infection includes the lower mediastinum, thoracotomy and open drainage is often necessary.

Mediastinitis following rupture of a mediastinal viscus requires open surgical drainage and repair of the perforated viscus. In the case of Boerhaave's syndrome, antibiotics with activity against aerobic gram-negative bacilli and anaerobes should be used. For example, an extended-generation cephalosporin in combination with metronidazole or clindamycin would be a reasonable empiric regimen. Other single-drug regimens might include a β-lactam/β-lactamase inhibitor combination such as piperacillin–tazobactam; or a carbapenem. Surgical intervention is guided by the degree of infection and the perforation. Large collections of infection require drainage, and large esophageal tears require local esophagectomy and repair.

Mediastinitis secondary to spread of a contiguous thoracic infection should be empirically treated with broad-spectrum antibiotics with activity against pulmonary pathogens such as *Streptococcus pneumoniae*, *S. aureus*, and gram-negative bacilli. In cases of suspected aspiration pneumonia, anaerobes should also be covered. An appropriate empiric regimen might include a third-generation cephalosporin or aztreonam in combination with vancomycin and either clindamycin or metronidazole. Definitive therapy

requires debridement of the mediastinum and drainage of infected thoracic collections, usually via chest tube. Antibiotic regimens should be tailored based on intraoperative culture results.

Fibrosing mediastinitis due to either mycobacterial infection or fungal infection is a therapeutic challenge. Empiric therapy for *Mycobacterium tuberculosis* includes the standard four-drug regimen (e.g., isoniazid, rifampin, pyrazinamide, and ethambutol). For the treatment of fungal infections, itraconazole, sometimes in combination with amphotericin for histoplasmosis, is used. However, the utility and effectiveness of antimicrobial therapy in the treatment of fibrosing mediastinitis due to these pathogens remains unclear. Surgical debridement is primarily used to relieve vascular and airway obstruction.

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41. Vascular infection

Susan E. Beekmann and David K. Henderson

Diagnosis and treatment of vascular infections is complex and depends on a variety of factors, including the location of the infected tissue, the microbiology of the infection, and patient-specific factors, such as anatomy and immune status. Purulent or suppurative thrombophlebitis is inflammation of a peripheral or central venous wall because of the presence of microorganisms. Endarteritis (or infective arteritis) and mycotic aneurysms are infections of the arterial walls; arterial aneurysms or pseudoaneurysms are usually present because endarteritis may be difficult to diagnose unless an aneurysm is present. The term *mycotic aneurysm* is a misnomer that refers to any arterial aneurysm of infectious cause, fungal or bacterial, and may also include secondary infections of pre-existing aneurysms or pseudoaneurysms. Vascular graft infections present an even wider spectrum of disease that depends on the type and location of the graft. Management of infections located on vascular prostheses is further complicated by the fact that prosthesis excision can jeopardize a patient's life and organ function, and alternative grafting techniques, including *ex situ* bypass, autologous reconstruction, and a variety of other graft materials, must be considered. Finally, endovascular repair of aneurysms has resulted in a variety of infectious complications of endovascular stents, stent-grafts, and other intra-arterial devices.

PURULENT PHLEBITIS OF PERIPHERAL AND CENTRAL VEINS

Pathogenesis and diagnosis

Septic thrombophlebitis is characterized by inflammation with suppuration of the vein wall. The various anatomic sites of this serious condition determine the clinical significance and manifestations. Superficial suppurative thrombophlebitis is most often a complication of indwelling intravenous catheters or intravenous substance use. Suppurative thrombophlebitis due to intravenous catheters occurs more commonly with plastic than with steel cannulas. Irritation of the vein wall and subsequent development of purulent thrombophlebitis occurs more often with polyethylene catheters than with Teflon or Silastic catheters and is higher in lower extremity cannulation. Central vein thrombosis is a relatively common complication of central venous catheterization, occurring in as many as one-third of patients in some autopsy and clinical series. Peripherally inserted central venous catheters are also associated with increased risk of symptomatic thrombosis. Suppurative thrombophlebitis of the thoracic central veins results from the bacterial or fungal contamination (sepsis) of these often asymptomatic thrombi. The second major type of septic thrombophlebitis occurs by invasion from adjacent primary nonvascular infections and includes Lemierre's syndrome (internal jugular vein septic thrombophlebitis) as well as other entities discussed elsewhere. Lemierre's syndrome, although rare, usually follows an oropharyngeal infection and occurs most often in previously healthy patients aged 16 to 25 years.

Diagnosis of peripheral suppurative thrombophlebitis may be difficult if local findings of inflammation are absent, as often occurs in lower extremity cannulization. Local findings are much more common in suppurative thrombophlebitis of the upper extremities. Bacteremia is present in as many as 90% of patients with peripheral suppurative thrombophlebitis, and gross pus within the vein may be apparent in half of the patients. Suppurative thrombophlebitis of the thoracic central veins should be considered in any septic patient with a central venous catheter when bacteremia (or fungemia) fails to resolve after removal of the catheter and institution of appropriate antimicrobial therapy. Diagnosis can be established by venography with the demonstration of thrombi in a patient with bacteremia or

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fungemia. Computed tomography (CT) with contrast is also likely to be diagnostic; presence of gas in the venular lumen is typical of this condition. Magnetic resonance imaging (MRI) may be even more sensitive for diagnosis. Fluorodeoxyglucose positron emission tomography (FDG-PET) may be useful, particularly in neutropenic patients suspected to have infection. In Lemierre's syndrome, the course is described by the triad of pharyngitis, a tender/swollen neck, and noncavitating pulmonary infiltrates. Septic pulmonary emboli occurred in 97% of cases in two series. Oropharyngeal findings alone, however, are not diagnostic, and a tender and/or swollen neck occurs in only about 50% of patients. CT with contrast, ultrasound, or MRI can document this syndrome.

Therapy

Treatment of superficial suppurative thrombophlebitis traditionally has consisted of surgical excision plus parenteral antimicrobials. Most of the literature, which is derived primarily from burn center studies, strongly recommends vein excision, indicating that patients treated with antibiotics alone had a much higher death rate than patients who underwent surgical exploration. Other studies suggest that local incision and drainage of the involved site plus appropriate antimicrobial therapy may be sufficient in many nonburn cases. Patients who fail less radical surgery should then be referred for extensive surgical excision with total removal of all involved veins and drainage of contiguous abscesses.

Enterobacteriaceae caused more than half of all cases of suppurative thrombophlebitis in recent reviews, followed by *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Candida* species. Initial empiric treatment might include vancomycin and either an aminoglycoside or a third- or fourth-generation cephalosporin with antipseudomonal activity to cover the Enterobacteriaceae, *Pseudomonas*, and *S. aureus* (both methicillin-resistant and methicillin-sensitive) until a culture of the infected material can be performed. Blood cultures should always be drawn before antibiotics are initiated. Empiric antibiotic choices should be tailored for known resistance patterns within hospitals and in geographic areas and may be adjusted based on Gram stain results. For example, a Gram stain of venular material showing gram-negative rods should result in discontinuation of vancomycin. Therapy with an appropriate antibiotic(s) should be continued once culture results are available. Treatment of superficial suppurative thrombophlebitis caused by *Candida albicans* is controversial because most of these infections can be cured by vein excision alone. Nonetheless, fluconazole, 400 to 800 mg/day, may be used, and amphotericin B or fluconazole is mandatory in the immunosuppressed patient or if metastatic complications occur.

Treatment of central suppurative thrombophlebitis consists of catheter removal and parenteral antibiotics. The addition of full-dose anticoagulation is more controversial, although one review concluded that the administration of heparin in these settings may be beneficial. Empiric antibiotic treatment is the same as for peripheral suppurative thrombophlebitis with the potential addition of an antipseudomonal penicillin. The antibiotics appropriate for the organisms identified from cultured material should be continued for at least 2 weeks after catheter removal. A minimum of 4 weeks of antimicrobial treatment is recommended after catheter removal when *S. aureus* is involved. Amphotericin B to a total dosage of at least 22 mg/kg $\pm$ 5-fluorocytosine is recommended for suppurative thrombophlebitis of the great central veins caused by *Candida* species; for the intrinsically resistant species, including *Candida glabrata* and *Candida krusei*, echinocandins may be an acceptable alternative. Lemierre's syndrome should be treated with a prolonged course of either clindamycin or metronidazole. Surgical treatment is usually not necessary.

ARTERIAL INFECTIONS (MYCOTIC ANEURYSMS AND ARTERITIS)

Pathogenesis and diagnosis

Mechanisms of arterial infection include (1) embolomycotic aneurysm secondary to septic microemboli (underlying infective endocarditis), (2) extension from a contiguous infected focus, (3) hematogenous seeding during bacteremia originating from a distant site, and (4) trauma to the vessel wall with direct contamination, with the latter mechanism occasionally associated with iatrogenic manipulation of the artery (e.g., cannulation). Normal arterial intima is quite resistant to infection, but congenital or acquired malformation or disease (e.g., atherosclerosis) lowers resistance to infection, and hematogenous seeding of a previously damaged arteriosclerotic vessel currently constitutes the most common mechanism

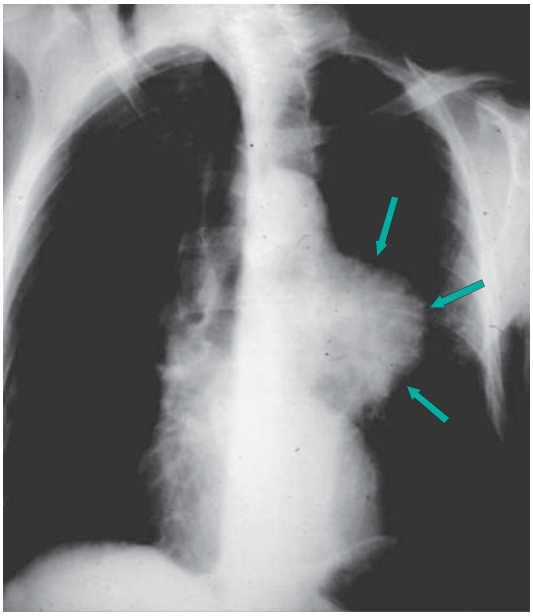

Figure 41.1 Infected atherosclerotic aneurysm of descending thoracic aorta (*arrows*): blood cultures grew *Salmonella*. (Courtesy of David Schlossberg, MD.)

of infection (Figure 41.1). Mycotic aneurysms complicate infective endocarditis in approximately 5% to 10% of cases, with about half of these aneurysms involving the brain. Brain MRI with angiography may be more sensitive than CT scans for neurologic manifestations of infective endocarditis, including cerebral mycotic aneurysms. Gram-positive organisms are the most common pathogens, with *S. aureus* accounting for approximately 30% to 40% of cases when bacteria seed an atherosclerotic vessel, and with *Enterococcus* species and *Streptococcus pneumoniae* as the most common pathogens associated with infective endocarditis. Gram-negative bacteria are the causative organisms in approximately one-third of cases, with *Salmonella* species found in about 20% of all cases. When aneurysms are associated with endocarditis, gram-positive organisms account for at least 80% of pathogens.

Clinical manifestations depend to a large extent on the site of the aneurysm (Table 41.1), although mycotic aneurysms are often clinically unsuspected. Most infected aortic aneurysms occur in elderly atherosclerotic men (4:1 ratio, men > women), but symptoms are nonspecific and may overlap with those of uninfected aneurysms. Fever and continuing bacteremia despite seemingly appropriate antimicrobial therapy are suggestive of an infected intravascular site. CT scan is considered the optimal initial imaging technique, with multiple newer imaging modalities including MRI, FDG-PET, and single-photon emission computed tomography (SPECT) emerging as increasingly feasible and helpful adjunctive imaging techniques.

A variety of intra-arterial prosthetic devices are now being used in cardiovascular medicine, including arterial closure devices, prosthetic carotid patches, coronary artery stents and endovascular stents, and stent-grafts. Infections of these devices remain either uncommon or extremely rare, but infectious complications associated with the placement of these devices are often devastating. *S. aureus* has been implicated in as many as three-quarters of these cases, and has been the primary pathogen, even in late-onset infections. Blood cultures should be obtained from all patients who have a history of endovascular stent placement and local or systemic signs of infection.

Therapy

Despite improved prognosis for infected aneurysms of the thoracoabdominal vessels associated with earlier diagnosis and treatment, the case-fatality rate for aortic aneurysms infected with gram-negative organisms is extraordinary and may be as high as 75%. Currently accepted management is intravenous antibiotic therapy, excision and debridement of the artery or aneurysm, and extra-anatomic vascular reconstruction along an uncontaminated path, where possible. As a general principle, antibiotic therapy alone is insufficient without surgical resection of the infected tissue. Despite this axiom, surgical management of asymptomatic intracranial mycotic aneurysms does depend on their size and location, because small lesions may resolve with antibiotic therapy alone. A reasonable approach would be to monitor by MRI every 2 to 3 weeks for 2 months, although this may carry a higher risk of rupture and bleeding. Surgery is indicated if the infected vessel is accessible or the lesions increase in size and should be considered if the lesions fail to decrease in size.

Basic principles of grafting in this situation include the use of autogenous rather than synthetic grafts and insertion only in clean, noninfected tissue planes. Use of cryopreserved allografts allows *in situ* reconstruction and these grafts are increasingly used, particularly for cases involving the thoracic or suprarenal aorta. Direct (*in situ*) reconstruction with synthetic or autologous grafts

Table 41.1 Diagnosis and management of mycotic aneurysms

Site	Frequency of diagnosis (range)	Clinical presentation	Imaging	Microbiology	Management
General					
All infected aneurysms	100%	Fever common (70%–94%) Malaise, weight loss Pain (100%) Rapidly expanding mass Leukocytosis (65%–85%) Positive blood cultures (50%–75%)	*Findings:* Aneurysm with lack of intimal calcification Perianeurysmal fluid/gas collection *Studies:* CT with contrast, MRI Ultrasonography (if accessible) Radionuclide-tagged WBC scans	*Staphylococcus* 40% (at least 66% *S. aureus*) *Salmonella* 20% *Streptococcus* 20% *Escherichia coli* 6% IVDU: *S. aureus*, *Pseudomonas* spp. *Enterococcus* spp., *Streptococcus viridans*	*Surgical:* Wide debridement, irrigation with antibiotic solution of involved tissues, complete resection of aneurysm if possible *Antibiotic:* Empiric treatment with IV antibiotics for 6–8 wk after surgery based on culture results of resected tissue Follow-up blood cultures Consider chronic suppressive oral antibiotic therapy when extra-anatomic bypass is not performed (i.e., for *in situ* repairs)
Specifics					
Aorta Infrarenal abdominal aorta[a] Ascending aorta and arch (secondary to endocarditis)	27% (11%–75%)	Abdominal or back pain Palpable abdominal lesions (about 50%–65%) Vertebral osteomyelitis (lumbar/thoracic)	Frontal, lateral abdominal x-ray studies Abdominal ultrasound	*Salmonella* spp. have predilection for suprarenal aorta *Staphylococcus* predominates in infrarenal aorta	Extra-anatomic arterial reconstruction (axillofemoral or aortofemoral) If risk too high, *in situ* reconstruction with cryopreserved allograft
Visceral artery Superior mesenteric,[a] splenic, hepatic, celiac, renal	24% (0%–29%)	Colicky abdominal pain Jaundice (hepatic artery) Hemoptysis or hemothorax (celiac artery)	Ultrasound may exclude other causes (e.g., pancreatic masses)	*Bacteroides fragilis* reported from supraceliac aorta and celiac artery	Complete excision may be hazardous; careful drainage and longer-term antibiotic therapy may be necessary
Iliac	4% (0%–25%)	Thigh pain, quadriceps wasting, depressed knee jerk Arterial insufficiency of extremity			Excision and arterial ligation; reconstruction usually can wait until infection has resolved
Arm Radial artery[a] Brachial artery Subclavian artery	10% (0%–9%)	Pain over site of lesion About 90% palpable May appear as cellulitis, abscess; distal embolic lesions; skin changes common			Proximal ligation of the vessel, resection of the aneurysm, and appropriate drainage should be followed by antibiotic therapy.
Leg Femoral artery[a]	12% (4%–44%)	Pain over site of lesion About 90% palpable Pulsatile mass, decreased peripheral pulses Possible local suppuration, distal embolic lesions; petechiae, purpura		*S. aureus* incidence as high as 65%	Excision and arterial ligation; reconstruction usually can wait until infection has resolved Autogenous grafting may allow reconstruction through the bed of the resected aneurysm if anastomoses performed in clean tissue planes
Intracranial Peripheral middle cerebral artery[a]	4%	Usually clinically silent May appear as severe unremitting headache Usually secondary to endocarditis	Four-vessel cerebral arteriography invaluable MRI	*Enterococcus* spp. *S. viridans* *Pseudomonas* spp. *Candida albicans*	

Abbreviations: CT = computed tomography; MRI = magnetic resonance imaging; WBC = white blood cell; IV = intravenous; IVDU = intravenous drug user.
[a] Most common site or manifestation.

has become increasingly common, and short- and midterm outcomes of this approach appear to be acceptable. At surgery the aneurysm must be sectioned, Gram-stained, and cultured; appropriate antibiotic therapy must be individualized and based on culture and sensitivity results. Bactericidal antibiotics should be continued for 6 to 12 weeks postoperatively, and some authors recommend indefinite antibiotics with *in situ* graft placement.

Endovascular aneurysm repair (EVAR) or endoluminal stenting for mycotic aneurysms is an additional alternative that reduces hospital stay and frequency of surgical complications but that raises significant concern because of persistent infection. In many cases, these endovascular stents are short-term solutions (i.e., "bridge" repairs) until definitive surgical treatment can be performed, and chronic oral antimicrobial therapy is required. Nonetheless, endovascular grafts may now be used preferentially in patients with limited life expectancy and multiple comorbidities for whom conventional surgical methods carry extremely high risk. A life-long follow-up strategy for patients treated with EVAR is vital given the relatively high complication rates.

VASCULAR GRAFT INFECTIONS

Pathogenesis and diagnosis

Reported incidence of vascular graft infections ranges from 0.8% to 6% and varies with the site of graft placement and the graft material selected for insertion. For example, procedures requiring an inguinal incision have an incidence of infection that is two to three times higher than procedures not requiring an inguinal incision; use of a vascular prosthesis results in significantly higher infection rates than autologous reconstruction. Most contamination likely occurs at the time of implantation, although hematogenous seeding, retrograde infection from superficial wound infection, as well as bacteria harbored in atherosclerotic plaques may account for some late graft infections. Prophylactic systemic antibiotics at time of graft placement have been associated with a decrease in vascular graft infections. Prophylactic antibiotics should be considered mandatory with placement of vascular grafts.

Staphylococci remain the most prevalent pathogens, with *S. epidermidis* infections often presenting months to years after the operation and *S. aureus* most commonly causing early infections (Table 41.2). More than 70% of infections involving vascular grafts of the groin and lower extremities develop within 1 to 2 months of surgery, whereas 70% of intra-abdominal graft infections do not manifest until months or years after surgery. An aortoenteric fistula can be the presenting sign in about 30% of aortic graft infections, while systemic symptoms, including fever, leukocytosis, and bacteremia, are much more variable.

Appropriate imaging of the infected area is vital to diagnosis because the extent of local infections may not be recognized if imaging techniques are inadequate. Angiography often is unhelpful in the diagnosis of vascular graft infections, but it is useful for identifying aortoenteric fistulas as well as for guiding the surgical procedure. An anatomic imaging study should be performed. Ultrasound can be used for superficial grafts, including dialysis shunts; a CT with contrast or an MRI with contrast and fat saturation should be performed for deeper grafts. If doubt about infection still exists, radioisotope imaging can be performed using either indium-111-labeled leukocytes or, if available, technetium-99 hexamethylpropyleneamine oxime (HMPAO)-labeled leukocytes. Other nuclear medicine techniques, including FDG-PET imaging and SPECT/CT, are being investigated for diagnosis of suspected vascular graft infections and appear promising. These studies, although sensitive, are limited by low specificity, particularly in the early postoperative setting (i.e., in the period up to 12 weeks following surgery). Imaging findings that suggest the presence of graft infection include the presence of fluid around the graft, air, the definition of abnormal tissue planes, extensive soft-tissue swelling, anastomotic aneurysms, and the identification of pseudoaneurysms, especially when more than one are apparent.

Therapy

Conventional treatment after vascular graft infection remains the gold standard and is defined as intensive antibiotic therapy and graft excision with extra-anatomic bypass revascularization if distal ischemia is present. Revascularization should be delayed, if possible, to establish potential collateral circulation and to decrease bacterial levels. Vascular graft material does appear to affect outcome, with autogenous (often the femoral vein) and cryopreserved allografts having the best overall success rates.

Although antibiotic treatment and local wound care are unsuccessful when used alone, a subset of patients may be managed without

Table 41.2 Diagnosis and management of vascular graft infections

Site	Clinical presentation	Microbiology	Imaging	Management
General				
Any infected vascular graft	*Early (≤4 mo):* Immediate postoperative infections rare; usually associated with wound sepsis Fever, leukocytosis, bacteremia Anastomotic bleeding (most common with gram-negative organisms) Wound healing complication *Late:* Systemic signs few or absent; WBC count often normal Tenderness, erythema of skin over prosthesis Anastomotic false aneurysm Graft-enteric erosion, fistula	*Staphylococcus aureus* Coagulase-negative staphylococci *Streptococcus* *Escherichia coli* *Klebsiella* *Pseudomonas*	*Findings:* Perigraft fluid, gas collection; abnormal appearance of perigraft soft tissues; abscess; pseudoaneurysm formation *Studies: Anatomic imaging study:* 1. CT with contrast, or 2. MRI with contrast and fat saturation; or, for superficial grafts: 3. Ultrasonography *Radioisotope studies that may be useful:* 1. WBC-labeled indium scan, or 2. Tc99-HMPAO-labeled WBC, if available	*Surgical:* Wide debridement, irrigation with antibiotic solution of involved tissues (commonly used but efficacy data not available), graft excision when possible with *ex situ* bypass reconstruction Consider thorough debridement with myocutaneous flap for patients with a patent graft, intact anastomoses, absence of hemorrhage, and sterile blood cultures *Antibiotic:* Empiric treatment with IV antibiotics for 4–6 wk after surgery based on culture results of resected tissue Follow-up blood cultures Consider chronic suppressive oral antibiotic therapy if infected graft not removed
Specific				
Aortoiliac	Higher incidence in months 8–15 First symptoms, fever, slightly increased WBC count Later, abdominal, back pain, false aneurysm formation Finally, hemorrhage Aortoenteric fistula (30% of aortic graft infections)	*E. coli* *S. aureus* *Streptococcus* *S. epidermidis* (or coagulase-negative staphylococci)	MRI more sensitive than CT for aortal graft infection	Place axillofemoral or bifemoral graft, then remove entire aortic graft Close arteriotomy sites with monofilament sutures, irrigate with antibiotic solution (no efficacy data)
Aortofemoral	False aneurysm in groin site Wound infection or abscess in inguinal incision Pulsatile mass at groin site	*S. aureus* *S. epidermidis* *Proteus* spp. *E. coli* *Streptococcus* Other gram-negative bacilli	Ultrasonography can be useful in femoral area	May be possible to remove only infected part of graft (one limb), although continued infection likely without removal of entire graft Extra-anatomic bypass when possible
Axillofemoral	Same as for aortofemoral	Same as for aortofemoral	Same as for aortofemoral	Remove entire graft Intra-abdominal graft may suffice for revascularization; high amputation and death rates
Femoropopliteal	Higher incidence in first 3 mo Small sinus tract, abscess, cellulitis in inguinal incision	*S. aureus* *Streptococcus* *S. epidermidis* Other gram-negative bacilli		Remove entire graft Nonviable limbs must be revascularized or amputated; delay amputation as long as possible to allow maximum development of collaterals

Abbreviations: WBC = white blood cell; MRI = magnetic resonance imaging; CT = computed tomography; IV = intravenous.

removal of the entire graft or with *in situ* grafting. Criteria for complete graft preservation include the following (at a minimum): a patent graft, intact and uninvolved anastomoses, absence of hemorrhage, and sterile blood cultures. Partial graft excision may be attempted with intact anastomoses but occluded grafts, while bacteremia, systemic sepsis, or involvement of anastomoses mandate complete graft removal. Diabetic patients and those receiving long-term systemic steroid therapy should be considered at highest risk for continued infection without graft removal and extra-anatomic bypass. Likelihood of successful graft preservation appears to be highest

with early, low-grade infections (e.g., early coagulase-negative staphylococcal infection) and lowest with gram-negative infections and *S. aureus*. Muscle flap coverage after aggressive perigraft debridement should be considered a vital component during attempts to salvage grafts. The optimal therapy of infected vascular grafts remains removal of the entire graft and revascularization where necessary through uninfected tissue planes.

If a new graft must be placed in the infected field (*in situ* grafting), use of autogenous artery or vein grafts may decrease susceptibility to infection. In the absence of available autologous vessels, cryopreserved arterial allografts may be used or prosthetic conduits (including rifampin-bonded or silver-coated prostheses) if necessary. Parenteral antibiotics should be administered for 4 to 6 weeks after the infected graft is removed, and some authorities have recommended administering oral antibiotics for an additional 1 to 3 months. Because of the risk of reinfection regardless of the treatment chosen, surveillance ultrasound examination should be performed every 3 to 6 months for life.

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42. Infections of cardiovascular implantable electronic devices and VAD

M. Rizwan Sohail and James M. Steckelberg

Cardiovascular implantable electronic devices (CIED) include permanent pacemakers (PPM), implantable cardioverter-defibrillators (ICD), and cardiac resynchronization therapy (CRT) devices. The reported risk of CIED infection ranges from 1% to 10% and depends on the complexity of the device and host comorbid conditions. Once infected, patients need to undergo complete device removal and systemic antibiotic therapy to achieve cure.

Earlier versions of CIEDs required surgical placement of epicardial leads, which was facilitated by sternotomy, and generators were mostly placed in the abdominal area. However, in contemporary practice, most device leads are placed percutaneously via the subclavian vein and the device generator resides in a subcutaneous pocket in the pectoral area. Use of epicardial leads is now reserved for special situations where transvenous lead placement is not possible or deemed high risk due to active or recent bloodstream infection.

Table 42.1 Risk factors for cardiovascular implantable electronic device infections

Procedure-related risk factors
• Generator or lead revision
• Lack of antibiotic prophylaxis at the time of implantation
• Prolonged surgery
• Postoperative hematoma at the generator pocket
Device-related risk factors
• CRT > ICD > PPM
• Multiple leads (>2)
• Presence of abandoned leads
• Epicardial leads
• Presence of other hardware (central venous catheters, prosthetic vascular grafts, etc.)
Host-related risk factors
• Diabetes mellitus
• Long-term corticosteroid therapy
• Chronic anticoagulation
• Malignancy
• Renal failure
• Older age
• Chronic skin conditions

RISK FACTORS FOR CIED INFECTION

Purported risk factors for CIED infection are summarized in Table 42.1. Presence of multiple comorbid conditions in the device recipient is associated with several folds increase in risk of CIED infection. The risk factors that present an opportunity for intervention are device and procedure-related, as outlined in Table 42.1. These are further discussed in the section on prevention.

Microbiology of CIED infections

Staphylococcal species (coagulase-negative staphylococci and *Staphylococcus aureus*) are the predominant organism responsible for CIED infection. CIED infections that present early (within 4 weeks of device implantation) generally are related to device or wound contamination at the time of surgery. *S. aureus* is the most common microorganism encountered in this situation. However, pocket infection with coagulase-negative staphylococcus can present weeks or months after device implantation. In contrast, the majority of late-onset CIED lead infections are caused by hematogenous seeding of device leads from remote sources of bloodstream infection. In published series, up to 30% of the patients with CIEDs who have blood cultures that are positive for *S. aureus* have underlying CIED lead infection, even when the generator pocket has no obvious inflammatory signs. Therefore, transesophageal echocardiography (TEE) is recommended in patients with CIEDs and positive blood cultures with *S. aureus*. In contrast, CIED lead infection with gram-negative bacteria is an exceedingly rare complication of gram-negative bacteremia and routine use of TEE is not recommended in these cases. Moreover, gram-negative bacteria are also an uncommon cause of CIED

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pocket infections but may be seen in patients with multiple comorbid conditions and those with long-term central venous catheters (e.g., hemodialysis populations). Mycobacterial or fungal CIED infections are exceedingly rare and subject of case reports.

CLINICAL PRESENTATION AND DIAGNOSIS

CIED infections primarily manifest in two distinct ways. Local infection, limited to the generator pocket; or systemic infection involving CIED leads, heart valves, or both. Pocket infection is the most common manifestation of device infection and these patients typically present with inflammatory changes at the pocket site that may include localized pain, erythema, drainage, or cellulitis around the pocket site. Occasionally, erosion of the device generator or leads through the skin is the sole manifestation of chronic smoldering infection. Systemic findings may or may not accompany local infections.

Systemic symptoms and signs such as fever, chills, rigors, malaise, or diaphoresis are hallmarks of CIED lead infection or endocarditis. Blood cultures are typically positive in these cases, but could be negative especially if drawn after administration of antibiotics. Patients with CIED lead infection or endocarditis could present with evidence of septic emboli to the lungs or other organs, especially if left-sided heart valves are also involved.

Diagnosis of CIED pocket infection is relatively straightforward based on inflammatory changes at the generator pocket site. However, blood cultures should be obtained in all cases prior to initiating antibiotic therapy, even if systemic symptoms are not overt. In cases where blood cultures are reported positive, echocardiography should be performed to look for evidence of CIED lead or valvular vegetations. TEE is preferred because it has a sensitivity of about 95% for the detection of lead or valve vegetation, compared with a sensitivity of about 30% with transthoraic echocardiography (TTE). Occasionally, additional testing such as computed tomography (CT), magnetic resonance imaging (MRI), or gallium scanning may be necessary to evaluate complications of CIED infection such as deep abscesses or metastatic foci of infection in the spine, brain, or other organs.

A particularly challenging aspect of diagnosing CIED infection is the cases where blood cultures are positive for staphylococci (especially *S. aureus*) but there are no inflammatory changes around the generator pocket and TEE shows no evidence of vegetations on CIED leads. Whether these devices should be left in place or taken out is a complex decision. Based on published series, the following factors increase the likelihood that the CIED is seeded with *S. aureus*: (1) no other identifiable source of infection, (2) persistently positive blood cultures for 72 hours or longer, (3) community-onset *S. aureus* bacteremia (SAB), and (4) SAB within 3 months of device implantation. If any of these factors are present, we favor removal of the CIED. In the absence of any of these features, it may be reasonable to treat for 2 to 4 weeks depending on the presumed source of SAB and closely follow-up for any evidence of relapse of infection. If the patient has relapse of SAB, the CIED should then be removed.

MANAGEMENT

For patients who present with systemic manifestations of infection, it is reasonable to start empiric antibiotic therapy once blood cultures have been obtained. However, for cases where infection is limited to the generator pocket without any systemic signs, it is prudent to wait until pocket and device cultures are submitted at the time of explantation and then start empiric therapy. Empiric coverage should include antimicrobials with activity against *S. aureus* and coagulase-negative staphylococci. Until sensitivities are known, vancomycin is a reasonable choice as it is active against methicillin-resistant staphylococci. If vancomycin cannot be clinically tolerated, daptomycin or linezolid are reasonable second-line agents for methicillin-resistant staphylococci or vancomycin-resistant enterococcus (VRE). Once culture data are available, antimicrobial therapy should be tailored accordingly.

Complete removal of all hardware (CIED generator and all leads) is generally required for eradicating CIED infection. In our institutional experience and that of others, conservative management of the device (antimicrobial therapy alone without device removal) is almost always associated with treatment failure and is the single most important predictor of relapse of infection. Based on these data, the most recent guidelines from the American Heart Association (AHA) recommend complete removal of the device for CIED infection (Class 1A recommendation). Duration of antimicrobial therapy for various CIED infection syndromes is summarized in Figure 42.1.

In contemporary practice, most device leads are removed percutaneously using a transvenous

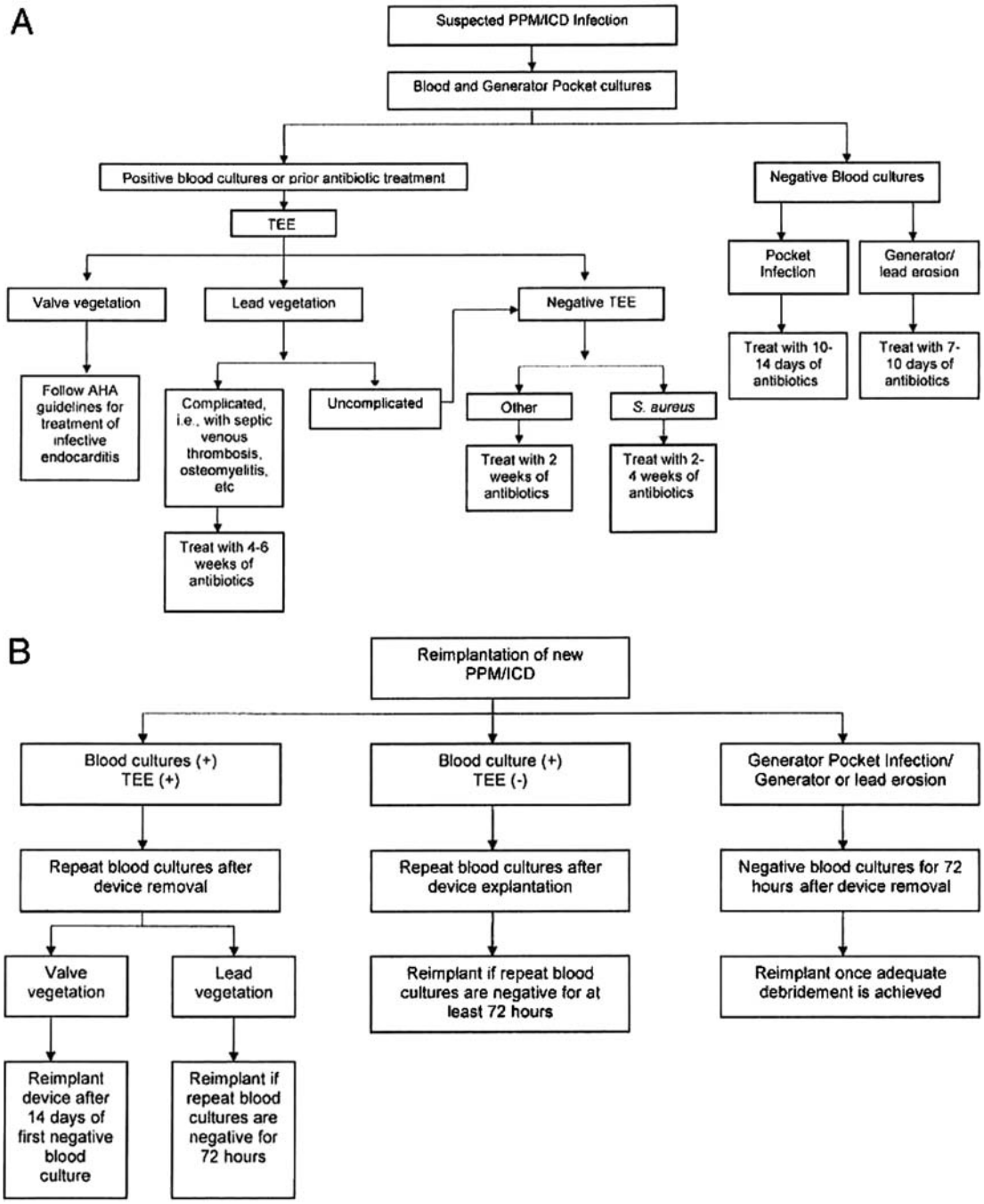

Figure 42.1 Approach to management of patients with CIED infections. (With permission from: Sohail MR, Uslan DZ, Khan AH, *et al.* Management and outcome of permanent pacemaker and implantable cardioverter defibrillator infections. *J Am Coll Cardiol.* 2007;49:1851–1859.)

approach. For CIED leads that were implanted relatively recently (weeks or months), removal by applying countertraction may be adequate. However, this procedure can be very difficult and can result in avulsion of the tricuspid valve, arteriovenous fistulas, or retention of the lead tip, especially if leads have been in place for a longer period of time (months to years). In these cases,

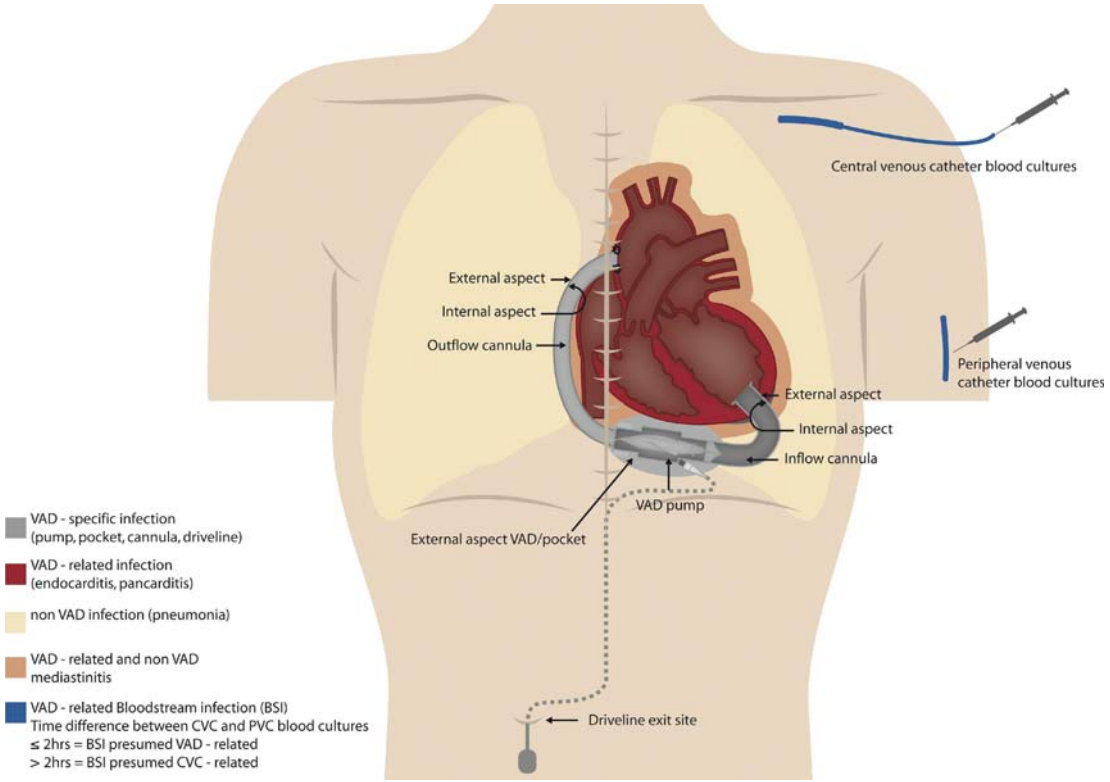

Figure 42.2 Illustration of ventricular assist device, VAD-specific, VAD-related, and non-VAD infection (From *J Heart Lung Transplant*. 2011;30(4):375–384, with permission.)

use of a laser sheath is more appropriate. In this approach, a laser sheath is slid over the length of the electrode and used to excise the implanted lead, allowing the entire lead to be withdrawn with little trauma. However, expertise in lead removal via laser sheath is usually limited to high-volume referral centers.

Percutanous lead extraction also appears safe in patients with lead vegetations. However, some experts recommend surgical removal of leads via cardiotomy in patients who have lead vegetations larger than 5 cm due to concern for clinically significant pulmonary emboli. Failure of the transvenous approach or the need to remove epicardial patches are other indications for open surgical procedures.

For patients who present with bloodstream infection, blood cultures should be repeated after device removal. Once blood cultures obtained after CIED lead removal are reported negative and the infected pocket has been adequately debrided, it is reasonable to implant a new device. However, a longer interval (up to 2 weeks or more) is usually recommended in the setting of CIED infection complicated by valvular endocarditis. Guidelines for timing of reimplantation of a new device are summarized in Figure 42.1.

Limited data suggest that same-day reimplantation may be reasonable in patients who present with CIED infection limited to the generator pocket and in whom physical examination, laboratory parameters, and blood cultures do not show any evidence of systemic involvement.

The new CIED system (when required) should be implanted at a distant site. However, it is worth noting that a significant proportion of patients (up to 30% in some studies) do not require ongoing device therapy. Therefore, it is critical that the need for ongoing CIED therapy be assessed prior to implantation of a new device (preferably even before removal of the infected device).

PREVENTION

Preventing CIED infections is fundamental due to morbidity, mortality, and financial considerations discussed earlier. Because most early-onset

infections result from wound or device contamination at the time of surgery, meticulous attention to aspetic techniques before surgery is essential. Efficacy of antistaphylococcal antimicrobial prophylaxis before CIED implantation has been demonstrated in randomized clinical trials. In general, cefazolin 1 g is administered intravenously within an hour prior to starting the device implantation procedure. However, for patients who are allergic to cephalosporins or have known colonization with methicillin-resistant staphylococci, vancomycin is a reasonable alternative. Some implanters continue antibiotic prophylaxis for 24 to 48 hours. However, there are no good data to support the added benefit of this practice.

Optimal management of host comorbidities (diabetes, renal failure, heart failure, etc.) is also important to minimize the risk of CIED infection. Another issue is optimal management of anticoagulation therapy to minimize the risk of pocket hematoma in patients who are on long-term oral anticoagulants for prosthetic heart valves or secondary prevention of venous thromboembolism. Earlier practice was to hold the oral anticoagulation therapy and "bridge" the perioperative period with unfractionated heparin. However, more recent clinical trials have demonstrated that continuation of oral anticoagulation is associated with a lower incidence of pocket hematomas compared with "bridge" therapy with heparin.

Guidelines from the AHA issued in 2007 do not recommend antimicrobial prophylaxis for patients with CIEDs undergoing dental or other procedures associated with transient bacteremias.

VAD infection

Ventricular assist devices (VADs) are increasingly being used in patients with end-stage heart failure for both bridge-to-transplantation and as myocardial surrogate (destination) therapy. VADs are undergoing rapid evolution and most recent devices use continuous flow pump mechanisms, which improve the device function and lower the risk of infection. However, infection remains a major complication of VAD therapy, with reported rates varying from 25% to 80%. The highest risk of infection is during the first 30 days and risk becomes relatively uncommon after 90 days.

Purported risk factors for VAD infection include length and complexity of the implantation procedure, hemorrhage at the surgical site, malnutrition, diabetes, obesity, and presence of central venous catheters. Moreover, friction-related trauma at the driveline exit site may result in cutaneous migration of microbes along the driveline and is a well-established risk factor for late-onset driveline infection. Use of an abdominal binder can minimize the movement at the exit site and reduce the risk of driveline infection.

VAD infections can present as local driveline or pocket infections that result in pain, erythema, or purulence at the exit site. More severe infections can involve pump or cannula infection, bloodstream infection, or endocarditis (Figure 42.2). The majority of VAD pocket or pump infections, with or without bacteremia, occur within 30 days of device implantation, though late infections have been reported.

The most common pathogens responsible for VAD infection include *S. aureus*, *Staphylococcus epidermidis*, *Enterococcus* spp., *Pseudomonas aeruginosa*, and *Candida* spp. VAD infections due to gram-negative pathogens are mostly of nosocomial origin and are difficult to eradicate or suppress due to multidrug resistance of the organisms.

Driveline exit site infections are usually managed with wound debridement and a short course (typically 2 weeks) of antimicrobial therapy. If local VAD infection is complicated by bloodstream infection, then treatment is prolonged to 4 weeks or longer. However, management of VAD pump or cannula infection presents a major challenge. Unlike other prosthetic devices where removal of the infected hardware is the cornerstone of management, VADs cannot be removed or replaced, unless a donor heart is available, because patients cannot survive without a device. Therefore, a 4- to 6-week course of intravenous antimicrobial therapy followed by chronic suppression, targeted at the causative pathogen and guided by antimicrobial susceptibility testing, is typically prescribed. Occasionally, VAD may be replaced, due to uncontrolled infection despite appropriate antimicrobial therapy. However, suppressive antibiotic therapy should be continued as the new device is placed in an actively infected pocket.

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PART VII

Clinical syndromes: gastrointestinal tract, liver, and abdomen

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43. Acute viral hepatitis

Kalyan Ram Bhamidimarri and Paul Martin

Acute viral hepatitis is a systemic infection with predominant hepatic involvement and remains a significant cause of morbidity and mortality in the United States despite the availability of effective vaccines against the two major causes of acute viral hepatitis, namely A and B. There are five major hepatotropic viruses (A, B, C, D, and E) that cause acute hepatitis with acute hepatic inflammation and necrosis. Acute viral hepatitis typically runs its course in 6 months or less, in contrast to chronic hepatitis, which persists for longer. However, with modern serologic and molecular diagnostic testing, the time course is less important in distinguishing acute from chronic viral hepatitis. The clinical illness produced by these viruses can range from asymptomatic or clinically inapparent to a fulminant and fatal acute infection. A major distinction between hepatitis A and hepatitis B, C, D, and E is that the former causes acute hepatitis only, in contrast to the latter four which cause acute and chronic hepatitis. Other viral infections, such as herpes simplex, Epstein–Barr virus (EBV), cytomegalovirus (CMV), and parvovirus B19, can present with prominent hepatic dysfunction, although they are usually multisystem disorders. Hepatitis G, human herpesviruses, adenovirus, coronavirus, and TT virus (TTV) have also been implicated in causing hepatic dysfunction, but their clinical significance remains dubious.

HEPATITIS A VIRUS

The hepatitis A virus (HAV) is an RNA virus, identified in 1973, transmitted via the fecal–oral route and is a common cause of acute viral hepatitis in North America. Community outbreaks due to contaminated water or food are well recognized. Inhabitants in low-socioeconomic areas, international travelers, intravenous drug users, and homosexual men are at particular risk of HAV infection. In the United States, the incidence has decreased remarkably since the introduction (1995) of HAV vaccination and its administration to all children as part of the universal childhood vaccination policy since 2006. In underdeveloped countries, HAV infection typically occurs in childhood and is subclinical (age $\leq$6 years, 70% are asymptomatic), with most of the population infected before adulthood acquiring life-long immunity. HAV infection occurring in older children and adults is more likely to be symptomatic, with increased morbidity and even mortality (Figure 43.1).

The average incubation period of HAV infection is 28 days (range 15 to 50 days), with peak fecal viral shedding and infectivity occurring before the onset of clinical symptoms, which may include anorexia, fever, malaise, fatigue, nausea, vomiting, diarrhea, and right upper quadrant discomfort. In acute HAV infection, these symptoms tend to occur 1 to 2 weeks before the onset of jaundice. Replication of HAV occurs exclusively within the cytoplasm of the hepatocyte, where the virus causes a noncytopathic infection. Hepatocellular damage is due to the host's immune response as the infected hepatocytes are cleared and is clinically observed by marked reduction of HAV RNA. Acute liver failure is rare and occurs in about 0.5% of infected individuals, more frequently in adults than in children. The overall case-fatality rate of acute HAV is 0.3% to 0.6% but reaches 1.8% among adults >50 years. Prompt referral of acute liver failure cases to a transplant center should be performed at the earliest. Patients with chronic liver disease who contract HAV are at particular risk of hepatic decompensation, which has led to the recommendation that HAV-naïve patients with chronic liver disease should be vaccinated against HAV. Most infected individuals recover uneventfully although the illness can occasionally be bimodal or relapsing. Chronic infection with HAV does not occur but a protracted cholestatic phase may be present with persistent jaundice and pruritus before the eventual recovery.

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Extrahepatic manifestations of HAV include acute pancreatitis, acalculous cholecystitis, autoimmune hemolytic anemia, aplastic anemia, reactive arthritis, effusions, mononeuritis multiplex, and Guillain–Barré syndrome. HAV-related acute kidney injury has been reported in cases from Asia, possibly mediated by immune complexes or interstitial nephritis.

Routine diagnosis of acute HAV infection is made by detection of IgM anti-HAV antibody in serum (Table 43.1), which becomes detectable 5 to 10 days before the onset of symptoms and persists for 3 to 12 months after infection. IgG anti-HAV antibody develops early in infection and persists indefinitely. The presence of IgG anti-HAV in the absence of IgM anti-HAV reflects immunity either from prior infection or from vaccination.

Table 43.1 Diagnostic testing for viral hepatitis

Type	Diagnostic tests	Comments
Hepatitis A virus (HAV)	IgM anti-HAV	Acute infection
	IgG anti-HAV	Resolved infection, immunity
Hepatitis B virus (HBV)	HBsAg	Indicates infection
	IgM anti-HBc	Acute infection
	HBeAg, HBV DNA	Indicates replication
	Anti-HBs	Indicates immunity
	IgG anti-HBc	Current or prior infection
Hepatitis C virus (HCV)	Anti-HCV	Indicates infection
	HCV RNA	Indicates infection/viremia
Hepatits D virus (HDV)	IgM anti-HDV	IgM anti-HBc positive indicates coinfection
	Anti-HDV	IgG anti-HBc positive indicates superinfection
		Indicates infection
	HDV RNA and HDV antigen	Research tools at present
Hepatitis E virus (HEV)	IgM anti-HEV	Acute infection
	IgG anti-HEV	Resolved infection
EBV	EBV IgM and PCR	Indicates infection
CMV	CMV IgM and PCR	Indicates infection

Abbreviations: EBV = Epstein–Barr virus; CMV = cytomegalovirus.

Therapy

Acute HAV infection is self-limited without chronic sequelae. About 85% of acute HAV cases have clinical and biochemical recovery within 3 months and nearly all have complete recovery by 6 months from the time of infection. Treatment is largely supportive and includes adequate nutrition, hydration, avoidance of hepatotoxic medications, steroids, and abstinence from alcohol (Table 43.2). Because acute HAV is more likely to lead to hepatocellular failure in adults, especially in those with underlying chronic liver disease, these patients require close follow-up until symptoms resolve.

Universal precautions to prevent transmission among close contacts, good personal hygienes and immunization are recommended. Passive prophylaxis with intramuscular polyclonal immunoglobulin before and after exposure is safe and efficacious. Pre-exposure prophylaxis with immunoglobulin should be reserved for nonimmune patients at risk for HAV who are allergic to HAV vaccine. Postexposure prophylaxis with immune globulin is recommended for the following high-risk groups in whom protective antibody titers should be generated quickly: (1) close household and sexual contacts of an index patient with documented acute HAV, (2) staff and patients of institutions for the developmentally disabled with outbreaks of HAV, (3) children and staff of day-care centers with an index case

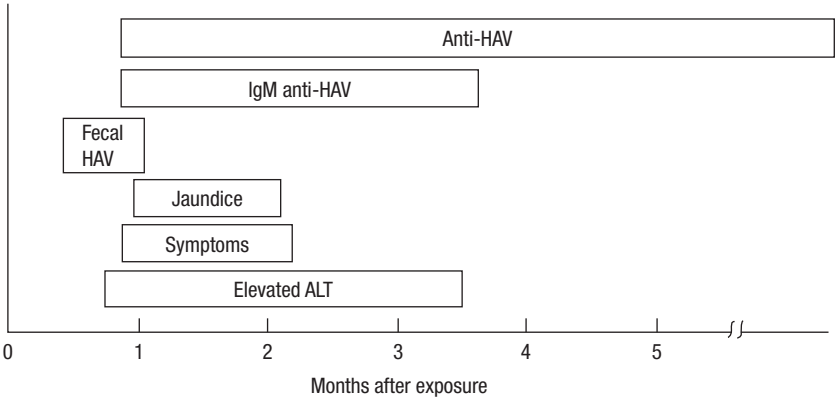

Figure 43.1 Course of acute hepatitis A. HAV = hepatitis A virus; ALT = alanine aminotransferase; anti-HAV = antibody to hepatitis A virus. (Adapted from Martin P, Friedman LS, Dienstag JL. Diagnostic approach to viral hepatitis. In: Thomas HC, Zuckerman AJ, eds. *Viral Hepatitis*. Edinburgh: Churchill Livingstone; 1993:393–409.)

Table 43.2 Therapy of acute viral hepatitis

Type	Major focus	Comments
Hepatitis A	Symptomatic therapy	Recognition of ALF and promptly refer to transplant center
Hepatitis B	Symptomatic therapy. Oral agents for acute severe HBV	Observe for ALF
Hepatitis C	Pegylated interferon +/− ribavirin	Treatment efficacious in acute HCV
Hepatitis D	Consider anti-HBV agents in severe cases Prevention: HBV vaccine	Clinically more severe than HBV alone
Hepatitis E	Ribavirin monotherapy is effective	FHF common in pregnant women. Transmission can be enteric or zoonotic. Can become chronic in immunocompromised
EBV	Symptomatic therapy	Risk factor for PTLD
CMV	Immunocompetent: monitor Immunocompromised: ganciclovir, forscarnet, or cidofovir	

Abbreviations: EBV = Epstein–Barr virus; CMV = cytomegalovirus; FHF = fulminant hepatic failure; PTLD = post-transplantation lymphoproliferative disease.

of HAV, (4) those exposed to protracted community outbreaks, and (5) travelers and military personnel who plan to visit countries endemic for HAV. Active immunization with an inactivated HAV vaccine has been available in the United States since 1995. Recent literature suggests that the efficacy and effectiveness of HAV vaccine is superior to passive immunization even for post-exposure prophylaxis.

HEPATITIS B VIRUS

Hepatitis B virus (HBV) is the most common cause of chronic viral hepatitis worldwide and is also a major cause of acute viral hepatitis, especially in developing nations. There are an estimated 400 million people chronically infected with HBV worldwide. In the Far East and sub-Saharan Africa, up to 20% of the population has serologic evidence of current or prior HBV infection. In the United States, although HBV infection is less frequent, the prevalence of chronic HBV is much higher in certain immigrant communities, including Asian Americans. After acute HBV infection, the risk of chronic infection varies inversely with age. Thus, children younger than the age of 5 have a high risk of chronicity after acute HBV infection, whereas an immunocompetent adult has $\leq$5% likelihood.

HBV is a DNA virus transmitted predominantly by a parenteral route or intimate contact with an infected subject. In Asia and other hyperendemic areas, vertical transmission is an important transmission route, whereas sexual and percutaneous transmission predominates in the Western world. The incubation period is 45 to 160 days. The typical course of a patient with acute HBV infection is illustrated in Figure 43.2. Typically, elevated alanine aminotransferase (ALT) levels and clinical symptoms appear earlier than jaundice. However, not all patients with acute HBV infection develop jaundice. About 70% of patients with acute HBV infection develop subclinical or anicteric hepatitis and only 30% develop icteric hepatitis. Paradoxically, the patient with anicteric and clinically less severe acute HBV infection is more likely to become chronically infected than the individual with more symptomatic acute infection because a brisk immune response causes more hepatic dysfunction but also a greater likelihood of ultimate clearance of HBV infection. The symptomatic patient should be reassured that full recovery is likely but should be warned to report back if symptoms such as deepening jaundice, severe nausea, or somnolence develop because these symptoms may herald acute hepatic failure. Acute liver failure occurs in approximately 0.1% to 0.5% of acute HBV cases. Like acute HAV, acute infection may be more severe in patients with underlying chronic liver disease.

The diagnosis of acute HBV hepatitis is made by detection of hepatitis B surface antigen (HBsAg) and IgM anti-hepatitis B core antibody (anti-HBc IgM) in the serum (Table 43.3). Resolution of HBV infection is characterized by loss of HBsAg. Development of the corresponding neutralizing antibody to HBsAg, anti-HBs, indicates resolution of infection. IgM anti-HBc declines and becomes undetectable whereas IgG ("total") anti-hepatitis B core antibody (anti-HBc IgG) persists after resolution of infection. Detection of IgG anti-HBc distinguishes immunity-acquired from prior infection rather than vaccination in a patient with detectable anti-HBs.

Individuals who are immunocompromised or have another chronic condition such as renal failure are more likely to develop chronic infection. Children younger than 5 years and the

elderly also have a greater likelihood of becoming chronically infected. The absence of a brisk immune response during acute HBV infection, implied by a relative absence of symptoms, with modest aminotransferase elevation in an anicteric patient, indicates that infection is more likely to become chronic. Chronic HBV infection is suggested by HBsAg positivity for longer than 6 months with absence of IgM anti-HBc. However, in severe reactivation of chronic HBV infection (spontaneous or iatrogenic due to administration of corticosteroids or chemotherapy to an infected patient), IgM anti-HBc may reappear in serum although usually in low titer. The presence of HBeAg and HBV DNA in the serum suggests ongoing active viral (wild type) replication or "high replicative state" in patients with chronic infection. The absence of these markers of active replication in a chronically infected patient with no clinical evidence of liver disease is referred to as the nonreplicative or inactive carrier state.

Table 43.3 Initial serologic workup of suspected acute hepatitis

IgM anti-HAV
HBsAg (if positive, then IgM anti-HBc, HBV DNA, HBeAg)
Anti-HCV antibody (if positive, then HCV RNA)
Consider testing for HEV, HSV, CMV and EBV if A, B, and C tests are negative. Testing for other viruses is at clinician's discretion

Therapy

Interferon-α, pegylated interferon-α 2a, lamivudine, adefovir dipivoxil, entecavir, telbivudine, and tenofovir are currently approved therapies in the United States for the treatment of chronic HBV infection. Interferon, entecavir, and tenofovir are the currently recommended first-line agents in the treatment of chronic HBV infection. Interferon's side effects have limited its use with the introduction of well-tolerated oral agents. Given the high rate of spontaneous resolution of acute HBV in otherwise healthy adults, antiviral therapy is generally not recommended. Treatment with oral agents should be initiated in acute severe cases of HBV or in those who are immunosuppressed. Early referral to a transplant center is highly recommended as some patients can progress to acute liver failure manifested by hepatic encephalopathy, worsening coagulopathy, or ascites. Post-transplant outcomes for HBV have been favorable. There has been a very low rate of recurrence of viral infection with current immunoprophylaxis regimens by using an oral antiviral agent with high-dose hepatitis B immunoglobulin (HBIG). However, indefinite HBIG therapy is both cumbersome and expensive. Accordingly, transplant programs are evaluating the use of alternative schedules of HBIG administration and combinations of antiviral agents to prevent allograft reinfection. Therapy for chronic HBV infection is discussed in Chapter 44, Chronic hepatitis.

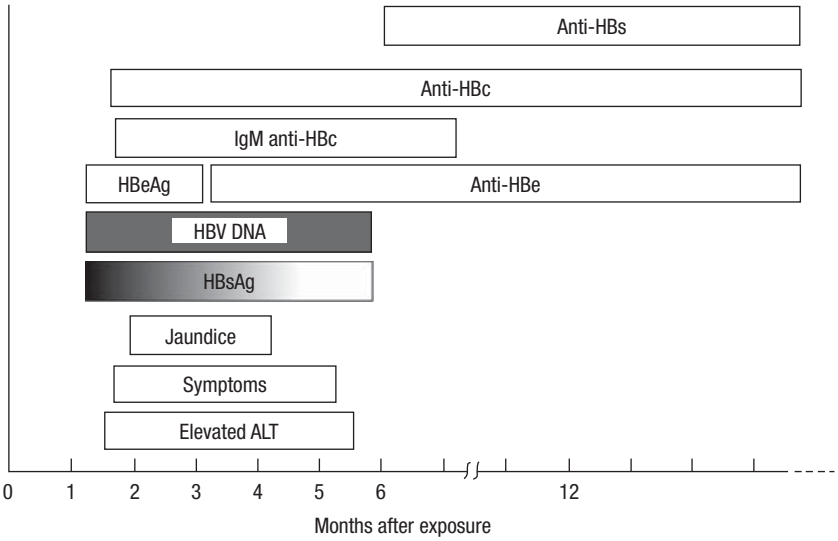

Figure 43.2 Typical course of acute hepatitis B. HBsAg = hepatitis B surface antigen; ALT = alanine aminotransferase; HBV DNA = hepatitis B virus DNA; HBeAg = hepatitis B e antigen; Anti-HBc = antibody to hepatitis B core antigen; Anti-HBe = antibody to hepatitis B e antigen; Anti-HBs = antibody to hepatitis B surface antigen. (Adapted from Martin P, Friedman LS, Dienstag JL. Diagnostic approach to viral hepatitis. In: Thomas HC, Zuckerman AJ, eds. *Viral Hepatitis*. Edinburgh: Churchill Livingstone; 1993:393–409.)

The highly effective recombinant HBV vaccine is recommended for newborns, infants, adolescents, healthcare workers, hemodialysis patients, household contacts, and sexual partners of HBV-infected individuals, international travelers to endemic areas, injection drug users, men who have sex with men or heterosexuals with multiple sexual partners, patients with chronic liver disease, and those who are potential organ transplant recipients. Postexposure prophylaxis should consist of a combination of HBV vaccination and passive protection with HBIG.

HEPATITIS C VIRUS

The hepatitis C virus (HCV) is a single-stranded RNA virus. It is estimated that about 170 million people in the world are chronically infected with HCV. Acute HCV is typically subclinical, with fewer than 25% of patients developing jaundice, and thus acute illness usually escapes medical attention. If symptomatic, acute HCV is less likely to lead to chronicity. HCV infection is usually transmitted parenterally. In the past, this was often by contaminated blood products. Now, most HCV infection is contracted by sharing contaminated needles among intravenous drug abusers or by other percutaneous or high-risk practices such as tattooing or possibly intranasal cocaine use, although the latter is controversial. Sexual and maternal–neonatal transmission can occur but are generally less efficient routes of transmission although maternal human immunodeficiency virus (HIV) coinfection appears to increase the risk of perinatal transmission. Sexual transmission of HCV is also recognized in men who have sex with men. Acute HCV infection results in a high rate of chronicity, up to 85% in some series.

Figure 43.3 illustrates the course of a patient with acute HCV infection progressing to chronicity. The incubation period is 14 to 180 days, after which elevation of ALT levels occurs and symptoms may appear, although, as noted, the acute illness is frequently subclinical. Fulminant hepatic failure due to acute HCV infection is very rare but may be more common in patients with underlying chronic HBV infection.

Routine diagnosis is made by detection of antibodies in serum to HCV (anti-HCV) by enzyme-linked immunosorbent assay (ELISA) testing. The recombinant immunoblot assay (RIBA) test was formerly used to enhance specificity as a supplemental test in ELISA-positive individuals. However, it has generally been supplanted by polymerase chain reaction (PCR) testing to confirm viremia. Fluctuating ALT levels are characteristic of chronic HCV infection. Perhaps a fifth of chronically infected patients have ALT levels regarded as within the normal range, although this reflects a lack of sensitivity of aminotransferases in detecting lesser degrees of necroinflammatory activity in the liver rather than an absence of liver injury. PCR techniques vary in their sensitivity in detecting HCV RNA. The more sensitive transcription-mediated amplification (TMA) technique can detect even minute quantities of HCV RNA (0.9–5.2 copies/mL).

Therapy

Acute HCV infection is most typically recognized in a healthcare worker after a needle-stick injury or rarely in someone who develops a hepatitis flare. A small subset of patients, especially those with favorable IL28B genotype (C/C), can have

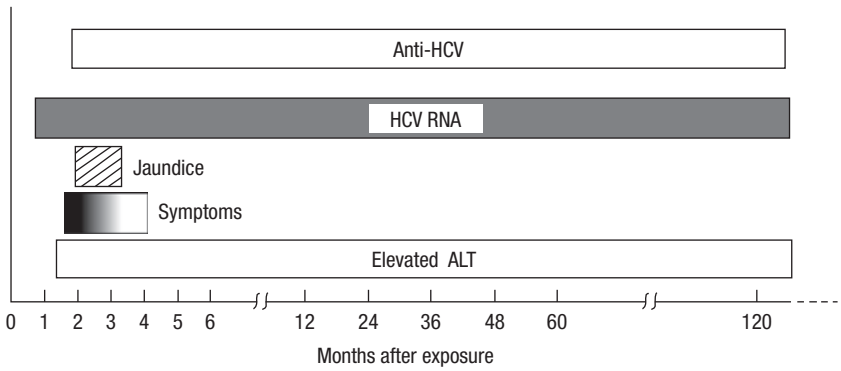

Figure 43.3 Typical course of acute hepatitis C progressing to chronic hepatitis C. HCV = hepatitis C virus; anti-HCV = antibody to the hepatitis C virus. (Adapted from Martin P, Friedman LS, Dienstag JL. Diagnostic approach to viral hepatitis. In: Thomas HC, Zuckerman AJ, eds. *Viral Hepatitis*. Edinburgh: Churchill Livingstone, 1993:393–409.)

spontaneous clearance of the virus. Therefore acute hepatitis C patients should be closely monitored and those with persistent viremia beyond 12 weeks should be offered treatment. It is important to note that treatment of HCV during the acute phase is highly effective and results in a sustained virologic response in up to 85% of treated patients. Although ribavirin is usually not required in the treatment of acute HCV, it should be added in patients who do not respond to 3 months of interferon monotherapy. It has been reported that delaying antiviral therapy for 2 to 4 months after acute HCV infection does not compromise efficacy. This delay allows spontaneous resolution of HCV without embarking on unnecessary treatment with interferon. Therapy of chronic HCV infection is discussed in more detail in Chapter 44, Chronic hepatitis.

An HCV vaccine is not yet available because of the virus' heterogeneity and the lack of seroprotective capability of HCV antibodies, and until recently, lack of a cell culture system. There is no benefit from gamma globulin administration following a needle-stick exposure to HCV. In the healthcare setting, universal precautions are mandatory because the risk of HCV transmission to healthcare workers is substantial, averaging about 3% particularly with hollow-bore needles. Routine screening by blood banks for HCV has reduced the risk of transmission by transfusion to a negligible level. Following liver transplant, HCV reinfection of the transplanted liver occurs in almost all the patients, with a subset of patients developing early severe recurrence of viral infection.

HEPATITIS D VIRUS

The hepatitis delta virus (HDV) is an incomplete RNA virus and depends on HBsAg to complete its replicative cycle. It is estimated that 5% of chronic HBV patients in the world are coinfected with HDV. HDV is transmitted parenterally in the developed countries, whereas in other areas of high endemicity (Mediterranean basin), the transmission is through close contact. Immigration from highly endemic areas is implicated in the recent increase in prevalence in Western Europe. HDV may be transmitted simultaneously with HBV (coinfection) or acquired in chronic HBV carriers (superinfection). Most cases of coinfection are self-limited but patients are more likely to develop fulminant hepatitis than with HBV monoinfection. If HDV is acquired by superinfection, the infection tends to become chronic with higher rates of progression to cirrhosis than with HBV alone. HBV viral load is typically suppressed by active HDV infection.

The diagnosis of HDV coinfection is made if serum IgM anti-HDV, HBsAg, and IgM anti-HBc are simultaneously present in serum. HDV superinfection is denoted by IgM anti-HDV, HBsAg, and IgG anti-HBc with absent IgM anti-HBc. During the acute infection, HDV serologies are often insensitive and repeat testing may be required in cases with high clinical suspicion (see Table 43.1). HDAg (direct immunofluorescence) or HDV RNA (reverse transcriptase assay) testing in the serum or on liver tissue can be performed but these techniques are not widely available for clinical use.

Therapy

There is no specific treatment for acute HDV infection as most patients have spontaneous resolution after the flare. Interferon is the only effective therapy against HDV but it is contraindicated during an acute flare as it can exacerbate the ALT flare, leading to acute hepatic failure. Antiviral agents against hepatitis B are generally not useful as HBV is usually suppressed but can be tried in patients who are developing fulminant liver failure. Liver transplantation is the only option for patients with acute liver failure from HDV coinfection. Liver transplant outcomes are better in patients with HDV than in those transplanted for HCV. Control of HBV with antiviral agents plus or minus HBIG prevents HDV recurrence in the graft. Vaccination against HBV prevents HDV infection.

HEPATITIS E VIRUS

The hepatitis E virus (HEV) is an RNA virus first identified in 1980 as an enterically transmitted hepatitis virus similar to HAV. Currently, there are four genotypes identified of which genotypes 1 and 2 are predominant in developing countries and have enteric transmission, whereas genotypes 3 and 4 are predominant in developed countries and have zoonotic transmission (consumption of contaminated uncooked meat, especially pork). The incubation period is 15 to 60 days with high infection rates in adults between the ages of 15 and 40. Antibodies against HEV have been found in up to 20% of the general population in developed countries and may account for 3% of cases of putative drug-induced liver injury presenting with acute liver failure.

HEV infection is usually acute and self-limited but chronic HEV progressing to cirrhosis has

been increasingly recognized especially in genotype 3 and immunocompromised subjects. A unique feature of this disease in developing nations is that fulminant hepatic failure occurs more frequently in pregnant women during the third trimester and carries a high mortality rate (15%–25%). HEV is diagnosed by IgM and IgG anti-HEV antibodies, and HEV RNA by PCR.

Therapy

Acute HEV infection is self-limited and treatment is mainly supportive. Pregnant women should not travel to endemic areas. There are no standard guidelines to treat HEV infection. Acute severe hepatitis can be treated with ribavirin monotherapy (dose 600 mg to 1000 mg/day) for 3 to 6 months, which can result in rapid clinical improvement. Ribavirin is teratogenic. Interferon is contraindicated in severe hepatitis as it can exacerbate the ALT flare, leading to fulminant hepatic failure. Chronic HEV in immunosuppressed transplant recipients can be treated with either lowering of immunosuppression, ribavirin monotherapy or pegylated interferon monotherapy or a combination of the above. Treatment decisions are usually individualized based on the patient's condition and assessment of therapeutic risks, especially in the post-transplant setting. HEV vaccines are currently in the developmental phases with promising preliminary results.

HERPES SIMPLEX VIRUS

Herpes simplex virus (HSV) is a capsulated double-stranded DNA virus and its infection can rarely lead to acute liver failure (1%–2% of all acute liver failure cases). Acute severe hepatitis is associated with high mortality rates of 75% to 90% and is commonly seen in immunocompromised patients, pregnant women (late trimester), neonates, and rarely in immunocompetent individuals.

Clinical features of HSV can vary from mild asymptomatic anicteric hepatitis to fulminant hepatic failure or severe HSV sepsis (pneumonitis, esophagitis, encephalitis) resulting in multiorgan failure. New-borns presenting with systemic infection called herpes neonatorum have high rates of brain injury and 25% mortality rate. Mucocutaneous lesions are found only in 50% of the cases and their absence often results in diagnostic delay. Most cases of acute HSV hepatitis occur as a result of acute infection rather than viral reactivation and fever, flu-like symptoms, and leukopenia can be present. Serologies are usually nondiagnostic and thus diagnosis rests on detection of viremia by HSV PCR and/or liver biopsy. Presence of viral Cowdry type A nuclear inclusion bodies, HSV immunohistochemical stains, HSV PCR, and electron microscopy on the liver biopsy aid in confirming the diagnosis.

Early treatment with high-dose acyclovir (10 mg/kg intravenous thrice daily) is highly effective. Delay in treatment can result in lowered efficacy and thus empiric treatment is recommended in cases with typical features of HSV hepatitis. Foscarnet can be used if there is concern with acyclovir resistance. Patients with fulminant liver failure should be carefully evaluated for liver transplantation as the 1 year post-transplant survival rate is around 43%, usually due to disseminated and uncontrolled HSV infection. Indefinite antiviral therapy is usually required to prevent recurrence following spontaneous resolution or transplant.

EPSTEIN–BARR VIRUS

EBV is the causative agent for infectious mononucleosis and causes asymptomatic liver enzyme and lactate dehydrogenase elevations up to three times the upper limits of normal in 80% to 90% of cases. Clinical manifestations include fever, pharyngitis, lymphadenopathy, abdominal pain, hepatosplenomegaly, and, rarely, jaundice. The serum aminotransferases typically rise over 1 to 2 weeks, and in most patients the disease is self-limited with resolution of symptoms and normalization of enzymes over the subsequent 4 to 6 weeks. Severe hepatitis and fulminant hepatic failure are rare but have been reported.

Leukocytosis (predominance of lymphocytes and monocytes) and mild thrombocytopenia is common. EBV IgM antibodies peak early and can persist for months, after which EBV IgG develops. Although the Monospot is sensitive in detecting heterophile antibodies, it is not specific for EBV infection. EBV DNA quantification can be accomplished through PCR assays on blood or plasma. Liver biopsy is not usually indicated although *in situ* hybridization or PCR of the biopsy sample may be used to confirm the diagnosis. Treatment is largely supportive as no specific treatment exists. Acyclovir has been used without effect on symptoms or outcome. EBV may rarely cause chronic infection in immunocompetent patients. EBV infection is an important factor in the development of post-transplantation

lymphoproliferative disease (PTLD) in transplant recipients.

CYTOMEGALOVIRUS

CMV infection frequently involves the liver, most commonly as an asymptomatic elevation of serum transaminases. It can be a result of a primary infection or reactivation of a latent infection in an immunocompromised host. In immunocompetent children and adults, primary CMV infection is usually subclinical but may cause an illness that can mimic mononucleosis. The clinical course is typically mild and self-limited, but CMV has been implicated in hepatic granulomata, cholestatic hepatitis (mimicking primary sclerosing cholangitis), and even rare cases of fatal hepatic necrosis. CMV can be severe and even life-threatening in patients with impaired cellular immunity, due to disseminated infection.

Antibody testing is of low utility in immunocompromised patients and therefore CMV PCR is the most reliable and specific diagnostic test. Liver biopsy may be indicated and confirmatory in an immunocompromised patient or a transplant recipient when the characteristic multinucleated giant cells and owl eye inclusions are identified. No definite therapy is required in immunocompetent patients with mild CMV infection. In immunocompromised patients, effective therapies include ganciclovir or alternatively foscarnet or cidofovir in ganciclovir failure. Therapy should be continued until patients become aviremic and preferably maintained during the intense immunosuppressive period.

PARVOVIRUS B19

Human parvovirus B19 is a small nonenveloped single-stranded DNA virus which is a rare (probably underdiagnosed) cause of acute hepatitis and liver failure in immunocompetent individuals. It is a common infection of childhood called erythema infectiosum or fifth disease and up to 50% of adolescents develop parvovirus antibodies by age 15. The virus is transmitted via respiratory droplets, blood products, and solid organ transplantation. Adults can present with acute upper respiratory viral syndrome, athropathy, and varying severity of bone marrow suppression and liver injury. Rare hematologic manifestations include pure red cell aplasia, pancytopenia, and hematopoietic failure which are thought to be due to viral interaction with P-antigen. Although most case reports showed a lesser degree of elevation of transaminases (<2000), levels of ALT greater than 9000 have also been reported. The pathogenic mechanisms involved in liver injury are unclear but may be due to caspase-mediated apoptosis from direct viral invasion. Diagnostic workup includes serum parvovirus B19 IgM, IgG, DNA, and liver biopsy. Bone marrow biopsy can show characteristic red cell aplasia and giant pronormoblasts. There are no standard treatment guidelines but there are several case reports reporting the use of supportive treatment, intravenous immunoglobulin (IVIG), tacrolimus, cyclosporine, mycophenolate mofetil, azathioprine, steroids and plasmapheresis with varying outcomes. Patients with fulminant hepatic failure require liver transplantation although there are limited data on the outcomes and hematopoietic recovery post-transplant. Recurrence of pure red cell aplasia after transplantation is approximately 10% and prolonged courses of IVIG appear to be beneficial.

MISCELLANEOUS VIRUSES

Non-hepatotropic viruses such as hepatitis G (HGV), TTV, human herpesvirus (HHV-6, HHV-8), varicella zoster virus (VZV), adenovirus, and coronavirus can all cause acute hepatic inflammation resulting in mild to modest increase in transaminases. HGV, also known as GBV-C, is a single-stranded RNA virus which is mainly transmitted parenterally and has some genomic similarity to HCV. HGV is lymphotropic but not hepatotropic and thus some authors debate its nomenclature as a hepatitis virus. HGV coinfection in HIV-positive patients is associated with favorable outcomes, including lower levels of HIV viremia, higher CD4 count, better response to antiretroviral therapy, lower transmission rates, and 2.5 fold reduction in mortality compared to those who are not coinfected with HGV. TTV is a single-stranded DNA virus first isolated in 1997 as a cause of post-transfusion hepatitis but current data suggest that TTV does not play a significant role in the genesis of acute or chronic liver disease. HHV-6 is associated with hepatic artery thrombosis, encephalitis, and sepsis and HHV-8 is associated with development of Kaposi's sarcoma especially in immunocompromised transplant recipients. Similar to HGV and TTV, other viruses such as Sanban, Yonban, and SEN viruses do not cause clinical hepatitis and their role in human pathogenesis is controversial.

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44. Chronic hepatitis

Michelle E. Freshman and Lawrence S. Friedman

Chronic hepatitis is defined as necroinflammation of the liver of more than 3 to 6 months' duration, demonstrated by persistently elevated serum aminotransferase levels and associated with characteristic histologic findings. The causes of chronic hepatitis include hepatitis B, C, and D viruses (HBV, HCV, and HDV) as well as noninfectious disorders, including nonalcoholic steatohepatitis (NASH), autoimmune hepatitis, hepatitis following medication exposure (such as isoniazid or nitrofurantoin), Wilson's disease, α_1-antitrypsin deficiency, and, infrequently, celiac disease. Hepatitis A virus does not cause chronic hepatitis, but hepatitis E virus may rarely lead to chronic hepatitis in immunosuppressed persons or transplant recipients. Chronic hepatitis is characterized on the basis of etiology; grade of portal, periportal, and lobular inflammation (minimal, mild, moderate, or severe); and stage of fibrosis (none, mild, moderate, severe, cirrhosis).

In the absence of advanced cirrhosis, patients are often asymptomatic or have mild, nonspecific symptoms. Infection caused by HBV may be associated with glomerulonephritis and polyarteritis nodosa. HCV is a pathogenetic factor in mixed cryoglobulinemia and membranoproliferative glomerulonephritis and may be related to lichen planus, autoimmune thyroiditis, lymphocytic sialadenitis, idiopathic pulmonary fibrosis, sporadic porphyria cutanea tarda, and monoclonal gammopathies. HCV infection confers a 20% to 30% increased risk of non-Hodgkin's lymphoma and may induce insulin resistance (which in turn increases the risk of hepatic fibrosis); moreover, the risk of type 2 diabetes mellitus is increased in persons with chronic hepatitis C. Hepatic steatosis is a particular feature of infection with HCV genotype 3 and may also occur in patients infected with other HCV genotypes who have risk factors for fatty liver. On the other hand, chronic HCV infection is associated with a decrease in serum cholesterol and low-density lipoprotein levels.

CHRONIC HEPATITIS B AND D

Chronic hepatitis B affects nearly 400 million people worldwide (Figure 44.1) and up to 2.2 million people (predominantly male) in the United States. Overall, 2 billion people have been infected, notably in endemic areas of Asia and sub-Saharan Africa. Perinatal transmission of HBV results in chronic hepatitis in 90% of cases compared with 60% in those who acquire HBV after infancy but by age 5, and 6% in those who acquire the infection after age 5. In adults, HBV infection is often acquired by percutaneous or sexual transmission. Of persons with chronic hepatitis B, an estimated 700 000 annually are estimated to die prematurely due to cirrhosis or hepatocellular carcinoma. Since 1990, the incidence of HBV infection in the United States has decreased from 8.5 to 1.5 cases per 100 000 population because of universal HBV vaccination.

Chronic hepatitis B may be recognized as a continuation of acute hepatitis B (Table 44.1) or as a result of repeated detection of hepatitis B surface antigen (HBsAg) in serum, often with elevated aminotransferase levels. Four phases of HBV infection are recognized (Table 44.2). In the *immune tolerant phase*, hepatitis B e antigen (HBeAg) and HBV DNA are present in serum and indicate active viral replication, but serum aminotransferase levels are normal, with little necroinflammation in the liver. This phase is common in infants and young children whose immature immune system fails to mount an immune response to HBV.

Those in the immune tolerant phase, as well as those who acquire HBV infection after early childhood, may enter an *immune clearance phase*, associated with aminotransferase elevations and necroinflammation in the liver, with a risk of progression to cirrhosis (at a rate of 2–5.5% per year) and of hepatocellular carcinoma (at a rate of >2% per year in those with cirrhosis). Low-level immunoglobulin M antibody to hepatitis B core

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Table 44.1 Interpretation of serologic tests for hepatitis B virus (HBV) infection

	Susceptible	Immune due to vaccination	Immune due to natural infection	Acute infection	Chronic infection	Various interpretations[a]
HBsAg	−	−	−	+	+	−
Anti-HBc	−	−	+	+	+	+
IgM anti-HBc	−	−	−	+	−[b]	−
HBeAg	−	−	−	+	±	−
Anti-HBe	−	−	±	−	±	±
Anti-HBs	−	+	+	−	−	−

[a] 1. Recovering from acute HBV infection.
2. Chronically infected with an undetectable level of HBsAg in serum.
3. Susceptible with a false-positive anti-HBc result.
4. Distantly immune and the test is not sensitive enough to detect a very low viral level of anti-HBs in serum.

[b] IgM anti-HBc may be positive (in low titers) in some persons with chronic hepatitis B.

Anti-HBc = antibody to hepatitis B core antigen; anti-HBe = antibody to hepatitis B e antigen; anti-HBs = antibody to hepatitis B surface antigen; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; IgM anti-HBc = IgM antibody to hepatitis B core antigen.

Adapted from http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/hepb.pdf.

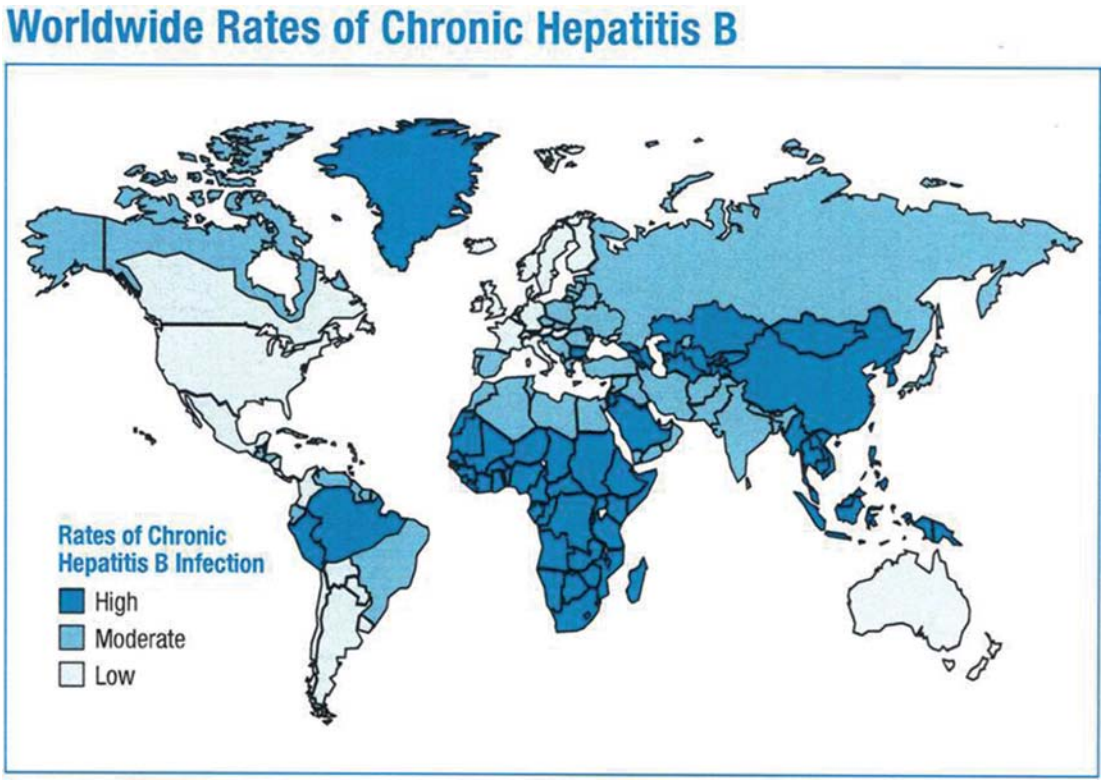

Figure 44.1 World map showing the prevalence of the chronic hepatitis B carrier state in areas of low (very light blue, <2%), medium (light blue, 2–7%), and high (dark blue, ≥8%) prevalence. (Adapted from the Centers For Disease Control and Prevention website, http://www.cdc.gov/hepatitis/HBV/PDFs/HepBAtRisk.pdf. [Accessed April 29, 2013.])

Table 44.2 Four phases of chronic hepatitis B virus (HBV) infection and associated biochemical, serologic, and histologic findings

Phase	ALT	HBeAg	Anti-HBe	HBV DNA (IU/mL)	Liver histology	Natural history
Immune tolerance	Normal	+	−	≥20 000	Minimal inflammation	Low risk of progression to advanced liver disease
Immune clearance	Elevated (fluctuating)	+	+/−	≥20 000 (fluctuating)	Variable inflammation +/− fibrosis	Associated with hepatitis flares
Inactive carrier state	Normal	−	+	<2000	Minimal inflammation and liver damage	Low risk of advanced liver disease HBsAg loss in 1% per year; 10–20% have reactivation of HBV replication after many years
Reactivated chronic hepatitis B	Elevated	−	+	2000 – 20000 (may be higher)	Inflammation and often significant fibrosis	High risk of progression to advanced liver disease

ALT = serum alanine aminotransferase level; anti-HBe = antibody to hepatitis B e antigen; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; IU = international units.

Adapted from Guirgis M, Zekry A. Natural history of chronic hepatitis B virus infection. In: Matthews G, Robotin M, eds. *B Positive–All You Wanted to Know About Hepatitis B: A Guide for Primary Care Providers.* Australasian Society for HIV Medicine (ASHM): Paragon Print; 2008: 42.

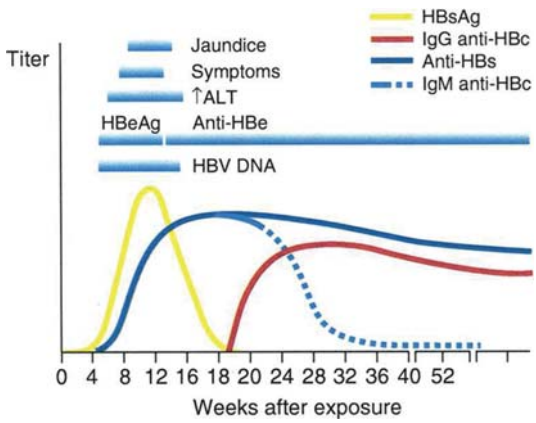

Figure 44.2 Typical serologic course of chronic hepatitis B virus infection. (Adapted from the Centers For Disease Control and Prevention website, Viral Hepatitis B, Educational Materials, CDC Viral Hepatitis Brochures/Posters, Hepatitis B 101, slide 10/20. [Accessed in 2006.])

antigen (IgM anti-HBc) is present in serum in about 70% of such persons.

Patients enter the *inactive HBsAg carrier state* when biochemical improvement follows immune clearance. This improvement coincides with sequential disappearance of HBeAg and reduced HBV DNA levels (<20 000 international units [IU]/mL, or $<10^5$ copies/mL) in serum, appearance of antibody to hepatitis B e antigen (anti-HBe), and integration of the HBV genome into the host genome in infected hepatocytes (Figure 44.2). Patients in this phase are at a low risk for cirrhosis (if it has not already developed) and hepatocellular carcinoma, and those with persistently normal serum aminotransferase levels infrequently have histologically active liver disease.

The *reactivated chronic hepatitis B phase* may result from infection by a pre-core mutant of HBV or spontaneous mutation of the pre-core or core promoter region of the HBV genome, with lack of synthesis of HBeAg, during the course of chronic hepatitis caused by wild-type HBV (often during the inactive HBsAg carrier phase). So-called HBeAg-negative chronic hepatitis B accounts for 10% of cases of chronic hepatitis B in the United States, up to 50% in Southeast Asia, and up to 90% in Mediterranean countries, reflecting in part differences in the frequencies of HBV genotypes A through J. In reactivated chronic hepatitis B, there is a rise in serum HBV DNA levels and possible progression to cirrhosis (at a rate of 8%–10% per year), particularly when additional mutations in the core gene of HBV are present. Risk factors for reactivation include male sex, advanced age, and HBV genotype C.

In patients with either HBeAg-positive or HBeAg-negative chronic hepatitis B, the risk of cirrhosis and of hepatocellular carcinoma correlates with the serum HBV DNA level. Other risk factors include advanced age, male sex, alcohol use, cigarette smoking, and coinfection with HCV or HDV or with human immunodeficiency virus (HIV) coinfection in association with a low CD4 count.

HDV (also called the delta agent) is a defective RNA agent that only infects (either concurrently or sequentially) persons also infected with HBV. New cases of HDV infection are now infrequent in the United States and are seen primarily in

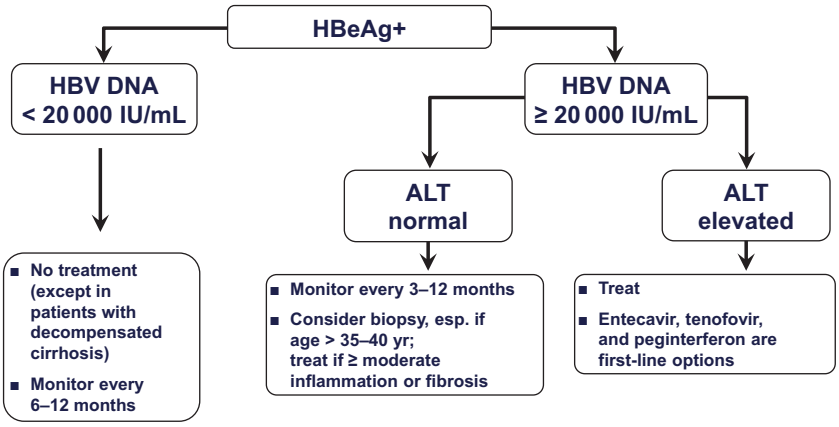

Figure 44.3 Suggested treatment algorithm for HBeAg-positive patients with compensated chronic hepatitis B virus (HBV). (Adapted from Keeffe EB, Dieterich DT, Han SH, *et al.* A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: an update. *Clin Gastroenterol Hepatol.* 2006; 4:936–962, with permission.)

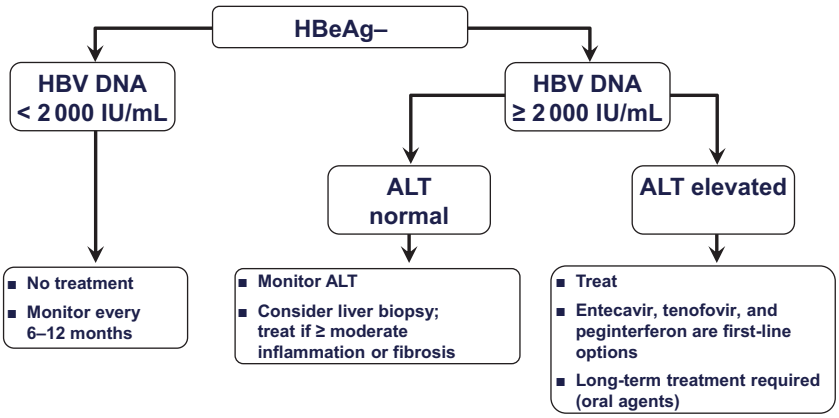

Figure 44.4 Suggested treatment algorithm for HBeAg-negative patients with compensated chronic hepatitis B virus (HBV). (Adapted from Keeffe EB, Dieterich DT, Han SH, *et al.* A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: an update. *Clin Gastroenterol Hepatol*. 2006;4:936–962, with permission.)

immigrants from endemic areas, including Africa, Central Asia, Eastern Europe, and the Amazon region of Brazil. Most cases seen today are usually from cohorts infected years ago who survived active infection and now have cirrhosis. Acute hepatitis D infection superimposed on chronic HBV infection may result in severe chronic hepatitis, which may progress rapidly to cirrhosis and may be fatal. Patients with long-standing chronic hepatitis D and B often have inactive cirrhosis and are at risk for decompensation and hepatocellular carcinoma. The diagnosis of hepatitis D is confirmed by detection of antibody to HDV or (where available) hepatitis D antigen or HDV RNA in serum.

Treatment

Patients with active HBV replication (HBeAg and HBV DNA [≥20 000 IU/mL, or $\geq 10^5$ copies/mL] in serum and elevated aminotransferase levels) may be treated with a nucleoside or nucleotide analog or with pegylated interferon (Figure 44.3). Nucleoside and nucleotide analogs are preferred because they are better tolerated and can be taken orally. For patients who are HBeAg negative, the threshold for treatment is a serum HBV DNA level of 2000 IU/mL, or 10^4 copies/mL (Figure 44.4). If the threshold HBV DNA level for treatment is met but the serum ALT level is normal, treatment may still be considered in patients over age 35 to 40 if a liver biopsy specimen demonstrates a fibrosis stage of 2 of 4 (moderate) or higher. Therapy is aimed at reducing and maintaining the serum HBV DNA level to the lowest possible level, thereby leading to normalization of the ALT level and histologic improvement. An additional goal in HBeAg-positive patients is seroconversion to anti-HBe, and a few responders eventually clear HBsAg (Figure 44.5 and Table 44.3). Although nucleoside and nucleotide analogs generally have been discontinued 6 to 12 months after HBeAg-to-anti-HBe

seroconversion, some patients (particularly those of Asian descent) serorevert to HBeAg after discontinuation and demonstrate a rise in HBV DNA levels and recurrence of hepatitis activity. They therefore require long-term therapy, which also is required when HBeAg-to-anti-HBe seroconversion does not occur. HBeAg-negative patients with chronic hepatitis B generally require long-term therapy as well.

The available nucleoside and nucleotide analogs – entecavir, tenofovir, lamivudine, adefovir, and telbivudine – differ in efficacy and rates of resistance (Table 44.4). HBeAg-positive patients, however, achieve an HBeAg-to-anti-HBe seroconversion rate of about 20% at 1 year, with higher rates after more prolonged therapy, regardless of the drug used (Table 44.5). The preferred, most potent, first-line oral agents are entecavir and tenofovir. Entecavir, a nucleoside analog, is rarely associated with resistance unless a patient is already resistant to lamivudine. Histologic improvement is observed in 70% of treated patients and suppression of HBV DNA in serum in up to 80%. Entecavir has been reported to cause lactic acidosis when used in patients with decompensated cirrhosis. Tenofovir, a nucleotide analog, also has substantial activity against HBV and is used as a first-line agent or when resistance to a nucleoside analog has developed. Like entecavir, tenofovir has a low rate of resistance when used as initial therapy. Long-term use may lead to an elevated serum creatinine level and reduced serum phosphate level (Fanconi-like syndrome) that are reversible with discontinuation of the drug.

Nucleoside and nucleotide analogs are well tolerated even in patients with decompensated cirrhosis (for whom the treatment threshold may be an HBV DNA level of <2000 IU/mL [$<10^4$ copies/mL]) and may be effective in patients with rapidly progressive hepatitis B ("fibrosing cholestatic hepatitis") following liver transplantation. Although therapy with these agents leads to biochemical, virologic, and histologic improvement in patients with HBeAg-negative chronic hepatitis B and baseline HBV DNA levels ≥2000 IU/mL ($\geq 10^4$ copies/mL), relapse is frequent when therapy is stopped, and long-term treatment is often required. The development of

Table 44.3 Goals of therapy for chronic hepatitis B virus (HBV) infection

Sustained suppression of HBV replication
HBV DNA undetectable in serum
HBeAg to anti-HBe seroconversion
HBsAg to anti-HBs seroconversion
Remission of liver disease
Normalization of serum ALT levels
Improvement in liver histology
Improvement in clinical outcome
Prevention of liver failure and hepatocellular carcinoma
Improved survival

ALT = alanine aminotransferase; anti-HBe = antibody to hepatitis B e antigen; anti-HBs = antibody to hepatitis B surface antigen hepatitis B virus; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen.

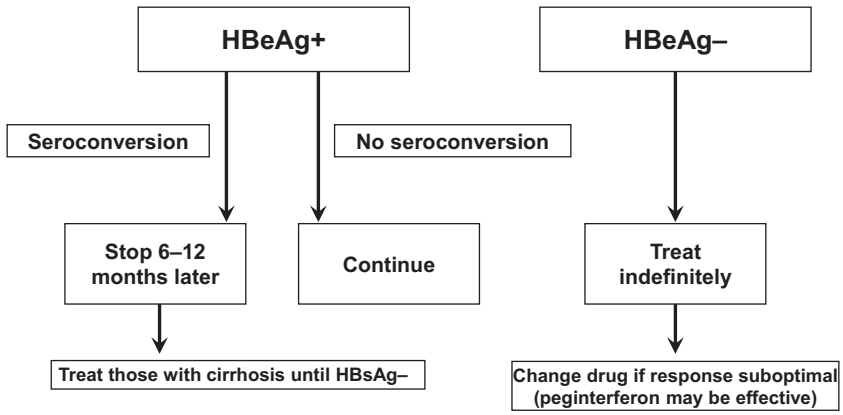

Figure 44.5 Treatment end points for patients with hepatitis B e antigen-positive (HBeAg+) and hepatitis B e antigen-negative (HBeAg–) chronic hepatitis B. (Adapted from Keeffe EB, Dieterich DT, Han SH, *et al.* A treatment algorithm for the management of chronic hepatitis B virus infection in the United States. *Clin Gastroenterol Hepatol*. 2004;2:87–106, and Marcellin P, Boyer N, Piratvisuth T, *et al.* Efficacy and safety of peginterferon alpha-2a (40KD) (Pegasys) in patients with chronic hepatitis B who had received prior treatment with nucleos(t)ide analogues–the Pegalam cohort. *J Hepatol*. 2006;44(Suppl 2):S187, with permission.) ALT = alanine aminotransferase; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; IU = international units; Peg-IFN = pegylated alfa interferon.

Table 44.4 Drugs used to treat chronic hepatitis B virus (HBV) infection and their advantages and disadvantages

Agent/dose	**Entecavir** (nucleoside analog) 0.5 mg daily (1.0 mg daily in lamuvidine-resistant patients)	**Tenofovir disoproxil** (nucleotide analog) 300 mg daily	**Lamivudine** (nucleoside analog) 100 mg daily	**Adefovir dipivoxil** (nucleotide analog) 10 mg daily	**Telbivudine** (nucleoside analog) 600 mg daily	**Peginterferon** alfa-2a 180 μg SC weekly for 48 weeks
Advantages	Oral Negligible side effects More potent than other oral agents; little resistance	Oral Negligible side effects More potent than other oral agents; little resistance	Oral Negligible side effects Has been used in pregnancy and prior to chemotherapy	Oral Negligible side effects Effective against lamivudine-resistant mutants	Oral Negligible side effects Effective against lamivudine-resistant mutants	Finite duration Durable response No resistant mutants HBsAg-to-anti-HBs seroconversion, common in responders
Disadvantages	Indefinite duration of therapy in incomplete responders Risk of lactic acidosis in patients with decompensated cirrhosis; hepatomegaly 10% cross-resistance with lamivudine; 94% undetectable at 5 years; for nucleoside-naïve patients, 1.2% resistance at 5 years	Indefinite duration of therapy in incomplete responders Renal toxicity in higher doses; caution in underlying kidney dysfunction; risk of Franconi syndrome Risk of lactic acidosis, hepatomegaly, gastrointestinal distress, rash, itching, osteopenia Low rate of resistance when used as initial therapy	Indefinite duration of therapy in incomplete responders Nausea, headaches; malaise and fatigue Risk of lactic acidosis, pancreatitis High rate of resistant mutants (>70% by 5 years); considered for hepatic decompensation or HCC	Indefinite duration of therapy in incomplete responders Risk of lactic acidosis, hepatomegaly Renal toxicity in higher doses; hypophosphatemia (Franconi-like syndrome); pancreatitis Risk of lower bone mineral density, SJS, TEN Resistant mutants (29% at 5 years); relatively weak agent when used alone; used as add-on to lamivudine or telbivudine	Indefinite duration of therapy in incomplete responders Risk of elevated CK level Some cross-resistance with lamivudine (up to 25% in HBeAg-positive and 11% in HBeAg-negative patients at 2 years)	Injection Side effects (see Table 44.6) Up to 60% sustainability of response over 4 years of therapy in patients with HBeAg-negative chronic hepatitis B; not appropriate for decompensated cirrhosis; 20–50% clearance of HDV

Abbreviations: CK = creatine kinase; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HCC = hepatocellular carcinoma; SJS = Stevens–Johnson syndrome; TEN = toxic epidermal necrolysis.

resistance occasionally results in hepatic decompensation. Sequential addition of a second antiviral agent is usually effective after resistance to the first agent has developed. Combined use of peginterferon and a nucleoside or nucleotide analog has not been shown convincingly to have a substantial advantage over the use of either type of drug alone.

To prevent reactivation, nucleoside analogs are recommended for inactive HBV carriers prior to the initiation of immunosuppressive therapy (including anti-tumor necrosis factor antibody therapy) or cancer chemotherapy and should be continued for at least 12 months after the therapy is completed. In patients infected with both HBV and HIV, antiretroviral therapy that includes two drugs active against both viruses (e.g., tenofovir plus lamivudine or emtricitabine) has been recommended when treatment of HIV infection is indicated. Telbivudine and tenofovir are classified as pregnancy category B drugs, and lamivudine, a category C drug, has been shown to be safe in pregnant women with HIV infection. Antiviral therapy, beginning in the third trimester, has been recommended when the mother's serum HBV DNA level is greater than or equal to 200 000 IU/mL to reduce levels at the time of delivery.

Peginterferon alfa-2a is an alternative to the oral agents in selected cases but is associated

Table 44.5 Features of therapy with nucleoside and nucleotide analogs for chronic hepatitis B virus (HBV) infection

HBeAg-to-anti-HBe seroconversion in 12–21% at 1 year
HBeAg-to-anti-HBe seroconversion increases over time
Serum ALT level predicts HBeAg loss
HBeAg-negative patients are more likely than HBeAg-positive patients to become HBV DNA-negative, but response is much less durable
Liver histology improves
Degree of viral suppression varies among drugs
Rate of serum HBsAg loss is low (<1%) after 1 year
Resistance profiles vary

Abbreviations: ALT = alanine aminotransferase; anti-HBe = antibody to hepatitis B e antigen; anti-HBs = antibody to hepatitis B surface antigen hepatitis B virus; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen.

with frequent side effects (see later). A 48-week course leads to sustained normalization of aminotransferase levels, disappearance of HBeAg and HBV DNA from serum, appearance of anti-HBe, and improved survival in up to 40% of patients. A response is most likely in patients with a low baseline HBV DNA level and high aminotransferase levels and is more likely in those who are infected with HBV genotype A than with other genotypes (especially genotype D) and who have certain favorable polymorphisms of the interleukin-28B (*IL28B*) gene. Moreover, a majority of complete responders eventually clear HBsAg and develop antibody to hepatitis B surface antigen (anti-HBs) in serum, and are thus cured. Relapses are uncommon in complete responders who seroconvert from HBeAg to anti-HBe. Peginterferon may be considered in order to avoid long-term therapy with an oral agent, as in young women who may want to become pregnant in the future. Patients with HBeAg-negative chronic hepatitis B have a response rate of 60% after 48 weeks of therapy with peginterferon, but the response may not be durable once peginterferon is stopped. A rapid decline in serum HBsAg titers predicts a sustained response and ultimate clearance of HBsAg. The response to peginterferon is poor in patients with HIV coinfection.

Peginterferon alfa-2b (1.5 μg/kg/wk for 48 weeks) may lead to normalization of serum aminotransferase levels, histologic improvement, and elimination of HDV RNA from serum in 20% to 50% of patients with chronic hepatitis D, but patients may relapse and tolerance is poor. Nucleoside and nucleotide analogs, used as monotherapy for a duration of 2 years or in combination with peginterferon and ribavirin, are not effective in treating chronic hepatitis D.

CHRONIC HEPATITIS C

Chronic hepatitis C develops in up to 85% of patients with acute hepatitis C. Worldwide, 170 million people are infected with HCV; more than 350 000 annually are expected to die with hepatitis C-related complications. In the US population, 3.2 million people are estimated to be infected. Peak prevalence in the United States is about 4% in persons born between 1945 and 1964 ("baby boomers"), and both the Centers for Disease Control and Prevention (CDC) and the US Preventive Services Task Force recommend universal, one-time HCV screening for this group. In approximately 40% of cases, serum aminotransferase levels are persistently normal.

The diagnosis of HCV infections is based on detection of anti-HCV by enzyme immunoassay (EIA) and confirmed by detection of HCV RNA in serum. In rare cases of chronic hepatitis C, the EIA for anti-HCV is negative, but HCV RNA is detectable by polymerase chain reaction (PCR) testing. Progression to cirrhosis occurs in 20% of affected patients after 20 years, with an increased risk in men, those who drink more than 50 g of alcohol daily, and those who acquire HCV infection after 40 years of age. The rate of fibrosis progression accelerates after age 50. African Americans have a higher prevalence of chronic hepatitis C but lower rates of fibrosis progression and response to interferon-based therapy than whites. Immunosuppressed persons – including patients with hypogammaglobulinemia or HIV infection with a low CD4 count or those receiving immunosuppressants – appear to progress more rapidly to cirrhosis than immunocompetent persons with chronic hepatitis C. Tobacco, cannabis smoking, and hepatic steatosis also appear to promote progression of fibrosis, but caffeinated coffee consumption appears to slow progression. Persons with chronic hepatitis C and persistently normal serum aminotransferase levels usually have mild chronic hepatitis with slow or absent progression to cirrhosis; however, cirrhosis is present in 10% of these patients.

Treatment

Treatment of chronic hepatitis C is generally considered in patients under age 70 with more than mild fibrosis on liver biopsy. A liver biopsy may be avoided in persons infected with HCV genotype 1 if the results of a serum FibroSURE test – a panel of five markers – suggest absence of fibrosis (F0) or presence of cirrhosis (F4). Liver biopsy is often deferred in those infected with HCV genotype 2 or 3, in whom cure rates are invariably high. The introduction of direct-acting and host-targeting antiviral agents is rapidly expanding the therapeutic armamentarium against HCV.

Standard therapy for HCV infection since the late 1990s has been a combination of peginterferon and ribavirin. Sustained virologic response rates (negative HCV RNA in serum at 24 weeks after completion of therapy) to peginterferon and ribavirin are 45% in patients with HCV genotype 1 infection and 70% to 80% in those with genotype 2 or 3 infection. Rates are lower in patients with advanced fibrosis, high levels of viremia, alcohol consumption, HIV coinfection, obesity, insulin resistance, severe steatosis, vitamin A or D deficiency, and early menopause in women, and are also lower in blacks and Latinos than in whites, in part because of a higher rate of HCV genotype 1 among infected black patients and in part because of intrinsic resistance to therapy. Response of genotype 1 infection to peginterferon is associated most strongly with the CC genotype of the *IL28B* gene, with sustained response rates to peginterferon and ribavirin as high as 80%, compared with 40% for the CT genotype and 30% for the TT genotype. Caffeinated coffee consumption of more than three cups per day has also been reported to improve virologic response to peginterferon and ribavirin.

Higher rates of response were achieved in persons infected with HCV genotype 1 when one of two first-generation direct-acting antiviral agents – telaprevir and boceprevir, which were NS3/4A serine protease inhibitors that were approved in 2011 by the United States Food and Drug Administration (FDA) – was added to peginterferon and ribavirin. Sustained response rates were as high as 75% for HCV genotype 1 with a standard three-drug regimen. With the addition of one of these two protease inhibitors, the treatment duration for HCV genotype 1 infection could be shortened to as little as 24 weeks depending on the rapidity of clearance of HCV RNA from serum – so-called response-guided therapy. Patients infected with HCV genotype 2 or 3 (without cirrhosis and with low levels of viremia) have been treated for 24 weeks with peginterferon and ribavirin and require a ribavirin total daily dose of only 800 mg. Treatment with peginterferon-based therapy is costly (up to $86 000 for 48 weeks of therapy with three drugs), and side effects are common and may be distressing (Tables 44.6 and 44.7). Contraindications to peginterferon-based therapy are shown in Table 44.8.

Peginterferon-based therapy has been shown to be beneficial in the treatment of cryoglobulinemia associated with chronic hepatitis C; an acute flare of cryoglobulinemia may first require

Table 44.6 Adverse effects of peginterferon alfa

Adverse effect	Frequency (%)
Fatigue	24–67
Headache	27–60
Fever	24–54
Myalgias	26–51
Rigors	25–47
Neutropenia	21–40
Hypertriglyceridemia	20–36
Irritability	19–33
Diarrhea	11–31
Injection site inflammation	10–31
Insomnia	19–30
Arthralgia	22–28
Alopecia	18–28
Abdominal pain	8–26
Nausea and vomiting	5–25
Anorexia	16–24
Injection site reaction	22–23
Dizziness	13–23
Depression	18–20
Pruritus	12–19
Dermatitis	8–16
Weight loss	4–16
Anemia	2–14
Dyspnea	4–13
Rare[a]	–

[a] Thrombocytopenia, graft rejection, hypersensitivity reaction, autoimmune disease (including thyroid disease), significant bacterial infection, seizure, suicide, psychotic disorder, others.

Adapted from www.micromedexsolutions.com.

Table 44.7 Adverse effects of ribavirin

Adverse effects	Frequency (%)
Teratogenicity	Common
Rash	Common
Itching	Common
Asthenia	63–68
Headache	43–62
Nausea	25–43
Insomnia	30–41
Neutropenia	8–40
Anorexia	24–32
Vomiting	11–29
Weight loss	10–29
Dyspnea	13–26
Cough	10–23
Diarrhea	10–22
Dizziness	14–21
Hemolytic anemia	10–13
Rare[a]	–

[a] Myocardial infarction, pancreatitis, others.

Adapted from www.micromedexsolutions.com.

Table 44.8 Contraindications to treatment with peginterferon-based therapy

Clinically decompensated liver disease[a]
History of solid organ transplant (except liver)
Severe extrahepatic disease (malignancy, blood disorders, unstable angina, severe chronic lung disease)
Uncontrolled autoimmune disorders
Pregnancy or planned pregnancy by the patient or patient's sexual partner
Unwillingness or inability to use adequate birth control
Documented nonadherence to prior medical treatment, procedures, and follow-up
Inability to self-administer or to arrange appropriate medication injection
Cognitive limitations or executive function disorder, unless in a supervised setting
Severe uncontrollable psychiatric disease, particularly depression with current suicidal risk
Ongoing injection drug use
Ongoing alcohol abuse

[a] Serum bilirubin $>$ 1.5 mg/dL; prothrombin time $>$ 15 seconds; international normalized ratio $>$ 1.7; albumin $<$ 3.4 g/dL; ascites; bleeding esophageal varices; hepatic encephalopathy. As defined by Hoofnagle JH, Seeff LB. Peginterferon and ribavirin for chronic hepatitis C. *N Engl J Med.* 2006;355:2444–2451.

treatment with rituximab, cyclophosphamide plus methylprednisolone, or plasma exchange. Patients with both HCV and HIV infections may benefit from treatment of HCV. Moreover, in HCV/HIV-coinfected persons, long-term liver-related mortality increases as mortality from HIV infection is reduced by highly active antiretroviral therapy.

Numerous other antiviral agents with various, often novel, mechanisms of action have been developed, and many have become commercially available (Table 44.9). Newer agents include other NS3/4A protease inhibitors (e.g., asunaprevir, danoprevir, faldaprevir, grazoprevir, paritaprevir, simeprevir, vaniprevir); NS5A inhibitors (e.g., daclatasvir, elbasvir, ledispavir, ombitasvir); NS5B non-nucleoside inhibitors (e.g., beclabuvir, dasabuvir); NS5B polymerase inhibitors (e.g., mericitabine, sofosbuvir); virus entry, assembly, and secretion inhibitors; microRNA-122 antisense oligonucleotides (e.g., miravirsen); cyclophilin A inhibitors (e.g., alisporivir); interferon lambda-3; and therapeutic vaccines. HCV genotype 1 has become easy to cure, with expected SVR rates above 90%, and virtually all HCV genotype 2 infection is curable with all-oral therapies. Treatment of HCV genotype 3 infection, particularly in association with cirrhosis, remains a challenge because few alternative compounds are yet available. Interferon is now rarely required, and the need for ribavirin will likely decline.

HCV protease inhibitors ("...previrs") generally have high antiviral potency but differ in respect to the development of resistance. Most of the compounds show better response rates in HCV genotype 1b than in genotype 1a infection. The first two protease inhibitors approved by the FDA in 2011 were boceprevir and telaprevir, and simeprevir became available in 2014. These drugs were used initially in combination with peginterferon and ribavirin for HCV genotype 1 infection, although simeprevir was less effective in patients with genotype 1a and a Q80K mutation than in those without the mutation.

NS5A inhibitors ("...asvirs") are characterized by high antiviral potency at picomolar doses. The cross-genotype efficacy of these agents varies. Ledipasvir was the first NS5A inhibitor approved by the FDA in 2014.

HCV polymerase inhibitors ("...buvirs") are categorized as nucleoside or nucleotide analog and non-nucleoside polymerase inhibitors. Non-nucleoside polymerase inhibitors are the weakest

Table 44.9 Direct-acting antiviral agents for HCV infection[a]

Agent	Genotype(s)	Dose[b]	Comment
NS3/4A protease inhibitors			
Boceprevir	1	800 mg three times daily	Used in combination with pegylated interferon and ribavirin; no longer recommended
Telaprevir	1	1125 mg twice daily	Used in combination with pegylated interferon and ribavirin; no longer recommended
Simeprevir	1 and 4	150 mg once daily	Used in combination with pegylated interferon and ribavirin or with sofosbuvir
Paritaprevir	1 and 4	150 mg once daily	Used in combination with ombitasvir and dasabuvir; ritonavir boosted
Asunaprevir	1b and 4	200 mg twice daily	Used in combination with daclatasvir
Grazoprevir	1, 2, 4–6	100 mg once daily	Used in combination with elbasvir
NS5A inhibitors			
Daclatasvir	1–6	60 mg once daily	Used in combination with sofosbuvir (genotypes 1–6) or with pegylated interferon and ribavirin (genotype 4) or with asunaprevir (genotypes 1b and 4)
Ledipasvir	1, 3, and 4	90 mg once daily	Used in combination with sofosbuvir
Ombitasvir	1 and 4	25 mg once daily	Used in combination with paritaprevir and dasabuvir
Elbasvir	1–6	50 mg once daily	Used in combination with grazoprevir
NS5B nucleos(t)ide polymerase inhibitor			
Sofosbuvir	1–6	400 mg once daily	Used in combination with pegylated interferon and ribavirin (all genotypes) or with ribavirin alone (genotypes 2 and 3) or with simeprevir (genotypes 1 and 4) or with daclatasvir (all genotypes) or with ledipasvir (genotypes 1, 3, and 4)
NS5B non-nucleos(t)ide polymerase inhibitor			
Dasabuvir	1 and 4	250 mg twice daily	Used in combination with paritaprevir and ombitasvir

[a] Some agents have not been approved by the FDA as of 2015; additional drugs are under study.

[b] The preferred regimen and duration of treatment may vary depending on HCV genotype, presence or absence of cirrhosis, or nonresponse to prior therapy for HCV infection.

class of compounds against HCV because of a low barrier to resistance. Most drugs in this class are more active against HCV genotype 1b than HCV genotype 1a. They are being developed to be used only in combination with the other DAAs, mainly protease inhibitors and NS5A inhibitors. Nucleoside analogs are active across all HCV genotypes and have a high barrier to resistance; nucleoside analog-resistant variants may emerge, but they have very low fitness and do not expand rapidly. The first approved HCV polymerase inhibitor was sofosbuvir in 2013.

Sofosbuvir was initially approved for use in combination with peginterferon and ribavirin in patients with HCV genotype 1 infection, and with ribavirin alone in patients with HCV genotype 2 or 3 infection. The majority of patients with HCV genotype 2 or 3 infection are cured with just 12 or 24 weeks of therapy, respectively. HCV genotype 2 responds much better to interferon-free sofosbuvir-based therapy than HCV genotype 3, but the SVR is 20–30% lower in patients with cirrhosis. Importantly, no sofosbuvir-resistant variants have been selected during therapy. The combination of sofosbuvir and simeprevir has been found to be effective in HCV genotype 1 infection and was approved by the FDA in 2014.

Ledipasvir, an NS5A inhibitor with potent activity against genotype 1 HCV, has been formulated in combination with sofosbuvir and is highly effective in treatment-naive and treatment-experienced patients, even those with cirrhosis. The combination was approved by the FDA in 2014 for HCV genotype-1 infection in a fixed dose of ledipasvir 90 mg and sofosbuvir 400 mg once daily for 12 weeks in treatment-naive patients and treatment-experienced patients without cirrhosis and for 24 weeks in treatment-experienced patients with cirrhosis. In treatment-naive patients without cirrhosis, the duration of treatment can be shortened to 8 weeks if the HCV RNA level is less than 6 million IU/mL. SVR rates are well above 90%, and this regimen has emerged as a first-line therapy for HCV genotype 1. Side effects are mild and include fatigue and headache.

The combination of paritaprevir (a protease inhibitor), boosted by ritonavir, plus ombitasvir (an NS5A inhibitor) and dasabuvir (an NS5B nonnucleoside polymerase inhibitor) is effective in both treatment-naive and prior non-responders to interferon-based therapy, with or without cirrhosis, and is expected to be another first-line option in 2015. Daclatasvir (which is not available in the United States) in combination with sofosbuvir has proved effective in genotypes 1-, 2-, and 3-infected patients. The combination of daclatasvir and asunaprevir is highly effective in genotype 1b-infected patients and also in genotypes 4-, 5-, and 6-infected patients but less effective in genotype 1a-infected patients and is not available in the United States. Other drugs and drug combinations are under study.

Useful websites include those of the CDC (http://www.cdc.gov/hepatitis/HCV/index.htm) and the US Department of Veterans Affairs (www.hepatitis.va.gov); for the lay and advocacy communities, the HCV Advocate (www.hcvadvocate.org) and the American Liver Foundation (hepc.liverfoundation.org) are worthwhile.

PROGNOSIS

The course of chronic hepatitis B is variable. Possible sequelae include cirrhosis, liver failure, and hepatocellular carcinoma. The 5-year mortality rate is 0% to 2% in those without cirrhosis, 14% to 20% in those with compensated cirrhosis, and 70% to 86% following decompensation. The risk of cirrhosis and hepatocellular carcinoma correlates with serum HBV DNA levels, and a focus of therapy is to suppress HBV DNA levels below 60 IU/mL (300 copies/mL). There is some evidence that HBV genotype C is associated with a higher risk of cirrhosis and hepatocellular carcinoma than other genotypes. Antiviral treatment improves the prognosis in responders, prevents (or leads to regression of) cirrhosis, and decreases the frequency of liver-related complications.

Chronic hepatitis C is an indolent, often subclinical disease that may lead to cirrhosis and hepatocellular carcinoma after decades. The overall mortality rate in patients with transfusion-associated hepatitis C may be no different from that of an age-matched control population. Nevertheless, mortality or transplantation rates clearly rise to 5% per year once cirrhosis develops, and mortality from cirrhosis and hepatocellular carcinoma due to hepatitis C is expected to increase until 2020. There is some evidence that HCV genotype 1b is associated with a higher risk of hepatocellular carcinoma than other genotypes and that HCV genotype 1a is less responsive than HCV genotype 1b to therapy. Emerging therapeutic strategies are expected to improve upon the known benefits of peginterferon-based treatment on mortality, quality of life, fibrosis regression, reduced risk of decompensated cirrhosis, and hepatocellular carcinoma in responders. Even patients who achieve a sustained virologic response, however, remain at an increased risk for mortality compared with the general population. The risk of mortality from drug addiction is higher than that for liver disease in patients with chronic hepatitis C.

PREVENTION

All newborns are screened for HBV in the United States and many other countries. Newborns of HBV-infected mothers should receive hepatitis B immunoglobulin within 12 hours of birth as well as the hepatitis B vaccine series in order to significantly reduce the likelihood of viral transmission. In healthy patients, efforts to prevent HBV and HDV infection are focused on reducing the opportunity for sexual transmission or exposure from injection drug use. Intravenous drug use is by far the most important source of HCV infection worldwide. The World Health Organization continues to advocate for and fund newborn vaccination, blood product screening, use of non-reuseable and autodisposable syringes, as well as healthcare worker vaccination against HBV, as part of the Global Plan of Action, 2008–2017.

As noted earlier, screening of "baby boomers" for HCV infection is now recommended in

the United States. Persons with HBV or HCV infection should be vaccinated against hepatitis A. Those with chronic hepatitis C should receive the HBV vaccine. In HDV-endemic areas, HBsAg-negative persons should receive the HBV vaccine. Furthermore, patients with chronic hepatitis should receive the pneumococcal and influenza vaccines. In patients with chronic hepatitis B and active viral replication, as well as in those with chronic hepatitis C and advanced liver fibrosis, surveillance for hepatocellular carcinoma with serum alpha-fetoprotein testing and abdominal ultrasonography every 6 months is recommended.

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45. Biliary infection: cholecystitis and cholangitis

Robert V. Rege

This chapter discusses the pathogenesis, diagnosis, and treatment of infections of the gallbladder and bile ducts. Bacterial disorders of the biliary tract range from simple colonization of bile with bacteria to serious, life-threatening problems requiring prompt diagnosis and treatment.

ACUTE CHOLECYSTITIS

Acute cholecystitis is a common disorder manifest as acute inflammation of the gallbladder. Ninety-eight percent of episodes exhibit cystic duct obstruction, usually by a gallstone impacted in the gallbladder neck. Cystic duct obstruction results in nonvisualization of the gallbladder on technetium radionucleotide cholecintography (HIDA) scan. In 2% to 5% of cases, termed acute acalculous cholecystitis, gallstones are not present. Acute acalculous cholecystitis is most often found in debilitated or critically ill patients who have not been fed by mouth for extended periods of time, but acalculous cholecystitis also occurs in normal individuals. It is believed that stasis of bile in the gallbladder lumen leads to gallbladder wall inflammation in both calculous and acalculous cholecystitis. Bacteria play a secondary role as superinfection of bile with bacteria, and eventually gallbladder wall compromise, are later events (Figure 45.1). If unchecked, the process progresses to complicated cholecystitis with gangrene or perforation of the gallbladder. It is imperative that acute cholecystitis be diagnosed and effectively treated before life-threatening complications of acute cholecystitis ensue.

Diagnosis

Acute cholecystitis must be distinguished from biliary colic and clues need to be sought to determine if complicated cholecystitis is imminent or already present. Both patients with acute cholecystitis and biliary colic experience right upper quadrant abdominal pain, but pain with acute cholecystitis is persistent, lasting more than 3 to 4 hours, and associated with abdominal tenderness. Tenderness is well localized in the right upper quadrant of the abdomen, directly over the gallbladder, and increases when the patient inspires as the gallbladder strikes the examiner's hand (Murphy's sign). The maneuver can be duplicated with the ultrasound probe (ultrasonic Murphy's sign). Diffuse right upper quadrant tenderness is suggestive of a liver problem, and severe tenderness or peritonitis is indicative of complicated cholecystitis or another upper abdominal cause of pain.

Systemic signs of inflammation such as low-grade fever and moderately elevated white blood cell (WBC) count are usually present. The presence of dark urine, acholic stool, or jaundice raises the question of common bile duct stones; malignant ductal obstruction is more often characterized by painless jaundice. Back pain and epigastric tenderness also heightens one's suspicion of choledocholithiasis or biliary pancreatitis.

Examination can, however, be misleading. Some patients exhibit few signs and symptoms of acute cholecystitis, delaying the diagnosis and severity of the disease. Such patients are more likely to be elderly, male, and have a history of cardiac disease and WBC greater than 15 000. It is important to have a heightened index of suspicion in patients who fit this profile and to promptly treat their disease (Figure 45.1).

Laboratory testing should include complete blood count with differential, liver function tests, serum amylase, and serum lipase. The latter three tests may suggest choledocholithiasis or biliary pancreatitis when abnormal. While WBC is usually moderately elevated, counts greater than 15 000 suggest severe disease (gangrene or perforation of the gallbladder). Ultrasound of the abdomen reliably demonstrates gallstones in the majority of patients. A typical clinical presentation coupled with a "positive" ultrasound for stones suffices for the diagnosis. More specific findings of acute cholecystitis such as gallbladder

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wall thickening and pericholecystic fluid are less frequent and suggest more severe disease. HIDA scan may be helpful in patients without gallstones or with atypical presentation. Non-visualization of the gallbladder on HIDA scan is specific for acute cholecystitis as this technique visualizes the gallbladder in only about 2% of patients with acute cholecystitis; demonstration of the gallbladder argues strongly against acute cholecystitis.

Bacteriology

Interestingly, bacteria are not isolated from bile in the great majority of patients undergoing operation early in the course of the disease. Bacteria in the bile increase as the duration from the onset of symptoms increases; the majority of patients demonstrate bacterobilia by 3 days. The relative proportion of organisms varies in studies, but in general the most common organisms isolated include the gram-negative bacteria *Escherichia coli, Klebsiella, Proteus*, and *Pseudomonas* and gram positives, especially *Enterococcus* (Table 45.1). The presence of multiple species of bacteria is also common. Anaerobic bacteria are reportedly isolated in less than 10% of cases but may be more common, because culturing these organisms using standard techniques is difficult. *Candida* species are uncommon in normal patients but frequent in immunosuppressed patients and patients with malignancy.

Table 45.1 Common bacteria in bile

Gram negative	Gram positive	Anaerobes	Fungi
Escherichia coli	*Enterococcus*	*Bacteroides* species	*Candida* species
Klebsiella species	*Streptococcus* species	*Clostridium* species	
Proteus species			
Pseudomonas species			
Enterobacter species			

Notes: Approximately 65% of patients are colonized with a single species of bacteria; 35% are polymicrobial.
Gram-negative bacteria are cultured from nearly 75% of patients.

Treatment

All patients should be evaluated and prepared for operation, which may be required at any time if the disease progresses. They should be given intravenous fluid resuscitation, placed on bowel rest, and begun on antibiotics. Antibiotics must cover the spectrum of bacteria outlined above, but complicated cholecystitis and immunosuppressed patients require even broader coverage (Table 45.2).

Some physicians recommend medical treatment with a delay of 6 weeks to definitive operation. Their rationale is that elective operation is safer than an emergent procedure and that conversion rates will be lower than after the acute attack. Although most patients respond, medical therapy is not safer and does not decrease conversion rates. It may play a role in a few selected

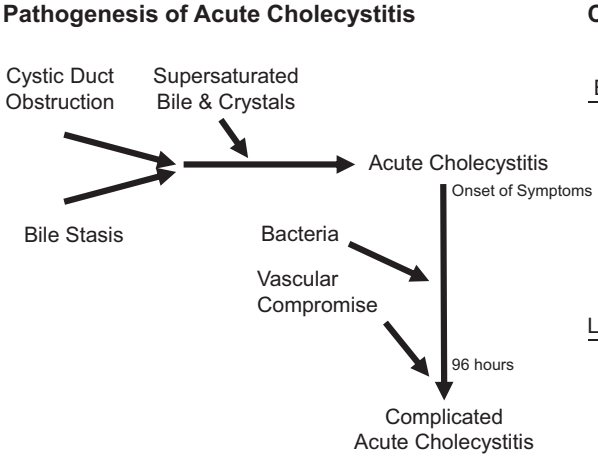

Figure 45.1 The pathogenesis of acute cholecystitis is illustrated on the left side of the figure, whereas differences in clinical presentation between acute cholecystitis and complicated acute cholecystitis are shown on the right. Note that bacteria do not play a primary role, but result in progression of the disease to its complicated form. WBC = white blood cell.

Table 45.2 Summary of antibiotic regimens for acute cholecystitis and acute cholangitis

Acute cholecystitis
Cefoxitin 1–2 g IV q6–8h
Ampicillin–sulbactam (Unasyn) 3 g IV q6h
Acute cholangitis
Single agents Ciprofloxacin 400–800 mg IV q12h or Piperacillin–tazobactam (Zosyn) 3.375 g IV q6h or Imipenem 500 mg IV q6h
Multidrug therapy Ampicillin 2 g IV q6h + gentamicin 5–7 mg/kg IV q24h or Cefazadime 1–2 g IV q8–12h + ampicillin 2 g IV q6h + metronidazole 500 mg IV q6h

patients with severe potentially reversible comorbidities. If such patients fail medical therapy, they can be salvaged with percutaneous drainage of the gallbladder. Cholecystectomy may be performed electively later, but it is arguable whether all patients require cholecystectomy after nonoperative therapy.

Early laparoscopic cholecystectomy is definitive treatment for most patients with acute cholecystitis. It is safe in the hands of experienced biliary surgeons, avoids the progression of the disease observed in as many as 30% of medically treated patients, and has conversion rates similar to elective cholecystectomy (<5%). As the duration of symptoms surpasses 96 hours, conversion rates rise because complicated cholecystitis develops. Although laparoscopic cholecystectomy can be performed in the majority of patients after 96 hours, the operation is more difficult and morbid. If laparoscopic surgery is attempted late in the disease, surgeons should convert to open operation liberally in patients with marked inflammation or fibrosis.

It is my preference to admit a patient with acute cholecystitis to the hospital and perform operation not longer than 72 hours from onset of symptoms. The patient is treated with medical therapy until operation. Patients with early disease often spend less than 24 hours in the hospital. Those with severe or late disease require urgent or emergent intervention and continued medical therapy postoperatively. Patients who are poor operative risks are the exception; medical therapy and/or percutaneous cholecystostomy tube drainage is a consideration.

ACUTE CHOLANGITIS

Acute cholangitis refers to inflammation and infection of the intra- and extrahepatic biliary tree. Bacteria are the most frequent cause, but cholangitis can result from parasitic infections, autoimmune disease, and chemical irritants. The term *toxic cholangitis* describes the situation when the bacteria in bile gain access to the sinusoids in the liver and are rapidly disseminated, causing sepsis.

The pathogenesis of acute cholangitis involves a combination of factors including ductal obstruction, injury to the biliary epithelium, and the presence of bacteria in bile. Most patients harboring bacteria in bile do not have an infection; asymptomatic colonization of bile with bacteria increases with advancing age. Bactobilia is a risk for acute cholangitis once biliary obstruction develops or the epithelial is injured, as might occur during an invasive biliary procedure. This is the rationale for antibiotic coverage during biliary tract invasive procedures.

Most cases of cholangitis in the United States are secondary to partial or complete biliary obstruction, usually by gallstones. Benign and malignant ductal strictures are also common. Patients with malignant obstruction usually have painless jaundice and sterile bile, but about 20% present with bacteria in bile. Patients with colonized bile are at risk for cholangitis after procedures in the biliary tract. The incidence of iatrogenic cholangitis is rising as endoscopic and radiologic bile duct procedures increase. Care must be taken to avoid colonizing sterile bile by using prophylactic antibiotics when patients undergo invasive diagnostic tests and providing adequate drainage after therapeutic interventions. If bacteria are introduced into sterile bile, the risk of cholangitis and other septic complications increases. Increased intraductal pressure behind a stricture or obstruction disrupts epithelia and intracellular junctions between epithelial cells in the proximal biliary tree. Bacteria then gain access to the liver sinusoids, and thus to the bloodstream, causing bacteremia, high fevers, and sepsis. Acute cholangitis is therefore a life-threatening disorder requiring prompt diagnosis and treatment.

Diagnosis

The classic description of patients with acute cholangitis – Charcot's triad – consists of abdominal pain, fever, and jaundice. Unfortunately, only 50% of patients present with all three signs and symptoms. Fever and chills, present in 90% of patients, are the most consistent signs of acute cholangitis. Fevers are most often high and spiking. Reynolds' pentad – Charcot's triad plus hypotension and altered sensorium – is indicative of toxic cholangitis. Regrettably, all five features are present in the minority of patients with toxic cholangitis, so acute and toxic cholangitis must be considered in patients who have any of these signs or symptoms.

Physical examination most often reveals right upper quadrant abdominal tenderness and jaundice. However, as many as 20% of patients with acute cholangitis have a serum bilirubin level of less than 2.0 mg/dL, so the lack of jaundice does not exclude acute cholangitis. Physical findings are typically accompanied by leukocytosis, fever, and/or abnormal liver function tests, but septic patients may have a low WBC. Ultrasound should be performed urgently to distinguish "medical" from "surgical" jaundice: dilated bile ducts are indicative of obstruction and surgical jaundice. Endoscopic retrograde cholangiography (ERC; see treatment) is diagnostic but can also be therapeutic. Percutaneous transhepatic cholangiography is helpful when ERC is unsuccessful.

Bacteriology

Causative organisms are similar to those isolated in acute cholecystitis. However, infections are more severe and blood cultures more often positive for the bacteria found in bile. Some studies show differences in the incidence of causative organisms between benign and malignant causes of ductal obstruction, but others do not. Most studies show that patients with malignant obstruction have a higher incidence of bile colonized with *Candida* species (Table 45.1).

Treatment

Acute cholangitis requires aggressively addressing both infection and biliary obstruction. The majority of nonseptic patients respond quickly to fluid resuscitation and appropriate antibiotics. Subsequent measures need to be taken promptly to address the problems causing acute cholangitis. On the other hand, toxic cholangitis is a life-threatening problem and patients with this disorder should be placed in the intensive care unit for aggressive monitoring. Intravenous hydration should correct the hypovolemia associated with biliary obstruction, and urine output should be followed closely. Restoration of normal intravascular volumes before undergoing invasive diagnostic and therapeutic procedures is essential to avoid renal failure. Patients often exhibit coagulation defects that must be corrected with vitamin K, fresh frozen plasma (FFP), and platelets.

Broad-spectrum antibiotic therapy is essential and should be instituted immediately before diagnostic and therapeutic interventions. Choice of an antibiotic should take into account the profile of organisms commonly cultured at your hospital, especially for hospitalized individuals undergoing invasive procedures. Coverage should be later tailored to match the sensitivities of isolated organisms. The long-standing regimen of ampicillin and an aminoglycoside continues to provide excellent coverage for the major culprits, including *Enterococcus* species, but nephrotoxicity of the aminoglycoside is a problem. Although first- and second-generation cephalosporins provide good prophylaxis for elective biliary surgery, they lack the breadth of gram-negative coverage required to treat patients with established infections. Third- and fourth-generation cephalosporins provide gram-negative coverage but do not treat *Staphylococcus* and *Enterococcus* species and anaerobic bacteria well. Triple therapy with ceftazidime, ampicillin, and metronidazole provides adequate coverage, but the trend has shifted to single-drug therapy with piperacillin–tazobactam or ampicillin/sulbactam, which is as efficacious as triple-drug therapy or ampicillin plus an aminoglycoside. Fluoroquinolones or carbapenems are good alternatives if first-choice antibiotics are ineffective and ciprofloxacin can be used long term orally to suppress recurrent attacks of cholangitis.

After adequate resuscitation and antibiotic administration, the primary goal is to relieve obstruction of the biliary tree. This is currently accomplished using either endoscopic retrograde cholangiopancreatography (ERCP)-mediated drainage or percutaneous transhepatic cholangiography (PTC). ERCP is the first choice because its risk is less than PTC in sick patients. Effective drainage of the biliary tree can be

accomplished by removal of obstructing gallstones or by stenting the duct. Cancers of the biliary tree can be visualized and biopsied. PTC is reserved for failure of ERCP, but is the procedure of choice for patients with cholangiocarcinoma in the proximal bile duct. Adequate drainage should result in prompt improvement.

Decisions about timing of intervention depend on the severity of disease. Factors associated with the need for emergent treatment include older age, high bilirubin levels, prolonged prothrombin time, dilated common bile ducts, and the presence of liver abscesses. Salek *et al.* developed scoring systems to determine mortality risk using the presence of liver abscess, total bilirubin, and prothrombin time and the need for urgent ERCP using alanine aminotransferase level and WBC with good sensitivity, specificity, and predictive values.

If appropriate, definitive procedures should be performed to treat the cause of biliary obstruction, because recurrent cholangitis is common. Cholecystectomy should be performed if choledocholithiasis was the inciting event. Curable malignancies should be resected. Benign strictures require balloon dilatation or choledochointestinal bypass, whereas unresectable tumors are either bypassed or palliated with internal drainage or external stents.

Timing of operation for patients who present with a transient episode of biliary pancreatitis (low to moderate risk of choledocholithiasis) is somewhat controversial; most stones pass from the common duct spontaneously without complication and the incidence of retained common bile duct stones is highest early after an attack and decreases with time. However, patients who do not pass their stones are at risk for recurrent pancreatitis, obstructive jaundice, and acute cholangitis. The timing of treatment then depends on a balance between the risk of intervention for and further complications from retained common duct stones. Low-risk patients with mild pancreatitis may be taken to the operating room for laparoscopic cholecystectomy with intraoperative cholangiography, if the surgeon is prepared to perform laparoscopic common bile duct exploration. The standard of care is to intervene during or shortly after the index admission.

However, patients who present with severe, complicated pancreatitis may be poor candidates for surgery. Most surgeons allow them to recover from their episode of pancreatitis before definitive intervention. The chance that cholangitis will ensue is low. Patients with unrelenting pancreatitis, persistently elevated liver enzymes, or jaundice are at high risk for common bile duct stones and should be considered for ERCP. Cholecystectomy is performed later to avoid recurrent complications of stones if the patient is an acceptable operative risk.

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46. Pyogenic liver abscess

Patricia Wong and H. Franklin Herlong

First described by Hippocrates around 400 BC, pyogenic liver abscess is an uncommon hepatic infection, but is associated with significant morbidity and healthcare costs. With the advent of imaging techniques that allow for prompt diagnosis, potent antibiotics, and effective drainage procedures, the mortality from pyogenic liver abscess has declined dramatically over the past several decades.

EPIDEMIOLOGY

The epidemiology of liver abscesses has changed significantly over the years. There is increasing recognition that geography plays a significant role in the demographics, etiologic factors, and clinical presentation of pyogenic liver abscesses. In the first large published series of cases of pyogenic liver abscess in the United States in 1938, there was an incidence of 8 cases per 100 000 admissions and a mortality rate of 72%. More recent US-based population studies estimate the annual incidence to be 3.6 per 100 000 population, with a higher incidence among men than women (incidence risk ratio 1.85). Significantly higher incidence rates have been reported in Taiwan at 17.6 per 100 000 population. Reported risk factors include diabetes, underlying hepatobiliary disease, and liver transplantation. In-hospital mortality ranges from 2% to 12% in developed countries and has been reported at 5.6% in the United States. Risk factors for mortality include older age; comorbidities such as cirrhosis, chronic renal failure, and malignancy; the presence of anaerobic infection; and open surgical drainage. The significant decline in associated mortality reflects changes in the underlying source of bacterial seeding and advances in diagnostic and treatment options.

ETIOLOGY

Pyogenic liver abscesses result from seeding of the liver from biliary tract disorders (choledocholithiasis, malignant obstruction, strictures, biliary procedures), portal vein pyemia (appendicitis, diverticulitis, colon cancer, inflammatory bowel disease), direct extension (peritonitis, subphrenic abscess), hematogenous spread (pneumonia, endocarditis), or hepatic trauma (infected necrosis, bile leak, or hematoma). Rarely, abscesses develop after arterial embolization or radiofrequency ablation of hepatic tumors. Biliary tract disorders have emerged as the most common causative condition, accounting for 40% to 60% of liver abscess cases. Cholangitis from obstructing cholangiocarcinomas is more common than infections resulting from calculus obstruction.

Liver abscesses from intra-abdominal infective processes have decreased dramatically because of improvements in the diagnosis and treatment of these primary infections. No identifiable source of infection, or "cryptogenic abscess," is found in up to 25% of cases. Most liver abscesses are solitary and occur in the right lobe of the liver, likely due to its greater blood supply compared to the left and caudate lobes.

CLINICAL PRESENTATION

Most patients with pyogenic liver abscesses appear acutely ill with fever and right upper quadrant pain. However, in elderly, debilitated patients, clinical signs may be minimal, potentially delaying diagnosis. Many patients have tender hepatomegaly, occasionally with focal tenderness over the intercostal spaces of the right upper quadrant. However, absence of right upper quadrant findings does not exclude the diagnosis and in patients with liver transplants, denervation may prevent the pain of hepatic enlargement. Nonspecific systemic symptoms such as fatigue, malaise, nausea, and weight loss are common. Jaundice is unusual unless the abscess compresses the biliary tact. An associated pleural effusion may obliterate breath sounds at the right

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Table 46.1 Clinical findings in pyogenic liver abscess

Signs and symptoms	Incidence (%)
Fever	75
Chills	60
Abdominal pain	60
Weight loss	30
Hepatomegaly	50
Right upper quadrant tenderness	40
Jaundice	25
Laboratory values	
Leukocytosis	70
Elevated bilirubin	40
Elevated alkaline phosphatase	50
Elevated aminotransferases	60

bases. Laboratory abnormalities frequently include leukocytosis and elevated C-reactive protein levels. A modest elevation of alkaline phosphatase is seen in up to 90% of cases. Serum aminotransferases and bilirubin are elevated in about one-half of cases. Blood cultures are positive in less than 50% of cases. No single test or combination of tests can accurately predict the outcome, size, or number of abscesses or complications.

Cultures from liver abscesses usually yield polymicrobial flora. Mixed enteric facultative and anaerobic species are the most common pathogens. A single organism indicates hematogenous spread. Enteric aerobic gram-negative bacilli, such as *Escherichia coli*, and enterococcus suggest a biliary source. Mixed enteric flora containing anaerobes such as *Bacteroides fragilis* originate from portal bacteremias. Monomicrobial *Klebsiella pneumoniae* infection is the most common cause of pyogenic liver abscesses in Taiwan and accounts for a large proportion of cases throughout Asia. These patients have a unique clinical presentation with classic symptoms but no identifiable coexisting intra-abdominal pathology and metastatic complications, such as endophthalmitis. Most patients also have diabetes mellitus. *Yersinia enterocolitica* is an unusual pathogen associated with patients with diabetes or underlying liver disease, particularly hemochromatosis.

Gram-positive organisms such as *Staphylococcus aureus* and *Streptococcus milleri* often originate from infections outside of the abdominal cavity. *S. aureus* is a common cause of liver abscess in children and trauma patients and has been associated with transarterial embolization for hepatocellular carcinoma. Species of *Candida* cause abscesses in immunosuppressed patients, particularly those receiving chemotherapy. The abscess may not be apparent until the neutrophil count rebounds (Table 46.1).

DIAGNOSIS

The diagnosis of pyogenic liver abscess is made through radiographic imaging and aspiration and culture of abscess material. Ultrasonography is the preferred initial test for diagnosing liver abscesses, with a sensitivity of 75% to 95%. Examination of the liver shows a round, focal defect with irregular walls and variable echogenicity. Abscesses may be septated or multiloculated and contain internal echoes caused by debris. Small abscesses, <2 cm in diameter, may not be detected. Contrast-enhanced computed tomography (CT) has a sensitivity of 95% and can detect abscesses as small as 0.5 cm. It can also identify associated intra-abdominal pathology. CT typically shows a fluid collection with surrounding edema or stranding. It is important to distinguish liver abscesses from tumors and cysts. Magnetic resonance imaging and tagged white blood cell scans are less effective at detecting and distinguishing abscesses from other liver lesions.

TREATMENT

The mainstay of treatment of pyogenic liver abscess is systemic antimicrobial therapy in combination with drainage. When pyogenic liver abscess is suspected, blood cultures should be obtained immediately, followed by initiation of broad-spectrum parenteral antibiotics before blood culture results are available, based on the most probable source of infections (Table 46.2). Initial antibiotic therapy should be tailored to information obtained from the Gram stain and cultures of aspirated abscess contents and blood cultures. Anaerobic coverage should be continued if multiple organisms are recovered, regardless of whether anaerobes are isolated, since they are difficult to culture. Most abscesses require at least 4 to 6 weeks of total antibiotic therapy with 2 to 4 weeks of parental therapy.

Successful treatment of pyogenic liver abscesses with antibiotics alone is rare, and some form of drainage procedure is almost always required. Exceptions include abscesses less than 3 cm in diameter or multiple small abscesses that are not amenable to surgical or catheter drainage.

Table 46.2 Empiric antibiotic therapy for pyogenic liver abscess

Potential source	Suggested regimen
Biliary	PipTz 4.5 g q8h IV or AMSB 3.0 g q6h IV or ERTA 1.0 g IV qd or MER 1.0 g q8h IV or CIP 400 mg IV BID + metro 1.0 g IV then 0.5 g q6h
Intra-abdominal	IMP 500 mg IV q6h or MER 1 g IV q8h or AMP 2 g IV q6h + metronidazole 500 mg IV q6h + CIP 400 mg IV q12h

Abbreviations: AMP = ampicillin; AMSB = ampicillin–sulbactam (Unasyn); CIP = ciprofloxacin; ERTA = ertapenem; IMP = imipenem cilastatin (Primaxin); MER = meropenem; metro = metronidazole; PipTz = piperacillin–tazobactam.

Drainage techniques include percutaneous approaches (closed aspiration or with catheter placement), surgical drainage, or drainage by endoscopic retrograde cholangiopancreatography (ERCP). Closed aspiration is a reasonable approach for single abscesses <5 cm. It is the simplest, quickest, and least costly approach with low risk of procedural complications. However, reaccumulation often requires repeat aspiration, catheter placement, or surgical intervention. Placement of a catheter into the abscess cavity under ultrasound guidance is an effective and widely used method of drainage at many centers. This technique is preferred over needle aspiration for single abscesses >5 cm, and is often used if closed aspiration is unsuccessful.

Open surgical drainage has decreased in popularity, with the trend towards percutaneous techniques. However, surgical treatment should be considered for single abscesses >5 cm, multiple or loculated abscesses, inadequate response to percutaneous drainage, viscous contents obstructing the drainage catheter, or concurrent intra-abdominal surgical pathology. Surgical intervention allows for exploration of the abdomen and liver for multiple abscesses. A laparoscopic approach to surgical drainage may also be considered.

Endoscopic abscess drainage has emerged more recently as a treatment option for patients with abscesses that communicate with the biliary tree. This is performed through ERCP with sphincterotomy, dilation, insertion of a nasobiliary catheter, or stenting. Successful endoscopic management of liver abscess complicated by biliary fistula has also been described.

PROGNOSIS

Current mortality rates associated with liver abscesses range from 2% to 12% in developed countries. Few patients die from complications of the abscess itself, such as sepsis or peritonitis. The most important factor in determining survival is the lethality of the primary disease process.

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47. Infectious complications of acute pancreatitis

Jodie A. Barkin and Jamie S. Barkin

Acute pancreatitis (AP) is an acute inflammatory process of the pancreas in which pancreatic enzymes are released and autodigest the gland with effects ranging from edema to necrosis. AP has a wide spectrum of disease from a mild, transitory illness to a severe, rapidly fatal disease. Approximately 80% of patients with the disease have a mild acute interstitial edematous pancreatitis with a low morbidity and mortality rate (≤1%). Mild pancreatitis is usually self-limiting, subsiding in most cases uneventfully within 3 to 4 days and rarely needing intensive care treatment or pancreatic surgery. Severe or necrotizing pancreatitis develops in about 20% of patients. Early death within 1 week of admission is related to systemic inflammatory response syndrome (SIRS), with infection of pancreatic and peripancreatic necrosis representing the single most important risk factor for a fatal outcome. Overall, AP is complicated by infection in approximately 10% of patients, with 70% to 80% mortality. With increasing amount of necrotic reaction, there is greater risk of subsequent infection of the gland. In patients with AP, organ failure and infected pancreatic necrosis indicate severe disease as they comparably influence mortality, with a doubled relative risk of mortality when both are present, indicating extremely severe disease.

The prognosis and initial severity of a pancreatitis attack may be assessed by monitoring clinical signs and symptoms. The clinical findings in severe disease may include the presence of hypotension, hypoxemia, renal failure, altered mental status, hemoconcentration reflective of intravascular volume loss, and the presence of SIRS. Other findings may include abdominal pain and nausea, fever (>38.6°C [101.5°F]), ascites, and ecchymoses. Several classification systems have been developed in an attempt to provide reliable prognostic classification for patients with AP. The APACHE II scale (*a*cute *p*hysiological *a*ssessment and *c*hronic *h*ealth *e*valuation), multiple organ system failure (MOSF) scale, and the BISAP criteria (*b*edside *i*ndex of *s*everity in *a*cute *p*ancreatitis) (Table 47.1) have all been used. These newer criteria may supplant the utility of Ranson's criteria, and can usually be performed within a few hours after admission. The APACHE II scores are generated from multiple parameters, are considered highly accurate, allow prediction of severity from the day of admission, and may be recalculated on a daily basis. Unfortunately, because of the time-consuming and cumbersome nature of the APACHE II evaluation, it is rarely used in clinical practice. The MOSF system has better clinical utility for evaluating patients at admission and at 48 hours than the APACHE II score. The BISAP score is a scale assessment for prognostication during the initial 24 hours after admission.

Table 47.1 Predictors of severity in acute pancreatitis

Bedside index for severity in acute pancreatitis: within the first 24 hours of presentation:
Blood urea nitrogen >25 mg/dL
Impaired mental status
Presence of SIRS
Age >60 years
Pleural effusion on imaging
A BISAP score ≥ 3 is associated with increased risk of complications

Adapted from Singh VK, Wu BU, Bollen TL, *et al. Am J Gastroenterol.* 2009;104(4):966–971.

COMPUTED TOMOGRAPHY

Rapid bolus computed tomography (CT) scanning using intravenous contrast effectively and accurately (>95%) detects pancreatic necrosis. It should only be used if the diagnosis of AP is in doubt, and should not be performed until after appropriate volume resuscitation, in order to minimize renal complications. In addition, its use should be restricted to patients who have

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severe AP, who do not show signs of clinical improvement despite supportive care over several days, or in whom infection is suspected, by either fever or positive blood cultures. The severity of AP can be estimated by the findings on CT scan, such as the presence of necrosis (nonviable tissue) with non-perfused areas of pancreatic parenchyma, pancreatic enlargement, peripancreatic inflammatory changes, and adjacent or parenchymal fluid collections.

NATURAL HISTORY OF ACUTE PANCREATITIS

Since the mid 1990s, it has become evident that there are two phases in the natural course of severe or necrotizing AP. It includes an early vasoactive and toxic phase and a late phase dominated by septic complications. The first 14 days after onset of the disease are characterized by SIRS, resulting in organ system failure. Inflammatory mediators released into the systemic circulation are associated with the development of cardiorespiratory and renal failure, fever, and tachycardia. Organ system failure may resolve or become increasingly severe. In the late phase, infection of pancreatic necrosis develops usually after the first week, peaks in the second and third week after onset of the disease, and is reported in 20% to 30% of patients with necrotizing pancreatitis. Infected necrosis is the single most important risk factor in death from necrotizing pancreatitis, with sepsis-related multiple organ failure as the main life-threatening complication with a mortality rate of up to 70%.

CLASSIFICATION OF FLUID COLLECTIONS AND INFECTIONS

There are two distinctive forms of infection in AP: that which follows interstitial edematous pancreatitis (IEP) and necrotizing pancreatitis (Table 47.2). In addition, infection is categorized by its timing, either <4 weeks or ≥4 weeks after onset of AP. CT of IEP demonstrates edema manifested by localized, diffuse enlargement with homogenous or minimally heterogeneous enhancement of pancreatic parenchyma. Conversely, there are three forms of necrosis: (1) limited to the pancreas alone; (2) peripancreatic tissue alone; and (3) the combination of the above, which is the most common CT finding. Pancreatic necrosis is graded on CT as being <30% or ≥30%.

Acute pancreatic fluid collections occur frequently (30% to 50%), and early in the course of interstitial edematous pancreatitis, and most (>50%) reabsorb spontaneously. If they persist > 4 weeks and are encapsulated, they are referred to as pseudocysts, which do not contain non-liquefied necrotic material. Either fluid collection may become infected.

Conversely, in patients with necrotizing pancreatitis, the fluid collection contains non-liquefied necrotic material. The initial collection is variably loculated and nonencapsulated. Over time, liquefaction develops as the necrotic tissue breaks down. Collections that contain non-liquefied necrotic elements are more likely to become infected. On CT, air bubbles within the collection suggest infection, but can also occur as a result of fistulization into the bowel. Subsequently, it may become encapsulated and is then referred to as walled-off necrosis. Similar to above, either fluid collection may become infected.

Table 47.2 Revised Atlanta classification of fluid collections in acute pancreatitis

Type of pancreatitis	Fluid collections
< 4 weeks after onset	
Interstitial edematous pancreatitis	APFC (acute peripancreatic fluid collection): sterile or infected
Necrotizing pancreatitis	ANC (acute necrotizing collection) Parenchymal necrosis alone: sterile or infected Peripancreatic necrosis alone: sterile or infected Pancreatic and peripancreatic necrosis: sterile or infected
≥ 4 weeks after onset	
Interstitial edematous pancreatitis	Pancreatic pseudocyst: sterile or infected
Necrotizing pancreatitis	WON (walled-off necrosis): sterile or infected

Adapted from: Sarr MG, Banks PA, Bollen TL, *et al.* Revision of the Atlanta classification of acute pancreatitis. Acute Pancreatitis Classification Working Group, April 2008. http://www.pancreasclub.com/resources/AtlantaClassification. (Accessed August 25, 2013.); and Thoeni RF. *Radiology* 2012 Mar;262(3):751–764.

PATHOGENESIS

The pathophysiology of infection of peripancreatic necrosis is essentially unknown. Upper gastrointestinal dysmotility has been observed in AP as well as in cholestasis and sepsis. There are several hypothetical mechanisms by which bacteria can enter pancreatic and peripancreatic necrosis leading to the infection and include (1) the

Acute pancreatitis with splanchnic hypoperfusion → increase in intestinal permeability.
Fasting with depletion of luminal nutrients→ disturbed motility → bacterial overgrowth.

Result → bacterial translocation

Figure 47.1 Factors possibly leading to bacterial translocation. Adapted from Bakker OJ, van Santvoort HC, Besselink MGH, *et al. Curr Gastroenterol Rep.* 2009;11:104–110.

hematogenous route via the circulation, (2) transmural migration through the colonic bowel wall to the pancreas (translocation), (3) via ascites to the pancreas, (4) via the lymphatics to the circulation, (5) via the biliary duct system, and/or (6) from the duodenum via the main pancreatic duct. Most pathogens in pancreatic infection are the gastrointestinal gram-negative bacteria, with the bowel seeming to be the main source of pancreatitis-related infections. It is, therefore, possible that bacterial translocation is the most important mechanism for contamination of pancreatic necrosis (Figure 47.1).

Several studies have examined the frequency of bacterial infection of necrotic areas in the natural course of severe AP, without antibiotic intervention. One series showed an overall contamination rate of 24% within the first week of the onset of AP in patients undergoing surgery for severe AP, increasing to 46% and 71%, respectively, in the second and third weeks. Thus, patients with severe AP have the highest risk of pancreatic infection in the third week after onset of the disease. The overall infection rate in this series was 39%.

Pancreatic necrosis may become infected after the fifth day of disease and is dependent on the extent of intra- and extrapancreatic necrosis. Through morphologic analysis by contrast-enhanced CT scanning, a higher rate of infection was found in patients with extensive pancreatic necrosis. Two-thirds of the patients with infected pancreatic necrosis had a total amount of necrosis of more than 30%, whereas 60% of patients with sterile necrosis had necrotic areas of less than 30%. Therefore, the presence of a significant extent of necrosis (>50% on CT scanning) is predictive of severe disease and helps to identify patients who might develop septic complications.

MICROBIOLOGY

Prior to the era of prophylactic use of antibiotics in AP, the predominant pathogens found in pancreatic infection were gastrointestinal gram-negative bacteria. The culture of infected pancreatic necrosis yielded monomicrobial flora in 60% to 87% of cases. A preponderance of gram-negative aerobic bacteria was usually present (*Escherichia coli, Pseudomonas* spp., *Proteus, Klebsiella* spp.), which suggested an enteric origin. These pancreatic infections are usually monomicrobial with *E. coli*. Gram-positive bacteria (*Staphylococcus aureus, Enterococcus faecalis, Enterococcus*), anaerobes, and, occasionally, fungi had also been found. The incidence of fungi in long-term disease may increase, especially after prolonged antibiotic treatment.

PREDICTIVE FACTORS

Several factors have been associated with the infection rate of pancreatic necrosis. It has been demonstrated that the frequency of infected necrosis correlates with the duration of the disease. In patients with necrotizing pancreatitis, the proportion of patients who had proven infected necrosis at the time of surgery rose from 24% in the first week to 36% and 72% in the second and third weeks, respectively. Using CT-guided fine-needle aspiration (FNA), infection was reported in 22% of patients within the first week after the onset of pancreatitis and in 55% within 2 weeks. Additionally, infection also correlates with the extent of pancreatic necrosis, with the highest infection rates reported in patients who had more than 50% necrosis of the pancreas.

Overall there seem to be no differences with regard to clinical course and infection rate depending on the etiologic factor in AP. This was shown in another prospective study with 190 patients that analyzed the severity of the disease, serum enzyme elevation, indicators for necrosis, systemic complications, and mortality with regard to etiology of the pancreatitis, showing no differences based on etiology of the pancreatitis.

DIAGNOSIS

Infection of pancreatic collections is usually suspected in patients who develop clinical signs of sepsis or ongoing organ system failure or when imaging suggests presence of infection. These patients should undergo CT-guided or endoscopic ultrasound-guided FNA of pancreatic necrosis or adjacent fluid to differentiate between sterile and infected necrosis. Complication rates of this procedure are low, with only very few serious complications such as contamination of a sterile collection, bleeding, aggravation of AP, or death reported in the literature. Bacterial testing of the aspirate, including Gram staining and culture of the aspirated material, yields diagnostic sensitivity and specificity of 88% and 90%. CT-guided FNA has an approximately 10% false-negative rate for diagnosis of infection. It is important to emphasize that only those patients who present with clinical signs of sepsis or ongoing organ system failure should undergo FNA, as FNA bears a potential risk of secondary infection.

TREATMENT

Infected pancreatic necrosis requires use of antibiotics and usually intervention with surgery or drainage. However, conservative treatment with antibiotic administration and supportive care is appropriate in select patients that are stable. Conversely, the management of sterile pancreatic necrosis is usually nonoperative. Surgical intervention in patients with sterile pancreatic necrosis is limited to patients with a deteriorating clinical course that does not respond to intensive care.

There is general agreement that interventional treatment of proven infected necrosis should be postponed for as long as possible, and to the third week or later to optimize operative conditions, and reduce morbidity and mortality. These improved outcomes are driven by allowing for demarcation of pancreatic and peripancreatic necrosis, improved liquefaction, and separation of necrosis from healthy parenchyma. In addition, there is often a reduction in the presence of SIRS by 3 weeks of supportive care. If less than 4 weeks have passed since onset of AP, percutaneous large-bore catheter drainage can be definitive or bridge therapy to stabilize critically ill patients prior to further interventions.

Traditionally, therapy for infected pancreatic necrosis was open necrosectomy. However, this approach is associated with a high rate of complications and mortality. More recently, a step-up approach using percutaneous drainage followed by a minimally invasive surgery has been proposed, with the goal of controlling septic complications rather than complete debridement of necrotic material. In a randomized trial of patients with suspected or confirmed infected pancreatic necrosis, patients underwent primary necrosectomy or a step-up approach using percutaneous drainage and then minimally invasive retroperitoneal necrosectomy if needed. Their composite primary end point of major complications (new-onset multiple-organ failure or multiple systemic complications, perforation of a visceral organ or enterocutaneous fistula, or bleeding) was found to be significantly less in the step-up approach than in those undergoing open necrosectomy (Figure 47.2).

Surgical methods for the treatment of necrosis are varied, and the best method has yet to be determined. The recommended, and currently

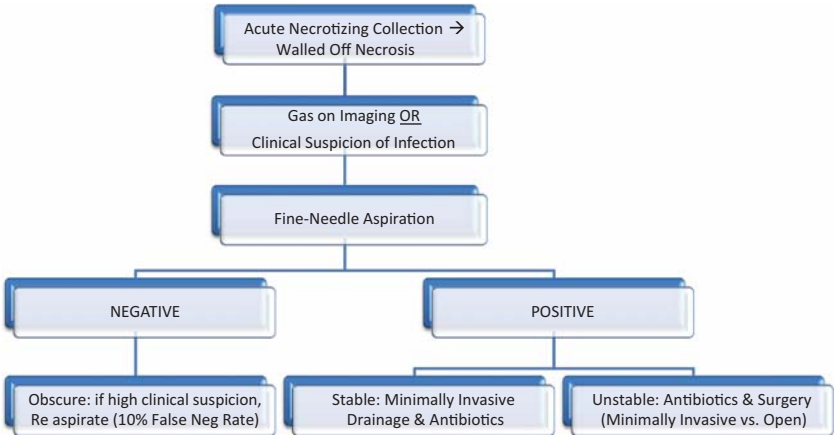

Figure 47.2 Approach to acute necrotizing pancreatitis.

Table 47.3 Minimally invasive approaches to infected pancreatic necrosis

	Endoscopic approach	Percutaneous interventional drainage	VARD	Transperitoneal laparoscopic debridement
Invasiveness	1 +	2 +	3 +	3 +
Fistula formation	1 +	3 +	3 +	2 +
Repeated procedures	Yes	Yes	Yes	No
Removal of necrosis	If WON, location dependent	NOT central gland	Yes	Yes
Failure rate/ complications	0–32%; local bleeding	31–87%	Cannot remove gallbladder	Intraperitoneal infection, 36% transmission
Adjunctive treatment required	Yes	Often	Often	Yes

Abbreviations: VARD = videoscopic-assisted retroperitoneal debridement; WON = walled-off pancreatic necrosis.
Adapted from Navaeethan *et al. Pancreas.* 2009;38(8):867–875.

accepted, surgical management technique should be an organ-preserving approach that involves debridement and necrosectomy, combined with a postoperative management concept that maximizes evacuation of retroperitoneal debris and exudate. Three comparable techniques are available: (1) closed continuous lavage of the retroperitoneum, (2) management by planned, staged re-laparotomy, and (3) the open packing technique. In experienced hands, these approaches have reduced mortality from severe AP to $\leq$15%. Minimally invasive approaches include percutaneous CT-guided catheter drainage, endoscopic ultrasound-guided intrapancreatic drainage and irrigation lavage, videoscopic-assisted retroperitoneal drainage and lavage, and laparoscopic transperitoneal necrosectomy and debridement. They can be used as a curative procedure, a temporizing measure prior to surgery, or as a follow-up procedure after surgery. Patients undergoing these minimally invasive approaches have a reduced need for postoperative intensive care and less systemic inflammatory response; however, minimally invasive approaches may need to be combined to achieve maximum efficacy (Table 47.3). In a small percentage of cases, minimally invasive methods fail, and open surgery is required.

PREVENTION OF INFECTION WITH ANTIBIOTICS AND PROBIOTICS

The role of prophylactic antibiotics to prevent secondary infection of pancreatic tissue has been a contentious issue. However, an updated meta-analysis including all published trials to 2009 that included 841 patients with severe AP found that antibiotic prophylaxis in severe AP patients was not associated with a statistically significant decrease in mortality or need for surgery. There was no decrease in the incidence of infected pancreatic necrosis or the incidence of extrapancreatic infections. Overuse of antibiotics may result in development of antibiotic resistance and delayed-onset fungal infections. Fungal infections of necrotic pancreatic tissue are associated with increased morbidity due to increased ICU-time, duration of hospitalization, and organ failure, with *Candida albicans* being the most prevalent fungal organism followed by *Torulopsis glabrata*.

The use of probiotics for infection prophylaxis in AP has also been examined. A recent randomized, double-blind, placebo-controlled trial of patients with severe AP showed no reduction in the risk of infections, but did show an increased risk of mortality in the population that received probiotics.

NUTRITIONAL SUPPORT OF PATIENTS WITH NECROTIZING PANCREATITIS

Classically, patients with severe AP were treated with total parenteral nutrition (TPN) because enteral feeding was thought to stimulate the pancreas and worsen pancreatic injury. In contrast, recent data suggest that TPN does not hasten pancreatic recovery and that enteral feeding is actually well tolerated. Potential benefits of enteral feeding include decreased gut permeability, prevention of bacterial translocation, and a reduction in secondary pancreatic infection. Enteral feeding is also significantly less expensive than TPN and is associated with fewer cases of catheter-related sepsis and TPN-related fungemia.

Several prospective randomized studies have examined the role of enteral feeding, initiated within 48 hours of the onset of severe AP, administered via a tube advanced into the jejunum under radiographic guidance. These studies, which included approximately 100 patients in total, suggest that enteral nutrition results in fewer total and septic complications, and significantly improves acute phase responses and disease severity scores.

A recent meta-analysis of randomized controlled trials compared enteral and parenteral nutrition in patients with predicted severe AP. Enteral feeding reduced the risk of infectious complications (relative risk 0.47), pancreatic infections (relative risk 0.48), and mortality (relative risk 0.32). However, there was no statistically significant reduction of organ failure. Unfortunately, patients in all of the five included studies received antibiotics, which thus may have a synergistic role with enteral nutrition. There is likely no difference in the outcomes whether there is nasogastric or nasojejunal feedings.

While the best time to start enteral nutrition is unknown, studies of patients admitted to the intensive care units with other diseases have reported a lower incidence of infections when enteral nutrition was started immediately compared with starting 36 hours later. Enteral nutrition can be delivered at one-third to one-fifth the cost of TPN. Therefore, in patients who are unable to take in oral nutrition by day 3, evaluation for enteral feedings should be initiated.

INFECTED PERIPANCREATIC COLLECTIONS AND PSEUDOCYSTS

Up to 40% of patients with AP have acute peripancreatic fluid collections that consist of enzyme-rich pancreatic secretions that occur during the first 2 weeks of the episode. These acute collections are usually peripancreatic, without a capsule, and confined to the anatomic space within which they arise. Extrapancreatic fluid collections can also occur in the lesser sac, perirenal, and spleen and liver. These collections, which can be single or multiple, result from pancreatic and gastrointestinal fistulas that usually close spontaneously. Most acute fluid collections resolve spontaneously so they do not need to be drained unless they become infected. If they become encapsulated, they are termed pancreatic pseudocysts, and can also become infected. If infected, percutaneous or endoscopic drainage of the infected acute peripancreatic fluid collection or pseudocyst can be performed. Once drainage ceases, and the collection is resolved via CT scan, a fistulogram can be performed to document that ductular communication has ceased, and then the catheter can be removed.

SUMMARY

In conclusion, our goal in patients with severe AP is to initiate supportive care primarily with volume resuscitation, and early enteral nutrition if they are unable to tolerate oral feeding. If the patient is clinically suspected of having an infected pancreatic or peripancreatic collection, CT-guided FNA with culture and sensitivity of the aspirate is performed. If infection is present in the culture of the aspirate, resulting cultures and sensitivities direct appropriate antibiotic therapy. Support for organ system failure is ongoing, with the goal to prolong the time to intervention, until the second week or thereafter. Initial intervention should be a stepwise combination of minimally invasive approaches, reserving open surgery for only nonresponsive cases.

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48. Esophageal infections

Mark Flasar and Jean-Pierre Raufman

Esophageal infections are encountered frequently in clinical practice, particularly in patients with impaired host defenses, and are an important contributor to morbidity and mortality. The acquired immunodeficiency syndrome (AIDS) epidemic and increasing use of immunosuppressive therapy for organ transplantation contributed to an increased incidence of esophageal infections. Fortunately, increased use of highly active antiretroviral therapy (HAART) to treat human immunodeficiency virus (HIV)/AIDS lessened the risk of opportunistic esophageal infections in this group. Although *Candida albicans* is a common etiologic agent in mildly immunosuppressed patients with infectious esophagitis, a variety of fungal, viral, and bacterial pathogens are capable of causing infection (see Table 48.1). Regardless of the causative organism, infection results in mucosal inflammation and the hallmark clinical complaint of odynophagia (painful swallowing). This may progress to erosions, ulcers, and fistulas. Rapid identification and treatment of the infecting organism is of paramount importance because, in contrast to underlying clinical states that predispose to their occurrence, esophageal infections generally respond rapidly and completely to appropriate treatment.

Table 48.1 Organisms associated with infectious esophagitis

Fungi
Candida species (especially *C. albicans*)
Aspergillus species
Histoplasma capsulatum
Blastomyces dermatitidis
Viruses
Herpes simplex virus type 1
Cytomegalovirus
Varicella-zoster virus
Human immunodeficiency virus Human papilloma virus
Bacteria
Mycobacterium tuberculosis and *M. avium*
Actinomyces israelii
Staphylococcus aureus
Streptococcus viridans
Lactobacillus acidophilus
Treponema pallidum
Idiopathic ulcerative esophagitis in AIDS
Parasite
Trypanosoma cruzi

FUNGAL INFECTIONS OF THE ESOPHAGUS

Candida species

Candida albicans is the fungal organism most frequently implicated in infectious esophagitis. Other *Candida* species (*Candida tropicalis, Candida parapsilosis, Candida krusei*, and *Candida glabrata*) less commonly cause disease in the absence of severe immunosuppression. *Candida* organisms are normal components of the oral flora, and colonization of the esophagus is not unusual. A population-based study revealed esophageal colonization in approximately 20% of healthy, ambulatory adults. Colonization involves adherence and proliferation of *Candida* organisms within the superficial mucosa. Progression to infectious esophagitis requires invasion of the epithelium, usually in the setting of defective cellular immunity. The spectrum of esophageal infection with *Candida* species is broad, ranging from scattered white plaques accompanied by mild or no symptoms to dense pseudomembranes consisting of fungi, sloughed mucosal cells, and fibrin overlying severely damaged mucosa. The latter are usually accompanied by severe symptoms.

Advanced infection with HIV is the most significant risk factor for the development of

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candidal esophagitis, although the prevalence of esophageal *Candida* infection is decreasing with the widespread use of HAART. Infection is primarily seen with CD4 counts $<200/mm^3$ and represents an AIDS-defining illness. The risk of infection increases with the degree of immune compromise, occurring most frequently in patients with persistently low CD4 counts. Additional risk factors include hematologic malignancies, diabetes mellitus, adrenal insufficiency, alcoholism, advanced age, radiation therapy (especially for cancers of the head and neck), systemic chemotherapy, and the use of topical oro-nasopharyngeal steroids. Esophageal motility disorders (e.g., achalasia) may also predispose to infection. Immunosuppression in organ transplant recipients imparts significant risk although the prevalence of infection is reduced by the frequent use of systemic fungal prophylactic therapy. Immunomodulatory and biologic therapy, increasingly utilized in the management of immunologic conditions such as inflammatory bowel disease and rheumatoid arthritis, does not appear to increase the risk for esophageal candidiasis.

CLINICAL PRESENTATION AND COMPLICATIONS

Candida esophagitis may not cause symptoms, particularly in those who are immunocompetent with few adherent esophageal plaques. When symptomatic, the most common complaint is odynophagia, usually localized to a discrete retrosternal area. Odynophagia may impair swallowing minimally, or the pain may be so intense that the patient avoids eating (sitophobia) and is unable to tolerate secretions. In severe cases, retrosternal chest pain or burning may be present without swallowing. In granulocytopenic patients, fungal infection may be disseminated, thereby resulting in fever, sepsis, and signs and symptoms related to hepatic, splenic, or renal fungal abscesses.

In AIDS, esophageal candidiasis is commonly associated with oropharyngeal thrush. However, *Candida* esophagitis occurs independently of thrush at least 25% of the time. Overall, positive and negative predictive values of thrush for diagnosing *Candida* esophagitis are 90% and 82%, respectively.

It is important to recognize that mucosal *Candida* infections frequently coexist with other esophageal infections. For example, in published case series, oral thrush was present in 7 of 14 patients with herpes simplex virus (HSV) esophagitis and in 2 of 10 with HIV-associated idiopathic ulcers. In a study including 52 HIV-infected patients diagnosed with symptomatic *Candida* esophagitis, concomitant cytomegalovirus (CMV) and HSV infections were found in 22 and 2 patients, respectively.

Severe complications of esophageal candidiasis include esophageal bleeding from ulceration; luminal obstruction from a fungus ball; mucosal scarring and stricture; fistulization into the trachea, bronchi, or mediastinum; and esophageal mucosal sloughing with replacement by pseudomembranes. Although life-threatening hemorrhage has been reported, bleeding from esophageal candidiasis is usually mild, not requiring transfusion.

DIAGNOSIS

Candida esophagitis should be suspected when at-risk patients complain of odynophagia or dysphagia. In this setting, empiric therapy is recommended, as uncomplicated cases should improve within several days. However, because of frequent coinfection, further evaluation (e.g., esophagoscopy) is appropriate for those not responding within 3 to 4 days.

The most accurate method for diagnosing fungal esophagitis is endoscopy with directed brushing and biopsy of lesions (Figure 48.1). Endoscopic appearance alone may be suggestive but is insufficient to diagnose *Candida* esophagitis. Typical candidal plaques are creamy white or pale yellow (Figure 48.2A). Brushings from involved surfaces and ulcers can be obtained with a sheathed cytology brush spread onto slides and stained by the periodic acid–Schiff (PAS), silver, or Gram methods. Mycelial forms and masses of budding yeast are consistent with *Candida* infection (Figure 48.2B). Fungal cultures are generally not helpful unless an unusual pathogen (e.g., a resistant *Candida* species, such as *C. glabrata*) is suspected.

Because findings are often nonspecific and concomitant infections will be missed, radiographic studies of the esophagus are not primarily utilized to diagnose esophageal infections. Radiographic examination may be useful when endoscopy is not available, when biopsies are contraindicated because of coagulopathy, or when perforation, stricture, or fistula is suspected (significant dysphagia or coughing with eating). When abnormal, barium esophograms may reveal a "shaggy" esophagus, plaques, pseudomembranes, cobblestoning, nodules, strictures, fistulas, or mucosal bridges.

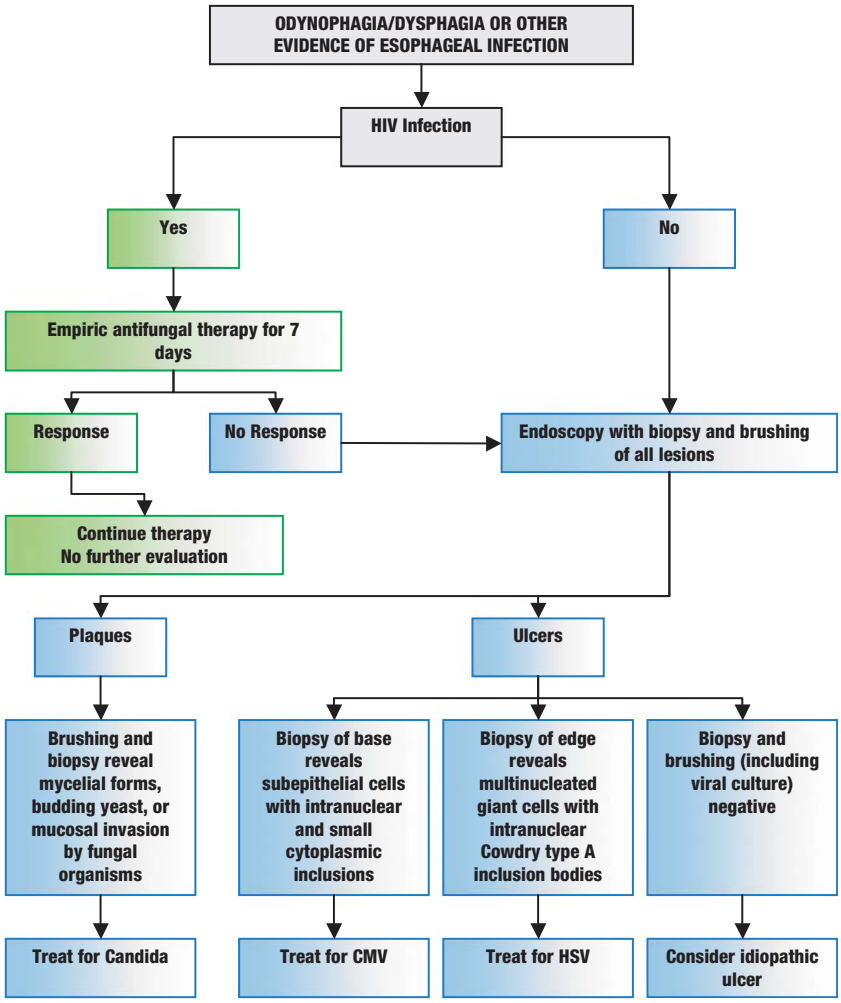

Figure 48.1 Suggested diagnostic approaches to common esophageal infections. HIV = human immunodeficiency virus; CMV = cytomegalovirus; HSV = herpes simplex virus type 1.

TREATMENT

Guidelines published by the Infectious Disease Society of America (IDSA) support the general approach that *Candida* esophagitis requires systemic therapy and should not be managed with local agents. High-risk patients with odynophagia or dysphagia can be treated empirically with oral antifungal therapy without endoscopic confirmation of disease, particularly if oral thrush is present. If symptoms do not improve after 3 to 4 days, further evaluation is necessary.

Antifungal treatment options for esophageal candidiasis include the imidazoles, echinocandins, and amphotericin B. Imidazoles alter fungal cell membrane permeability by inhibiting ergosterol synthesis. Potential agents in the imidazole class include fluconazole, itraconazole, voriconazole, and posaconazole. Fluconazole (400 mg loading dose followed by 200 to 400 mg daily for 14 to 21 days orally or intravenously) is favored due to its excellent efficacy (as high as 90%), ease of administration, infrequent toxicity, and low cost. Itraconazole oral solution (200 mg daily) appears as effective as fluconazole in randomized trials but can be limited by associated nausea. Itraconazole capsules are available, but absorption may be unpredictable compared to the solution. Additionally, itraconazole inhibits the cytochrome P450 enzymes, increasing the potential for drug interactions. In a large, randomized, double-blind, multicenter trial, voriconazole (200 mg twice daily orally or 4 mg/kg every 12 hours intravenously) was as effective as fluconazole and may be effective in cases refractory to fluconazole. Posaconazole oral solution (400 mg twice daily) has likewise shown efficacy

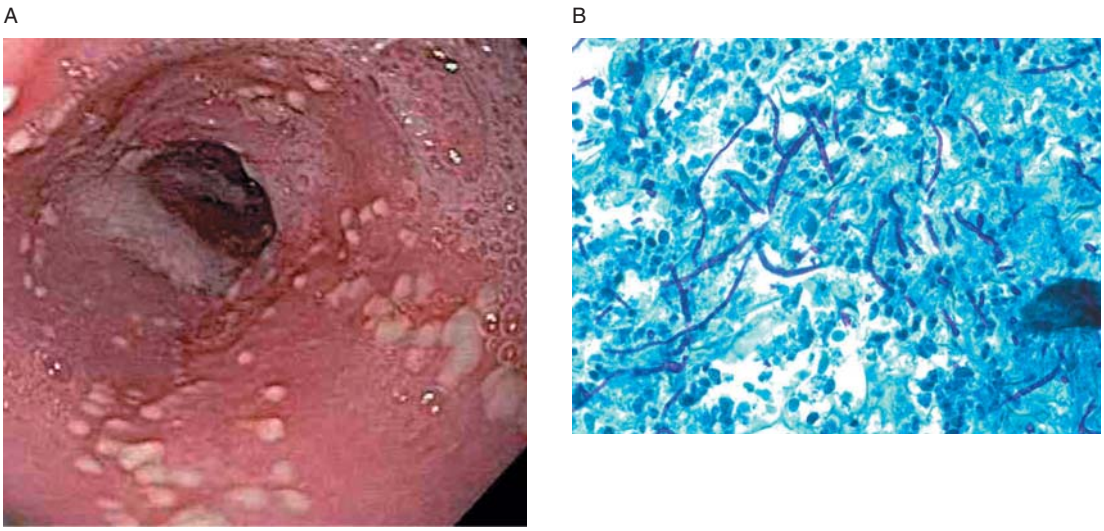

Figure 48.2 (A) Endoscopic appearance of *Candida* esophagitis with multiple raised white plaques. (B) Biopsy revealing budding yeast cells, hyphae, pseudohyphae, and mucosal invasion by the organisms (periodic acid–Schiff 60×; courtesy of Harris Yfantis, MD, Baltimore VA Medical Center, MD).

in itraconazole- or fluconazole-refractory *Candida* esophagitis. Echinocandins inhibit the synthesis of β(1,3)-D-glucan, an essential component of *Candida* cell walls. Options include caspofungin, micafungin, and anidulafungin. The echinocandins are administered intravenously and are therefore utilized in hospitalized patients with severe *Candida* esophagitis. In addition, echinocandins are associated with higher relapse rates and cost more than azoles, so they are generally reserved for azole-refractory or -intolerant cases. In a double-blind, randomized trial of patients with advanced HIV and confirmed *Candida* esophagitis, caspofungin (50 mg daily intravenously) was efficacious and well tolerated compared to fluconazole (200 mg daily intravenously). Caspofungin also appears effective in fluconazole-resistant cases, and provides an attractive alternative to the more toxic amphotericin B. Studies with micafungin (150 mg daily intravenously) and anidulafungin (100 mg on day 1 followed by 50 mg daily intravenously) also suggest similar initial efficacy and tolerability compared to fluconazole. However, higher relapse rates were seen with anidulafungin than with fluconazole, and the current recommended treatment dose is 200 mg daily intravenously.

Amphotericin B binds irreversibly to fungal membrane sterols, thereby altering membrane permeability. Amphotericin B (0.3 to 0.7 mg/kg daily intravenously) has similar efficacy compared to fluconazole but, due to increased toxicity relative to other agents, its use should be limited in patients with *Candida* esophagitis. Current indications for amphotericin B include infections associated with drug resistance and pregnancy. Imidazoles are teratogenic and should not be used during the first trimester of pregnancy. No data are available regarding the use of echinocandins in pregnancy.

Of the different types of agents used for treating esophageal candidiasis, drug resistance has been associated predominantly with imidazoles. Risk factors include advanced immunosuppression and chronic imidazole exposure, regardless of whether continuous or episodic. Resistant cases can usually be managed with the echinocandins or amphotericin B.

For chronically immunosuppressed patients, long-term therapy with fluconazole (100 mg daily) effectively prevents oropharyngeal and esophageal candidiasis. However, because therapy for acute infection is generally effective and resulting mortality infrequent, and prophylactic therapy incurs cost and the potential for developing resistance and drug interactions, it is generally not advocated. Nonetheless, secondary prophylaxis may be appropriate for patients with frequent or severe infections, especially if they have not achieved immune reconstitution on HAART.

Other fungal infections of the esophagus

Esophageal aspergillosis, histoplasmosis, and blastomycosis, acquired from the environment

rather than from endogenous flora, are much less common than infection with *Candida* species. Blastomycosis and histoplasmosis commonly invade the esophagus from paraesophageal lymph nodes. *Aspergillus* infection results in large, deep ulcers, whereas esophageal histoplasmosis and blastomycosis are characterized by focal lesions and abscesses. Severe odynophagia results from involvement of muscle layers. Complications of atypical fungal infections include esophageal stricture and tracheoesophageal fistula. *Aspergillus* species have a distinctive microscopic appearance. *Histoplasma* organisms usually do not invade the esophageal mucosa. Hence, endoscopic brushing and biopsy specimens may be nondiagnostic, and bronchoscopy, mediastinoscopy, or surgery may be needed to diagnose this infection. Intravenous amphotericin B is the preferred treatment for *Aspergillus* infection and is also used for complicated histoplasmosis and blastomycosis. Itraconazole, voriconazole, and caspofungin may also have a role for these uncommon infections.

VIRAL INFECTIONS OF THE ESOPHAGUS

Herpes simplex virus type 1 (HSV-1)

HSV-1 is the most common herpesvirus that infects the esophagus; the others are CMV and varicella-zoster virus (VZV). HSV type 2 (HSV-2) has also been reported. HSV-1 esophagitis usually occurs in the setting of immunocompromise although infection may also occur in immunocompetent individuals without predisposing risk factors. Most infections occur in those receiving immunosuppressive medications, such as solid organ and bone marrow transplant recipients, as opposed to HIV-infected individuals. In three series, HSV was the sole cause of infectious esophagitis in <5% of patients with HIV.

HSV is a large, enveloped, double-stranded DNA virus that infects squamous epithelium. Latency in the root ganglia of nerves supplying the affected regions may follow resolution of acute HSV infection. Although primary HSV esophagitis occurs, most cases result from virus reactivation in the root ganglia of nerves that supply the affected regions, such as the laryngeal, superficial cervical, or vagus nerves.

Presenting symptoms are usually odynophagia (often abrupt onset) and/or dysphagia. Other common symptoms include persistent retrosternal pain, fever, nausea, and vomiting. Bone marrow transplant recipients may have continuous nausea and vomiting as the sole manifestation of HSV esophagitis. Herpes labialis (i.e., cold sores) or perioral skin involvement may precede or occur concurrently with esophageal infection. About 25% of HSV esophagitis cases are accompanied by either HSV or *Candida* infection in the oropharyngeal or genital area. In untreated immunocompetent persons, HSV esophagitis generally resolves 1 to 2 weeks after the onset of symptoms, although early initiation of antiviral therapy may hasten recovery. In immunodeficient patients, esophageal infection with HSV can cause hemorrhage, perforation with tracheoesophageal fistulas, food impaction, or dissemination to the liver, lungs, and central nervous system.

A diagnosis of HSV esophagitis is usually established initially by endoscopy (see Figure 48.1). Early, vesicular herpetic lesions (round 1- to 3-mm vesicles in the mid to distal esophagus) are characteristic but rarely seen. More commonly, by the time endoscopy is performed, vesicles have sloughed to reveal discrete, circumscribed ulcers (usually <2 cm) with raised edges (Figure 48.3A). These "volcano" lesions result in the classic appearance of HSV esophagitis on double-contrast barium studies of the esophagus, although similar radiographic findings may rarely be seen in *Candida* esophagitis. Discrete HSV ulcers seen at early stages can coalesce into large lesions or, in severe cases, progress to near-total denudation of the esophageal epithelium. Hence, diffuse herpetic esophagitis results in cobblestoning or a "shaggy" mucosa that is similar in appearance to *Candida* esophagitis.

HSV infection is confirmed with viral culture and histologic or cytologic examination of brushings and biopsies from ulcer edges. This is because HSV preferentially infects squamous epithelial cells, where viral cytopathic changes are most likely present. Material from the ulcer base, where epithelial cells are absent, is not adequate to establish a diagnosis. Viral culture is more sensitive than routine histologic examination of brushings and biopsy specimens. Findings observed with histologic staining of HSV-infected epithelial cells include multinucleated giant cells, ballooning degeneration, "ground-glass" intranuclear (Cowdry type A) inclusions, and margination of chromatin (Figure 48.3B). Immunohistochemical stains using monoclonal antibodies to HSV glycoproteins are also available. More recently, polymerase chain reaction (PCR) testing has been utilized, though this has specificity and positive-predictive-value limitations.

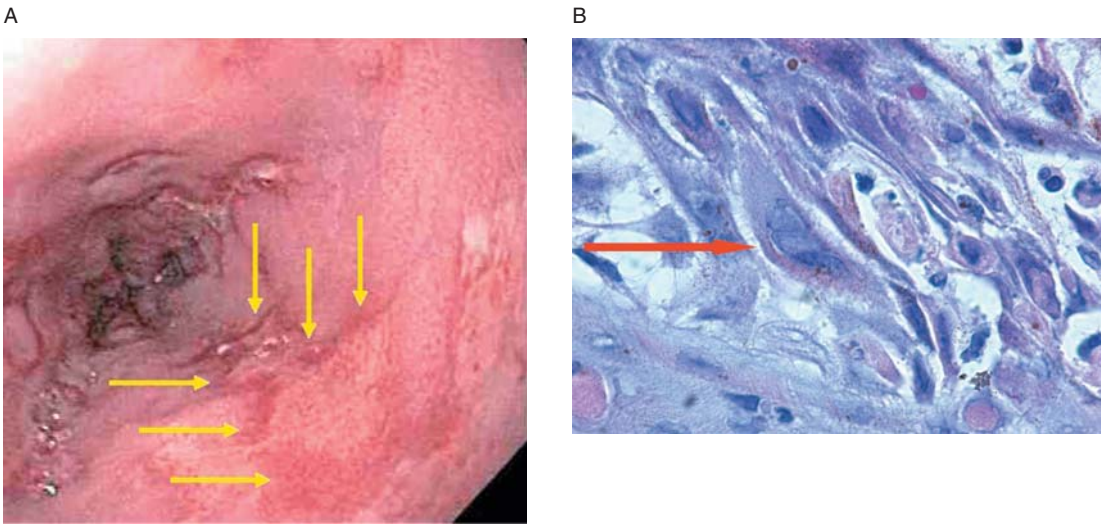

Figure 48.3 (A) Endoscopic photograph revealing a large sharply demarcated ulcer with raised edges in the middle third of the esophagus. Ulcer borders are defined by arrows. (B) Biopsy from the ulcer margin demonstrating a multinucleated giant cell (hematoxylin and eosin stain, 100×; courtesy of Harris Yfantis, MD, Baltimore VA Medical Center, MD).

For immunocompromised patients able to tolerate oral medications, HSV esophagitis should be treated for 14 to 21 days primarily with acyclovir (400 mg five times daily). Famciclovir (500 mg three times daily) and valacyclovir (1000 mg three times daily) for the same duration are reasonable (though more costly and less established) alternatives. Those unable to swallow should be treated with intravenous acyclovir (5 mg/kg every 8 hours) for 7 to 14 days. Oral therapy should be used to complete treatment when feasible. This is especially important given the ongoing manufacturing shortage of intravenous acyclovir since November 2012. Alternative intravenous options include ganciclovir and foscarnet. Immunocompetent patients with HSV esophagitis may experience spontaneous resolution after 1 to 2 weeks, although a short course of oral acyclovir may accelerate clinical improvement. Oral dosing regimens of 200 mg five times daily or 400 mg three times daily for 7 to 10 days have been anecdotally effective. Unfortunately, strains of HSV resistant to acyclovir have emerged, especially in immunocompromised patients. Due to cross-resistance to valacyclovir and famciclovir in such cases, intravenous foscarnet at a dose of 40 mg/kg three times daily is required. Viscous lidocaine solutions have been utilized for pain relief, though this is limited by modest efficacy and potential for systemic absorption and toxicity.

Prophylaxis with oral acyclovir may be indicated for immunocompromised persons at high risk for reactivation of HSV such as HSV-seropositive transplant recipients and AIDS patients with recurrent herpetic infections. Famciclovir, an acyclovir analog with a similar spectrum of activity and superior bioavailability, may also be employed for oral prophylaxis and treatment.

Cytomegalovirus (CMV)

CMV, a ubiquitous herpesvirus, infects most of the world's adults. In healthy people with latent infection, CMV viral DNA can be detected in many tissues, including circulating leukocytes. Latent infection is responsible for the high transmission rate of the virus from CMV-seropositive donors to CMV-seronegative recipients after blood transfusion or organ transplantation. In contrast to HSV, esophageal infection with CMV, either primary or reactivation of latent virus, occurs only in immunodeficiency states (AIDS and others). Risk factors for esophageal involvement include viremia and advanced immunosuppression, especially CD4 counts <50 cells/mm^3. In published series, CMV was an esophageal pathogen or co-pathogen in 33 of 110 patients with HIV infection and esophageal symptoms and in 7 of 21 symptomatic bone marrow transplant recipients. Other differences

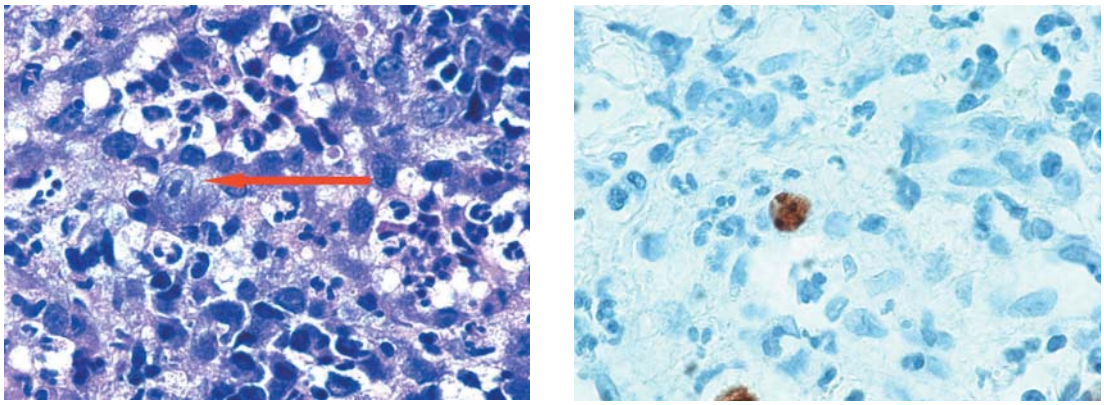

Figure 48.4 (A) Biopsy specimen from the base of an esophageal ulcer revealing a perinuclear "halo" suggestive of herpes simplex virus infection (hematoxylin and eosin stain, 100×, courtesy of Harris Yfantis, MD, Baltimore VA Medical Center, MD). (B) Biopsy specimen revealing subepithelial cytomegalovirus by immunohistochemical staining (100×; courtesy of Harris Yfantis, MD, Baltimore VA Medical Center, MD).

between these herpesviruses are that, in CMV esophagitis, the virus infects subepithelial fibroblasts and endothelial cells of the esophagus, not squamous epithelial cells, and the onset of symptoms with CMV is typically more gradual than with HSV or *Candida* esophagitis. Because CMV disease is systemic and involves multiple organs, nausea, vomiting, fever, epigastric pain, diarrhea, and weight loss are prominent symptoms, whereas dysphagia and odynophagia are less commonly observed than in HSV infection.

To diagnose CMV esophagitis, it is necessary to obtain tissue for biopsy (see Figure 48.1). Alone, clinical assessment, radiographic findings, or endoscopic findings do not suffice to distinguish CMV from other viral causes of esophagitis. In some cases, radiographs may show flat elongated, tear-drop, or stellate giant ulcers. Endoscopically, superficial erosions or deep ulcers with geographic, serpiginous, flat borders in the mid-distal esophagus are suggestive of CMV esophagitis, but findings may be indistinguishable from HSV esophagitis. Deep ulcers may extend longitudinally for several centimeters and may reach the muscularis, occasionally causing stricture formation. Numerous biopsies should be taken from ulcer bases, where CMV-infected subepithelial fibroblasts and endothelial cells are most likely to be present. Superficial brushings for cytologic examination do not increase diagnostic yield. Because CMV may infect gastric and intestinal epithelial and lamina propria cells, biopsy of abnormal mucosa in these areas should also be obtained for histology and viral culture.

Histologic features indicative of CMV infection include the presence of large cells in the subepithelial layer with amphophilic intranuclear inclusions, a "halo" surrounding the nucleus, and, in contrast to HSV and VZV, multiple, small cytoplasmic inclusions (Figure 48.4A). Although immunohistochemical staining and *in situ* hybridization can confirm CMV infection (Figure 48.4B), viral cultures from ulcer base tissues are more sensitive and less costly. Testing for CMV DNA with PCR is more sensitive than viral culture, but interpretation of a positive test may be difficult as latent CMV infection can yield a positive result.

CMV esophagitis is effectively treated with ganciclovir and foscarnet, alone or in combination (see Table 48.2). Ganciclovir (5 mg/kg intravenously every 12 hours for 2 weeks) is highly effective in eliminating CMV from esophageal ulcers, but symptoms are slow to respond and large ulcers are slow to heal. Furthermore, without restoration of the normal immune system, recurrence after short courses of therapy is common. Therefore, it is recommended that full-dose antiviral therapy for 2 to 3 weeks be followed by maintenance therapy until immunosuppression resolves (see Table 48.2). Persons with AIDS and recurrent CMV infection often require indefinite maintenance therapy with ganciclovir. Bone marrow suppression is the major adverse effect of ganciclovir and may be particularly severe when used in combination with other marrow-toxic agents. An additional concern with long-term therapy is emergence of ganciclovir-resistant CMV. Ganciclovir-resistant CMV usually responds

Table 48.2 Recommended treatment of common esophageal infections

Cause	Primary treatment	Alternative treatment
Candida	Fluconazole, 200–400 mg PO/IV daily for 14–21 days (preferred); an echinocandin; or amphotericin B deoxycholate 0.3–0.7 mg/kg daily	Itraconazole oral solution 200 mg daily; or posaconazole 400 mg BID; or voriconazole 200 mg BID
Herpes simplex virus	Acyclovir, 400 mg PO 5 times daily for 14–21 days or 250 mg/m^2 IV q8h (change to PO when feasible) Valacyclovir, 1 g PO 3 times daily for 14–21 days	Foscarnet, 90 mg/kg IV q12h for 14–21 days (for acyclovir-resistant infection) Famciclovir, 500 mg PO twice daily for 14–21 days
Cytomegalovirus	Ganciclovir, 5 mg/kg IV q12h for 14–21 days, followed by maintenance therapy until immunosuppression resolves	Foscarnet, 90 mg/kg IV q12h for 14–21 days, followed by maintenance therapy with 90–120 mg/kg/d
Varicella-zoster virus	Acyclovir, 250 mg/m^2 IV q8h for 7–10 days Famciclovir, 500 mg PO twice daily for 14 days	Foscarnet, 90 mg/kg IV q12h for 14–21 days
HIV-idiopathic ulcers	Prednisone, 40 mg PO daily for 4 weeks, then taper	Thalidomide, 200 mg PO daily for 4 weeks

to foscarnet (90 mg/kg intravenously every 12 hours for 2 to 3 weeks followed by maintenance therapy [90 to 120 mg/kg/d]). Cidofovir, a highly nephrotoxic agent, may be used in cases with ganciclovir and foscarnet resistance.

As CMV is an important cause of morbidity in transplant recipients, prophylaxis against CMV-related disease is important. Morbidity and mortality related to primary CMV infection in CMV-naïve transplant recipients can be reduced by screening donor blood products for CMV antibodies. For patients who are CMV seropositive or who are recipients of organs from CMV-seropositive donors, ganciclovir prophylaxis can prevent CMV infection.

Varicella-zoster virus (VZV)

The frequency of VZV esophagitis during the course of chickenpox or herpes zoster infections is unknown. Symptomatic VZV esophagitis is extremely rare. Although VZV esophagitis may be severe in profoundly immunocompromised individuals, it is relatively minor compared with other manifestations of disseminated infection such as varicella encephalitis, pneumonitis, and fulminant hepatitis. The clinical presentation and esophageal findings with VZV mimic HSV esophagitis. Finding concurrent dermatologic VZV lesions (shingles) is often crucial for diagnosing VZV esophagitis. VZV esophagitis may be treated with acyclovir or famciclovir. Foscarnet is an alternative for acyclovir-resistant VZV (see Table 48.2).

Idiopathic esophageal ulcers in AIDS

HIV infection is often associated with esophageal ulcers that lack identifiable pathogens. These lesions, called *HIV-associated or idiopathic esophageal ulcers*, appear as multiple, small aphthoid ulcers during seroconversion in early HIV infection and, later, as giant, deep ulcers extending up to several centimeters (Figure 48.5). The latter are associated with severe, incapacitating odynophagia. Clinical, radiologic, and endoscopic presentation mirrors that of CMV. Clinical and endoscopic improvements have been reported following systemic prednisone (40 mg/day for 4 weeks followed by a 1-month taper) or intralesional corticosteroid injection. A thorough search for infectious pathogens, including endoscopic brushing and biopsy, must be undertaken before corticosteroid therapy is initiated. Thalidomide (200 mg daily for 4 weeks), a sedative with tumor

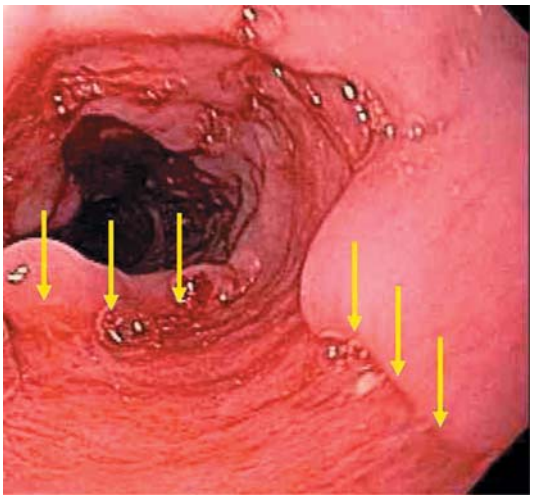

Figure 48.5 Endoscopic photograph of a large idiopathic esophageal ulcer crater in a patient with acquired immunodeficiency syndrome and odynophagia. Ulcer borders are defined by arrows.

necrosis factor-α inhibitory properties, has been used successfully to treat these ulcers, as has the initiation of HAART therapy.

Human papillomavirus (HPV)

HPV is a small DNA virus which can cause warts and condylomata after infecting squamous epithelium following sexual transmission. Esophageal involvement is generally asymptomatic and does not require treatment, with the exception of large lesions causing mechanical symptoms. Endoscopy reveals erythematous macules, nodules, plaques, or exophytic lesions in the mid-distal esophagus. Diagnosis is based on histologic finding of koilocytosis (atypical haloed nucleus), giant cells, or positive immunostaining.

BACTERIAL, MYCOBACTERIAL, TREPONEMAL AND PARASITIC INFECTIONS

Esophageal infection with oropharyngeal flora rarely occurs, although invasive bacteria may account for 11% to 16% of infectious esophagitis in immunodeficient patients, especially those with granulocytopenia. Use of gastric acid-suppressing medications, such as proton pump inhibitors, may increase the risk of bacterial esophagitis. Symptoms of bacterial esophagitis include dysphagia and odynophagia; fever is uncommon. Endoscopic findings are nonspecific, including mucosal friability, plaques, pseudomembranes, and ulcerations. Diagnostic biopsies reveal sheets of confluent subepithelial bacteria. Culture of biopsy material is often contaminated by multiple organisms and of little utility. A broad-spectrum, β-lactam antibiotic combined with an aminoglycoside is standard therapy.

Formerly, esophageal infection with *Mycobacterium tuberculosis* or *Mycobacterium avium* was considered extremely rare, present in less than 0.15% of autopsies. The prevalence of pulmonary and extrapulmonary tuberculosis has increased with the advent of the AIDS epidemic, though esophageal involvement remains rare, accounting for 0.2% to 1% of gastrointestinal tuberculosis cases. Esophageal involvement with tuberculosis almost always results from direct extension of infection from adjacent mediastinal structures, with few cases of primary esophageal tuberculosis. Symptoms of esophageal mycobacterial infection include odynophagia, dysphagia, weight loss, cough, chest pain, and fever, depending on the extent of involvement. Fistulas within the wall of the esophagus (so-called "double-barreled esophagus") and connecting to the mediastinum, trachea, or bronchi are not infrequent. Contrast radiology findings, including ulcers, fistulas, and strictures, are not specific. Gross endoscopic findings include shallow ulcers, malignant-appearing mid-esophageal ulcerating lesions (most common), and extrinsic compression of esophagus from adenopathy (the latter can also be evaluated by computed tomography of the chest). Biopsy sensitivity for caseating granulomas is poor (25% to 60%), as the density of tuberculous granulomas in the infected organ may be low. Additionally, their location in the submucosal layer (not typically sampled with standard mucosal biopsy technique) highlights the possible need for multiple and deep tissue sampling in suspected cases. Visible lesions should be biopsied extensively and brushed. Specimens should be sent for histology, routine culture, mycobacterial culture, acid-fast stain, and PCR. Microbiologic detection methods can likewise suffer from limited sensitivity, but the infection can be confirmed when endoscopic biopsies reveal granulomas or acid-fast bacilli. A positive PCR is also diagnostic. Esophageal infection with mycobacteria is treated with standard multidrug therapy, guided in part by the sensitivity profile in the community. In addition to pharmacologic therapy, endoscopic stenting or surgery is sometimes required to treat fistulas and perforations.

Esophageal syphilis is rare. Classically, tertiary syphilis may be associated with gummas, diffuse ulceration, fistulas, and stricture of the upper third of the esophagus. The diagnosis may be suspected if syphilitic periarteritis is present on endoscopic biopsy specimens; however, immunostaining for *Treponema pallidum* should be performed for definitive diagnosis.

Trypanosoma cruzi, a parasite endemic to South America, can result in progressive destruction of nerve ganglion cells throughout the body, known as Chagas disease. Esophageal involvement with corresponding motor dysfunction can result in dysphagia, cough, aspiration, and chest pain decades following infection. Patients have esophageal manometry findings similar to that seen in achalasia, and undergo similar treatments with vasodilators, gastroesophageal junction myectomy, and esophagectomy.

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49. Gastroenteritis

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GASTROENTERITIS

Gastroenteritis, broadly defined, refers to any inflammatory process of the stomach or intestinal mucosal surface. However, the term usually refers to acute infectious diarrhea, a diarrheal syndrome of less than 2 weeks' duration, which may be accompanied by fever, nausea, vomiting, abdominal pain, dehydration, and weight loss. This chapter provides an overview of the infectious enteritides. Other chapters consider food poisoning, travelers' diarrhea, antibiotic-associated diarrhea, sexually transmitted enteric infections, and *Helicobacter pylori* disease.

Gastroenteritis in high-income countries (HICs), similar to upper respiratory infections, is common and an inconvenience, but it usually does not require a physician visit, laboratory evaluation, or antibiotic treatment. In a US surveillance network with a population-based telephone survey of 12 075 adults (1998–1999), about 0.72 episodes per person-year were documented. In the 2009 US National Ambulatory Medical Care Survey, diarrhea was the second leading gastrointestinal (GI) symptom prompting an outpatient clinic visit, an estimated 4.2 million in total. The Centers for Disease Control and Prevention (CDC) estimates that known foodborne pathogens account for an estimated 14 million illnesses, 60 000 hospitalizations, and 1800 deaths. In the United States in children, it is estimated that acute diarrhea causes 300 to 400 deaths annually. Globally, gastroenteritis is the second principal cause of mortality, after cardiovascular disease. It is the leading worldwide cause of childhood death and of years of productive life lost, with approximately 12 600 deaths per day. Annual per-person attack rates range from 5 to 20 in the low- and middle-income countries (LMICs).

PATHOPHYSIOLOGY

The GI tract is remarkably efficient at fluid reabsorption. Normally, of the 1 to 2 L of fluid ingested orally and the 7 L that enter the upper tract from saliva, gastric, pancreatic, and biliary sources, less than 200 mL of fluid are excreted daily in the feces. Thus, small increases in secretory rate or decreases in the absorptive rate can easily overwhelm the intestinal absorptive capacity. Diarrhea is generally defined as increased frequency (more than three bowel movements) or increased volume (>200 mL/day).

Intestinal infection with bacteria, viruses, and parasites that produce gastroenteritis usually follows fecal–oral transmission. Multiple host defenses are in place to protect the human GI tract (Table 49.1). The principal defenses include gastric acidity and the physical barrier of the mucosa. A gastric pH less than 4.0 will kill more than 99% of ingested organisms, although rotavirus and protozoal cysts can survive. Patients with achlorhydria or hypochlorhydria from chronic atrophic gastritis, gastric surgery, human immunodeficiency virus (HIV) infection, or proton pump inhibitor (PPI) use are at increased risk

Table 49.1 Host defenses

Host defense factor	Example disease state
Barrier	
Gastric acid	Achlorhydria (PPI, HIV, gastric surgery)
Mucosal integrity	Mucositis (chemotherapy)
Intestinal motility	
Peristalsis	Blind loop, antimotility drugs, hypomotility states (diabetes, scleroderma)
Commensal microflora	Antibiotics, age extremes
Sanitation	Contaminated water
Intestinal immunity	
Phagocytic	Neutropenia
Cellular	HIV
Humoral	IgA deficiency

Abbreviations: PPI = proton pump inhibitor; HIV = human immunodeficiency virus; IgA = immunoglobulin A.

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of developing infectious diarrhea. Disruption of the mucosal barrier, as with mucositis associated with chemotherapy or irradiation, may predispose patients to gram-negative bacteremia. Increased peristalsis in gastroenteritis propels organisms along the GI tract, analogous to the cough reflex with clearing of the lungs. The intestinal flora forms an important element of the host defense, both in terms of quantity and composition. The small intestine and colon contain approximately 10^4 and 10^{11} organisms per mL, respectively. More than 99% of the colonic bacteria are anaerobes. Their production of fatty acids with an acidic pH and their competition for mucosal attachment sites prevent colonization by invading organisms. At the extremes of age, in children and the elderly, and after recent antibiotic use, the flora is altered and the risk for gastroenteritis may be increased in some individuals. Impairment of intestinal immunity is also a risk factor for intestinal infections.

Virulence factors play a complementary role in acute infectious diarrhea. Whether an individual ingests an inoculum sufficient to establish clinical gastroenteritis is directly related to the organisms, community sanitation, and personal hygiene. Most organisms require an inoculum of 10^5 to 10^8 to establish infection. Exceptions include *Shigella* and protozoa such as *Giardia, Cryptosporidium*, and *Entamoeba*, which may cause diarrhea when only 10 to 100 organisms are ingested. Certain bacteria may produce toxins, which lead to a variety of clinical syndromes, and include enterotoxin (watery diarrhea), cytotoxin (dysentery), and neurotoxin. Botulinum toxin is the classic example of a preformed neurotoxin, but interestingly, both *Staphylococcus aureus* and *Bacillus cereus* also produce neurotoxins, which act on the central nervous system to produce emesis. Adherence and invasion factors facilitate colonization and contribute to virulence. Various forms of *Escherichia coli* express the gamut of virulence factors (Table 49.2).

Table 49.2 Virulence factors

Virulence factors	Examples
Inoculum size	*Shigella, Entamoeba, Giardia*
Adherence	Cholera, EPEC
Invasion	*Shigella, Salmonella typhi, Yersinia*, EIEC
Toxins	
Enterotoxin	Cholera, *Salmonella*, ETEC
Cytotoxin	*Shigella, Clostridium difficile*, EHEC
Neurotoxin	*Clostridium botulinum, Staphylococcus aureus, Bacillus cereus*

Abbreviations: EPEC = enteropathogenic *Escherichia coli*; EIEC = enteroinvasive *E. coli*; ETEC = enterotoxigenic *E. coli*; EHEC = enterohemorrhagic *E. coli*.

Table 49.3 Clinical syndromes

	Noninflammatory	Inflammatory	Invasive
Syndrome	Watery diarrhea, emesis	Dysentery	Enteric fever
Site	Small intestine	Colon	Ileum, colon
Stool			
Volume	Large	Small	Small
Fecal WBCs	Absent	Present	Present
Common organisms			
Bacteria	*Vibrio cholerae*	*Shigella* spp.	*Salmonella typhi*
	ETEC	*Salmonella* spp. *Campylobacter jejuni*	*Yersinia* spp. *Brucella*
Viruses	Rotavirus Norovirus[a] Adenovirus Astrovirus	—	—
Parasites	*Giardia Cryptosporidium*	*Entamoeba*	*Entamoeba*

Abbreviations: WBC = white blood cell; ETEC = enterotoxigenic *E. coli*; EIEC, enteroinvasive *E. coli*.

[a] Formerly known as the Norwalk agent or calicivirus.

CLINICAL SYNDROMES

The acute infectious diarrheas can be divided into noninflammatory, inflammatory, and invasive (Table 49.3). Overall in the United States, the most common bacterial or protozoal pathogens in the acute setting are *Campylobacter*, *Salmonella*, *Shigella*, *E. coli* O157:H7, and more recently, *Clostridium difficile*. While the majority of noninflammatory episodes are viral, the more severe cases are often bacterial. The bacteria causing a noninflammatory diarrhea, such as *Vibrio cholerae* and enterotoxigenic *E. coli* (ETEC), typically secrete an enterotoxin, which affects the small intestine, producing a large volume of watery diarrhea without fecal leukocytes. Most forms of viral gastroenteritis fall into this group. The four most common enteric viral infections are norovirus, rotavirus, adenovirus, and astrovirus. The three most common parasites responsible for noninflammatory diarrhea are *Cryptosporidium*, *Giardia*, and *Cyclospora*.

The inflammatory diarrheas typically affect the colon, causing frequent small-volume stools, often with fecal white cells and either occult or gross blood. Fever, tenesmus, and bloody

Table 49.4 Etiologic agents by clinical presentation

Population	Bacteria	Viruses	Parasites	Other
Food poisoning	*Salmonella* *Staphylococcus aureus* *Shigella* *Clostridium perfringens* *Bacillus cereus* *Listeria*	Norwalk Hepatitis A	*Trichinella* *Giardia* *Cryptosporidium*	Ciguatera Histamine fish
AIDS	*Salmonella* *Campylobacter* *Shigella* MAC	CMV	*Cryptosporidium* *Cystoisospora belli* Microsporidia	AIDS Enteropathy
Travelers' diarrhea	*Escherichia coli* ETEC *Shigella* *Aeromonas* *E. coli*, other	Rotavirus	*Giardia* *Cyclospora*	No pathogen (40%)
Acute proctitis	*Neisseria gonorrheae* *Chlamydia* *Treponema pallidum* *Shigella* *Salmonella*	HSV Condyloma, HPV CMV	*Entamoeba* *Cryptosporidium*	
Day-care centers	*Shigella* *Campylobacter jejuni*	Rotavirus	*Giardia* *Cryptosporidium*	
Antibiotic associated	*Clostridium difficile*			*Candida albicans*
Seafood ingestion	*Vibrio* spp.		Anisakidae	

Abbreviations: AIDS = acquired immunodeficiency virus; CMV = cytomegalovirus; MAC = *Mycobacterium avium* complex; ETEC = enterotoxigenic *E. coli*; HSV = herpes simplex virus; HPV = human papilloma virus.

diarrhea are characteristic of dysentery. A pathogen is identified in about one-fifth of cases of bloody diarrhea, most commonly, enterohemorrhagic (EHEC) *E. coli* O157:H7, *Shigella*, *Campylobacter*, and *Salmonella*. Certain bacteria that cause inflammatory diarrhea produce cytotoxins. The invasive diarrheas may be considered a subset of the inflammatory diarrheas with invasion of the intestinal mucosa, and a propensity to cause bacteremia and distant disease. *Salmonella typhi* is the prototype. Typhoid bacteria are taken up and proliferate within the Peyer's patches of the distal ileum, then disseminate and multiply in the reticuloendothelial system to produce systemic disease. *E. coli* O157:H7 in human and animal studies has been shown to affect both the small and large intestines often with hemorrhage noted throughout. Both the *Shigella* and the EHEC pathogens have been associated with sequelae such as hemolytic-uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP).

Patients with neutropenia, particularly with an absolute neutrophil count $<500/mm^3$ and secondary to immunodeficiency or cytotoxic medications (e.g., bone marrow transplantation) can develop neutropenic enterocolitis or typhlitis (from *typhlon*, the Greek term for cecum). In these patients, cytotoxic mucosal injury and neutropenia affect host defenses and mucosal integrity to allow invasion and produce fever, abdominal pain (often right lower quadrant), watery or bloody diarrhea, and thickening of the bowel wall on computed tomography (CT) imaging.

Certain populations of patients with gastroenteritis merit surveillance because of the organisms involved, the potential for severe disease, and the possible need for intervention (Table 49.4). Foodborne disease should be considered in outbreaks of acute GI symptoms affecting two or more persons. The most common causes include *Salmonella* species, *Campylobacter*, *Shigella* species, EHEC (Shiga toxin), *B. cereus*, and the parasites *Cryptosporidium* and *Cyclospora* (see Chapter 50, Food poisoning). The microbial pathogens responsible for travelers' diarrhea are dependent upon the region visited, with some of the most common being enteroaggregative *E. coli* (EAEC), ETEC, *Salmonella*, *Campylobacter*, and *Shigella* (see Chapter 121, Travelers' diarrhea). Patients with advanced acquired immunodeficiency syndrome

(AIDS), particularly with CD4 counts <50/μL, are predisposed to a number of unique infections (microsporidia, *Cyclospora*, *Cystoisospora* – formerly known as isosporiasis, cytomegalovirus) which may be chronic, and more severe manifestations of otherwise common infections *(Salmonella, Campylobacter, Cryptosporidium)*. Acute infectious proctitis, which is often sexually transmitted, leads to tenesmus, hematochezia, and rectal pain. Syphilis, gonorrhea, and chlamydia are additional organisms to consider. The incidence of sexually transmitted proctitis is decreasing in the AIDS era with safer sex practices. Other important subpopulations include patients with antibiotic-associated diarrhea, especially those from hospitals or chronic care facilities (see Chapter 51, Antibiotic-associated diarrhea). *Helicobacter pylori* is the most common chronic bacterial infection in the world, and is associated with chronic gastritis, peptic ulcer, gastric adenocarcinoma, and gastric MALToma (Chapter 138, *Helicobacter pylori* infection).

Gastroenteritis is a major cause of global mortality and morbidity among infants and children. In HICs, acute diarrheal illnesses account for an estimated 7% of pediatric ambulatory visits and hospitalizations. Peak attack rates involve young schoolchildren and their younger siblings. Most cases are caused by viral agents: rotaviruses (10% to 50%), *Norovirus* (Norwalk agent, 10% to 30%), and the enteric adenoviruses (2% to 5%). Bacterial agents cause less than 15% of disease but may cause severe disease in patients with *Campylobacter* species, *E. coli* species, *Salmonella* species, or *Yersinia* species. EHEC O157:H7 is an important cause of hemolytic-uremic syndrome in children. *Yersinia* causes a watery diarrhea in children ages 1 to 5, but it may mimic appendicitis in older children and adolescents. Important pathogens in day-care and institutional settings are the above-mentioned bacterial species, as well as *Giardia lamblia, Cryptosporidium* species, and *C. difficile*.

PATIENT EVALUATION

Most cases of acute gastroenteritis are self-limited and do not require medical attention. Physician consultation generally is advised for patients with a fever (>38.5°C [101.3°F]), dysentery (bloody stools), significant abdominal pain, dehydration, and risk factors for disease requiring intervention (e.g., elderly, pregnancy, recent antibiotic use). Initial evaluation consists of the history, physical examination, and screening stool examination. Laboratory testing and antimicrobial therapy are recommended in a limited subset of patients based on this initial evaluation, which is underscored by the fact that overall few stool cultures will be positive (1.5% to 9%), of which only a minority will have indications for antibiotic therapy.

The history should focus on the severity of disease and the risk factors for specific types of infectious diarrhea. The patient should be questioned regarding symptom duration, fever, abdominal pain, tenesmus, and dehydration. The description of the diarrhea is important: frequency, volume, and any blood, pus, or mucus. Diarrhea persisting longer than 2 to 4 weeks qualifies as chronic, with an alternate differential, and should be fully investigated. Inquiry should also be made into factors that may place the patient in a specific subgroup at increased risk for significant infection. Examples include advanced age (over 70), pregnancy, recent international travel or camping, recent antibiotic use, immunosuppression (e.g., HIV, prednisone therapy, chemotherapy), anal intercourse, seafood consumption, household contacts of day-care workers or children, and the potential for a common source outbreak (e.g., friends or relatives with similar symptoms). Short incubation periods of less than 6 hours, or 6 to 16 hours, suggest ingestion of an enterotoxin produced by *S. aureus* and *B. cereus*, or *Clostridium perfringens*, respectively. Vomiting may be the dominant complaint with viral infections and food poisoning (*S. aureus*, *B. cereus*, noroviruses [Norwalk-like]).

A broad differential diagnosis is initially appropriate as acute diarrhea may be the initial presentation of noninfectious and potentially life-threatening diseases. Important etiologies to consider include inflammatory bowel disease, mesenteric vascular disease, GI hemorrhage, and hyperthyroidism. Patients should be questioned regarding the use or recent initiation of medications that may cause diarrhea, such as ACE inhibitors, metformin, colchicine, diuretics, PPIs, magnesium-containing antacids, and sorbitol.

The physical examination is helpful to gauge the severity of the disease. Orthostasis, tachycardia, decreased skin turgor, and dry mucous membranes are signs of significant dehydration. The presence of fever, abdominal tenderness, and skin rash should be documented. All patients should undergo a rectal examination when rectal bleeding is reported.

Patients who present for medical evaluation may warrant a screening stool examination,

Table 49.5 Fecal leukocytes

Present	Variable	Absent
Campylobacter	*Salmonella*	Toxigenic bacteria
Shigella	*Yersinia*	ETEC, EPEC
EIEC, EHEC	*Clostridium difficile* *Vibrio parahaemolyticus* Noninfectious causes: ischemic colitis, IBD	Viruses Parasites

Abbreviations: EIEC = enteroinvasive *E. coli*; EHEC = enterohemorrhagic *E. coli*; IBD = inflammatory bowel disease; ETEC = enterotoxigenic *E. coli*; EPEC = enteropathogenic *E. coli*.

based upon the history and physical exam. A fresh-cup specimen is preferred because there is evidence that swab and diaper specimens have decreased sensitivity. The stool should be evaluated for fecal leukocytes and fecal occult blood. Some studies in the literature have questioned their utility, sensitivity, and specificity, but they can be helpful to suggest a bacterial etiology (Table 49.5). Fecal leukocytes are detected in the clinical laboratory either with staining techniques or with lactoferrin testing. Microscopic examination of the stool is facilitated by the methylene blue stain. A wet mount is prepared with two drops of methylene blue mixed with fecal mucus; 2 minutes should be allowed for adequate staining of the leukocyte nuclei before high-power microscopy of the cover-slipped slide. The presence of three or more fecal leukocytes per high-powered field in at least four fields is considered a positive examination. The fecal lactoferrin latex agglutination assay appears to be a more precise marker of fecal leukocytes. With fecal leukocytes, there is some overlap between the inflammatory and noninflammatory diarrheas. The finding on screening stool examination of either fecal leukocytes, lactoferrin, or occult blood has equal predictive values for diffuse colonic disease, positive stool cultures, and disease requiring antimicrobial therapy. The organisms most commonly associated with a positive screening test include *Salmonella, Shigella, E. coli* O157, *Campylobacter, Yersinia, Aeromonas, Vibrio*, and *C. difficile*.

The history, physical examination, and office stool evaluation are screening steps prior to further laboratory evaluation and consideration of treatment. As noted, most patients require only symptomatic therapy for a self-limited, noninflammatory infectious diarrhea. Laboratory evaluation is indicated in patients with the following findings or risks: severe or persistent disease (fever greater than 38.5°C, dehydration, grossly bloody stools, duration of more than 1 week), at-risk subpopulations (see above), and those with a positive stool screening examination (fecal leukocytes or occult blood). In these cases, the initial laboratory evaluation should include a complete blood count, serum electrolytes, and stool processed for bacterial culture. Stool cultures can identify *Salmonella, Shigella*, and *Campylobacter*, *E. coli* O157, *Yersinia* and *Aeromonas*. Many stool cultures are ordered inappropriately. The probability of a positive culture is less than 2% to 5% for patients without fever, occult blood, or fecal leukocytes. The yield increases to approximately 20% and 50%, respectively, when one or two of the three findings are present. Stool examination for ova and parasites is not cost-effective, and should be limited to patients with appropriate risk factors (e.g., appropriate travel history, day-care infant exposure, bloody diarrhea). Formed stools should not be sent for testing. Patients hospitalized for more than 3 days, who subsequently develop diarrhea are unlikely to have a bacterial or parasitic pathogen, and stool cultures are inappropriate, with *C. difficile* being the exception.

Additional laboratory or diagnostic evaluation will depend upon the clinical situation. Routine stool examination for ova and parasites is not recommended. Studies for parasites are indicated in the setting of persistent diarrhea, international or wilderness travel, AIDS, and infants attending a day-care center (or their caretakers). Fecal leukocyte-negative, bloody diarrhea has been associated with *Entamoeba histolytica, Schistosoma, Dientamoeba fragilis*, and *Balantidium coli*. The sensitivity of three ova and parasite examinations on three separate days is 95% to 98%. Stool testing for *C. difficile*, previously reserved for those with a history of antibiotic use or hospitalization, is now broadened with the current epidemic and advent of community-acquired infection. Differentiation of pathogenic and nonpathogenic strains of *E. coli* requires specific serotyping, although testing for *E. coli* O157:H7 is now commonplace. Commercial enzyme immunoassay kits are available for detection of rotavirus and enteric adenovirus and may be useful in the pediatric population and in elderly patients. Colonoscopy is rarely needed, but is appropriate where the differential includes ischemic colitis, inflammatory bowel disease, or other etiologies which require visualization or biopsy (e.g., immunocompromised patients, individuals with concern for *C. difficile* with negative stool studies). In addition, cross-sectional

abdominal imaging (e.g., CT scan) may be helpful in complex presentations to help differentiate infectious and noninfectious causes of acute diarrhea and/or bleeding.

The initial evaluation of AIDS-associated diarrhea should include stool examination for culture, ova and parasites, and acid-fast stain. Specialized stool studies are required for the detection of *Cryptosporidium, Cyclospora*, microsporidiosis, and *Cystoisospora belli*. Mucosal biopsies are required for the diagnosis of cytomegalovirus (cytopathogenic effect) and *Mycobacterium avium-intracellulare* complex (MAC). Sigmoidoscopy may be considered for persistent or severe cases in patients with CD4 counts less than 100/μL and for those who have experienced weight loss. Colonoscopy/ileoscopy and upper endoscopy generally are reserved for refractory cases.

MANAGEMENT

Rehydration is the primary focus of initial management. This can be accomplished with oral fluids. Oral rehydration solutions (ORS) have decreased worldwide cholera mortality rates from 50% to 1%. The World Health Organization (WHO) ORS is made up of 3.5 g sodium chloride, 2.5 g sodium bicarbonate, 1.5 g potassium chloride, and 20 g glucose per liter of water. Rice-based ORS also may be used (e.g., CeraLyte). Prepared forms are available in solution (e.g., Pedialyte, Rehydrolyte) and packets (e.g., Orlyte). Various homemade alternatives are available, for example alternating a glass of fruit juice (8 oz) with honey (½ tsp) and salt (¼ tsp), with a second glass of water (8 oz) with baking soda (¼ tsp). Sport drinks such as Gatorade are reasonable for adults who are not dehydrated. The goal is the passage of relatively dilute urine every 2 to 4 hours. Patients are advised to eat judiciously until stools are again formed. Cereals (rice, pasta), boiled foods (potatoes, vegetables), bananas, and crackers are recommended initial foods. Alcohol (cathartic effect), caffeine (increases intestinal motility), and carbonated drinks (gastric distension with reflex colonic contraction) should be avoided. Recommendations vary regarding dairy products, as transient lactose intolerance may occur.

In addition to rehydration, symptomatic therapy includes administering agents to control the diarrhea. These agents include bulking agents, antimotility drugs, and antisecretory medications (Tables 49.6 and 49.7). Antimotility agents should not be used if there is a possibility of a severe inflammatory bacterial diarrhea, particularly a febrile dysentery syndrome. Loperamide (Imodium) is the drug of choice in most situations because of its efficacy and safety. Bismuth subsalicylate (BSS) has antisecretory and antibacterial properties and is considered when vomiting is a significant part of the patient's presentation. It should not be used in the immunosuppressed patient, particularly the HIV population, because bismuth encephalopathy may occur. Diphenoxylate–atropine (Lomotil) has both antimotility and antisecretory activity, but may cause central nervous system depression, especially in children. Despite their popularity, kaopectate, cholestyramine, lactobacilli, and the anticholinergics have not been shown to be consistently effective. Severe AIDS diarrhea should be treated in stepwise fashion with Imodium (2 to 4 mg PO four times daily), Lomotil (1 to 2 tablets PO four times daily), morphine (MS Contin 30 mg twice daily) or tincture of opium (DTO 0.5 to 1 mL PO four

Table 49.6 Symptomatic therapy for diarrhea

General	Intraluminal	Antimotility	Antisecretory
Rehydration	Bulking agents	Opiates	BSS
ORS	Psyllium	Loperamide	Octreotide
IV	Adsorbents	Diphenoxylate	
Diet therapy	Kaolin-pectin	Codeine	
	Attapulgite	Tincture of opium	
	Cholestyramine	Anticholinergics	
	Bacterial agents	Atropine	
	Lactobacillus *Saccaromyces*	Scopolamine	

Abbreviations: ORS = oral rehydration solution; IV = intravenous; BSS = bismuth subsalicylate.

Table 49.7 Antidiarrheal therapy

Agent	Dosing	Comments
Loperamide[a] (Imodium)	2 mg PO q3h	Initial dose, 4 mg Maximum, 16 mg/day
Diphenoxylate (Lomotil)	2 tablets or 10 mL PO QID	Maximum, 8 tablets/day
BSS[b] (Pepto-Bismol)	2 tablets or 30 mL PO QID	Maximum, 8 tablets/day
Tincture of opium	0.5–1.0 ml PO q4–6h	
Octreotide	100–500 μg SC TID	

Abbreviations: BSS = bismuth subsalicylate; SC = subcutaneous.
[a] Loperamide is the drug of choice. BSS may be used in presentations with significant vomiting.
[b] BSS should not be used in patients with human immunodeficiency virus because of the risk of bismuth encephalopathy.

Table 49.8 Antibiotic therapy by etiologic agent

Etiologic agent	Therapy	Duration	Comments
Bacteria			
Empiric therapy[a]	Quinolone[b]	5–7 days	Indications: Fever and positive stool screen[c] Dysentery syndrome Travelers' diarrhea, severe
Campylobacter	Erythromycin, 500 mg PO bid Quinolone[b] Azithromycin, 500 mg PO qd	5 days 3 days 3 days	See text for treatment indication
Clostridium difficile[a]	Metronidazole, 500 mg PO tid Vancomycin, 125 mg PO qid Fidaxomicin, 200 mg PO bid	10–14 days 10–14 days 10 days	Metronidazole is the drug of choice given VRE risk. Bactericidal but very expensive
EIEC, ETEC[a]	Quinolone[b] TMP–SMX-DS PO BID	5 days 5 days	Treatment is not indicated for EHEC, including O157:H7
EPEC	Quinolone[b]	5 days	
Salmonella	Quinolone[b] TMP–SMX-DS PO BID	3–7 days 5–7 days	See text for treatment indication 14 days if immunocompromised or relapsing
Shigella[a]	Quinolone[b] TMP–SMX-DS PO BID Azithromycin, 250–500 mg PO qd	3–5 days 3 days 3 days	7–10 days if immunocompromised
Vibrio cholerae[a]	Doxycycline, 300 mg PO Ciprofloxacin, 1 g PO	1 dose 1 dose	
Yersinia	Ceftriaxone, 2 g IV qd Quinolone[b]	5 days 3 days	For severe infection
Parasites			
Cyclospora	TMP–SMX-DS PO BID	710 days	
Entamoeba[a]	Metronidazole, 750 mg PO TID Tinidazole, 2 g PO qd	10 days 3 days	Follow with cyst eradication regimen
Giardia[a]	Metronidazole, 250 mg PO TID Tinidazole, 2 g PO	7–10 days 1 dose	
Cystoisospora Cryptosporidium	TMP–SMX-DS PO BID Nitazoxanide 500 mg PO BID	7–10 days 3 days	14 days if immunocompromised

Abbreviations: VRE = vancomycin-resistant enterococcus; EIEC, = enteroinvasive *E. coli*; ETEC = enterotoxigenic *E. coli*; TMP–SMX-DS = trimethoprim–sulfamethoxazole, 160–800 mg double-strength tablet; EHEC = enterohemorrhagic *E. coli*; EPEC = enteropathogenic *E. coli*.

[a] Treatment clearly indicated. Treatment for the other listed microbes will depend on the clincal situation.

[b] Quinolone oral therapy options include: ciprofloxacin 500 mg bid, ofloxacin 300 mg bid, levofloxacin 500 mg qd.

[c] Positive stool screen: fecal leukocytes or hemoccult positive.

times daily), and octreotide (100 to 500 μg SC three times daily, increasing the dosage 200 μg every 3 days until response is seen).

Antibiotic therapy is usually not indicated for patients with community-acquired acute diarrhea. Antibiotics are appropriate in a limited subset of patients, such as those with dehydration, severe travelers' diarrhea, and immunocompromised hosts, and may be appropriate for those with fever and/or blood and those considered for hospitalization (Table 49.8). Patients with EHEC (*E. coli* O157) should not receive antibiotics, due to the reported association with HUS. Empiric therapy with a quinolone (norfloxacin, ciprofloxacin, levofloxacin) is generally recommended. Macrolides (e.g., azithromycin) may be used when drug allergies or quinolone resistance are factors, with the caveat that abdominal cramping is a common side effect. Patients with a positive stool culture or parasitic examination should be treated in specific situations: symptomatic infections with certain bacteria (*Shigella*, enteroinvasive *E. coli, C. difficile, V. cholerae*), sexually transmitted pathogens, and parasites. Therapy is reserved for subgroups

of patients with *Salmonella, Campylobacter, Yersinia, Aeromonas*, noncholera *Vibrio*, and other strains of *E. coli* (EPEC, EAEC). Treatment of *Salmonella* and *Campylobacter* is indicated for patients with dysentery, systemic illness, bacteremia; or significant comorbidity (immunosuppression, malignancy, sickle cell anemia, prosthetic device, age extremes). In light of the epidemic, therapy for *C. difficile* infection is in evolution (see Chapter 51, Antibiotic-associated diarrhea).

In summary, community-acquired acute gastroenteritis, although common, is usually a self-limited disease. Oral rehydration and symptomatic therapy are appropriate for the majority of patients. Medical evaluation is advised for patients with significant fever, dysentery, abdominal pain, dehydration, or risk factors for severe disease. Laboratory evaluation and antibiotic treatment should be limited to very specific situations.

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50. Food poisoning

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Foodborne illnesses are caused by ingestion of foods containing microbial and chemical toxins or pathogenic microorganisms. This chapter concentrates on toxin-mediated syndromes, usually called *food poisoning*, rather than on syndromes reflecting enteric infection, such as salmonellosis, shigellosis, vibriosis, and Shiga toxin-producing *Escherichia coli* (STEC) infection. Treatment of these infections is covered in Chapter 49, Gastroenteritis, and in chapters on the specific organisms.

CLINICAL PRESENTATION AND DIAGNOSIS

Initially, the diagnosis of specific food poisoning syndromes is suggested by the clinical presentation, the incubation period from exposure to onset of symptoms, and the food consumed. The incubation periods, symptoms, and commonly associated foods for specific syndromes are shown in Table 50.1. Incubation periods range from a few hours or less in the case of preformed chemical and bacterial toxins, such as histamine poisoning (scombroid), staphylococcal food poisoning, and *Bacillus cereus*, to several days for bacterial infections (e.g., *Campylobacter jejuni, Salmonella, Yersinia enterocolitica*, and *E. coli* O157:H7 or other STEC) and some types of mushroom poisoning. Therefore, it is essential to obtain a diet history covering 3 to 4 days before the onset of symptoms. A careful history of illness in meal companions may help point to the responsible food. It is clinically useful to consider syndromes grouped by incubation period and symptoms.

Nausea and vomiting within 1 hour

Symptoms developing within 5 to 15 minutes of exposure that resolve over 1 to 2 hours are typical of contamination of food or drink with heavy metals or other nonspecific chemical irritants.

Nausea, vomiting, or diarrhea within 1 to 16 hours

When gastrointestinal symptoms develop 1 to 16 hours after exposure, the likely agents include *Staphylococcus aureus, B. cereus*, and *Clostridium perfringens*. Vomiting is the dominant feature of *S. aureus* and short-incubation, or emetic, *B. cereus* food poisoning. These syndromes result from preformed centrally acting toxins elaborated by the organisms in food when the food is mishandled. In contrast, abdominal cramps and diarrhea are most prominent in long-incubation, or diarrheal, *B. cereus* poisoning and *C. perfringens* food poisoning. In these syndromes, toxins are also elaborated in the small intestine. The duration of illness is usually less than 24 hours. Diagnosis of these syndromes is usually made on epidemiologic and clinical grounds. Laboratory confirmation of *S. aureus* food poisoning is based on isolation of *S. aureus* from food handlers and demonstration of more than 10^5 colonies per gram of the same strain in food or enterotoxin production by enzyme immunoassay. Laboratory confirmation of *B. cereus* and *C. perfringens* can be performed in epidemiologic investigations; it requires collection of food and stool for toxin detection or quantitative cultures.

Watery diarrhea and cramps within 16 to 48 hours

Diarrhea following a slightly longer incubation period is typical of viral foodborne illness, particularly Norovirus (Norwalk virus), and enterotoxin-producing bacteria, including enterotoxigenic *E. coli* (ETEC), *Vibrio cholerae* O1 and non-O1, and other *Vibrio* species. Most microbiology laboratories can diagnose *Vibrio* infections from stool culture provided the laboratory is aware that *Vibrio* is being considered. Diagnosis of ETEC infection requires detection of enterotoxin production by *E. coli* isolates or detection of the genes for enterotoxin and is limited to reference

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Table 50.1 Incubation period, symptoms, and common vehicles for microbial causes of food poisoning

Organism	Incubation period (hours) median (range)	Vomiting	Diarrhea	Fever	Common vehicles
Staphylococcus aureus	3 (1–6)	+++	++	0	Ham, poultry, cream-filled pastries, potato and egg salad
Bacillus cereus (emetic syndrome)	2 (1–6)	+++	++	0	Fried rice
Bacillus cereus (diarrheal syndrome)	9 (6–16)	+	+++	0	Beef, pork, chicken, vanilla sauce
Clostridium perfringens	12 (6–24)	+	+++	0	Beef, poultry, gravy
Vibrio parahaemolyticus	15 (4–96)	++	+++	++	Fish, shellfish
Vibrio cholerae 01 and non-01	24 (12–120)	++	+++	+	Shellfish
Norovirus	24 (12–48)	+++	++	++	Shellfish, salads, ice
Shigella	24 (7–168)	+	+++	+++	Egg salads, lettuce, sandwiches
Clostridium botulinum	24 (12–168)	++	+	0	Canned vegetables, fruits, sauces and fish; salted fish; bottled garlic, baked potatoes
Salmonella	36 (12–72)	+	+++	++	Beef, poultry, pork, eggs, dairy products, fruit and vegetables, sprouts
Campylobacter jejuni	48 (24–168)	+	+++	+++	Poultry, raw milk
Enterohemorrhagic *Escherichia coli* (e.g., 0157:H7)	96 (48–120)	++	+++	+	Beef (especially hamburger), raw milk, salad dressings, lettuce, sprouts, apple cider
Yersinia enterocolitica	96 (48–240)	+	+++	+++	Pork, chitterlings, tofu, milk
Cyclospora cayetanensis	168 (24–336)	+	+++	++	Raspberries, basil, lettuce

Key: 0 = rare (≤10%); + = infrequent (11%–33%); ++ = frequent (33%–66%); +++ = classic (>67%).

laboratories. Antigen detection-based enzyme immunoassays using recombinant antigens have been developed for the diagnosis of several gastroenteritis-causing viruses such as rotavirus and adenovirus 40/41; PCR testing can detect norovirus. Multiplex PCR platforms that can detect many of these organisms in one test are in advanced development.

Fever, diarrhea, and abdominal cramps within 16 to 96 hours

Bacterial infections of the gastrointestinal tract and gut-associated lymphatics with *Salmonella, Shigella, C. jejuni, Y. enterocolitica*, and STEC typically follow a longer incubation period and are marked by more prominent signs of colonic inflammation or systemic illness. Diarrhea that becomes bloody within 12 to 36 hours of onset is typical of *E. coli* O157:H7 and other STEC. These organisms are now among the most common causes of bacterial gastroenteritis in North America (see Chapter 49, Gastroenteritis).

Diarrhea, fatigue, and weight loss within 1 to 14 days

Cyclospora infection should be suspected in a patient with diarrhea of several days' duration associated with loss of appetite and weight and prominent fatigue. The incubation period is highly variable, ranging from 1 to 14 days, with a median of 7 days. Recent outbreaks have definitively shown that *Cyclospora* infections in developed countries can result from consumption of contaminated foods, notably fresh raspberries, mesclun lettuce, and basil.

Paresthesias within 6 hours

Chemical food poisoning caused by niacin, histamine fish poisoning, ciguatera poisoning, neurotoxic and paralytic shellfish poisoning, and Chinese restaurant syndrome (monosodium glutamate) present with paresthesias and other symptoms after a brief incubation period. Chinese restaurant syndrome is characterized by a burning sensation in the neck, chest, and abdomen with

Table 50.2 Clinical features of fish and shellfish poisoning

Syndrome	Incubation period	Symptoms	Vehicles	Duration
Histamine (scombroid)	5 min–1 h	Facial flushing, headache, nausea, cramps, diarrhea, urticaria	Tuna, mackerel, bonito, mahi-mahi, bluefish	Hours
Ciguatera	1–6 h	Diarrhea, nausea, vomiting, myalgia, arthralgia, shooting pains, perioral and extremity paresthesias, hot–cold reversal, fatigue	Barracuda, snapper, grouper, amberjack	Days to months
Neurotoxic shellfish poisoning	5 min–4 h	Paresthesias, nausea, vomiting, ataxia	Shellfish	Hours to days
Paralytic shellfish poisoning	5 min–4 h	Paresthesias, cranial nerve weakness, ataxia, muscle weakness, respiratory paralysis	Shellfish	Hours to days
Domoic acid	15 min–38 h	Vomiting, cramps, diarrhea, confusion, amnesia, cardiac irritability	Mussels	Indefinite
Haff disease		Muscle pain, stiffness, brown urine	Buffalo fish, pomfret, burbot	2–3 days
Pufferfish (tetrodotoxin) poisoning	15 min–20 h	Paresthesias, vomiting, diarrhea, abdominal pain, ascending paralysis, respiratory failure	Pufferfish	Several days

chest tightness and occasionally facial flushing, headache, nausea, and abdominal cramps.

The features of fish and shellfish poisoning are summarized in Table 50.2. Histamine fish poisoning (scombroid) is caused by bacterial decarboxylation of histidine in fish that are inadequately refrigerated, resulting in production of large amounts of histamine. Signs and symptoms are facial flushing, headache, nausea, and, less commonly, urticaria or diarrhea. The fish is often reported to have a peppery or bitter taste. Demonstration of high levels of histamine in the implicated fish confirms the diagnosis.

Ciguatera fish poisoning results from ingestion of fish containing toxins produced by the dinoflagellate *Gambierdiscus toxicus*. Predatory fish such as grouper, amberjack, snapper, and barracuda are usually implicated. The symptoms, which are quite distinctive, usually involve the combination of gastrointestinal and neurologic symptoms, most commonly perioral and distal extremity paresthesias, and reversal of hot and cold sensation. Other symptoms include sensation of loose teeth, arthralgias, headaches, muscle weakness, pruritus, lancinating pains, and hallucinations. Bradycardia, hypotension, and respiratory paralysis may occur. The symptoms may last from a few days to 6 months. The diagnosis is based on the clinical picture; detection of ciguatoxin in the fish by high-performance lipid chromatography (HPLC), radioimmunoassay (RIA) or enzyme-linked immunoassay (EIA), or a new neuro-2a cell-based assay is confirmatory.

Paralytic shellfish poisoning (PSP) and neurotoxic shellfish poisoning (NSP) are closely related syndromes caused by heat-stable neurotoxins produced by dinoflagellates (*Gonyaulax catenella* and *Gonyaulax tamarensis* cause PSP; *Gymnodinium breve* causes NSP). During periodic blooms of the dinoflagellates, which may cause red tides, shellfish concentrate the heat-stable toxins. PSP is more severe and occurs in colder waters. Patients develop symptoms a median of 30 minutes after exposure. Symptoms consist of paresthesias and dysesthesias, beginning with the lips, mouth, and face and progressing to the extremities, and then dysphonia, dysphagia, ataxia, muscle weakness, and, in severe cases, respiratory paralysis occur. NSP occurs primarily near warmer waters and is characterized by similar paresthesias, reversal of hot and cold sensation, nausea, vomiting, and ataxia. Toxin can be detected in samples of the shellfish by bioassay or several investigational assays. Amnesic shellfish poisoning is a recently described syndrome associated with mussels contaminated with domoic acid elaborated by *Nitzchia pungens*. In some patients, gastrointestinal symptoms are followed by memory loss, coma, cardiac arrhythmias, and death. Haff disease is a syndrome of acute rhabdomyolysis thought to be caused by palytoxin in certain bottom-feeding fish, notably buffalo fish, crayfish, pomfret, and burbot. Patients present 6 to 21 hours after ingestion with vomiting, severe myalgia, and stiffness. Elevated creatine phosphokinase (CPK) and other muscle enzyme levels confirm the diagnosis.

Table 50.3 Clinical syndromes of mushroom poisoning

Syndromes (toxins)	Incubation period	Symptoms	Mushrooms
Parasympathetic (muscarine)	30 min–2 h	Sweating, salivation, lacrimation, blurred vision, diarrhea, bradycardia, hypotension	*Inocybe* spp. *Clitocybe* spp.
Delirium (ibotenic acid, muscimol)	30 min–2 h	Dizziness, incoordination, ataxia, hyperactivity, visual disturbance, hallucinations, stupor	*Amanita muscaria, Amanita pantherina*
Disulfiram-like (coprine)	30 min after alcohol	Flushing, metallic taste, nausea, vomiting, sweating, hypotension	*Coprinus atramentarius, Clitocybe clavipes*
Hallucinations (psilocybin)	30–60 min	Mood elevation, anxiety, tachycardia, muscle weakness, hallucination	*Psilocybe cubensis, Panaeolus* spp., *Conocybe cyanopus*
Gastroenteritis	30 min–2 h	Nausea, vomiting, abdominal cramps, diarrhea	Various
Allergic pneumonic syndrome	3–6 h	Nausea, vomiting, rhinitis followed within days by fever, malaise, dyspnea, and reticulonodular infiltrates on chest x-ray	*Lycoperdon* spp. (puffballs)
Methemoglobin poisoning (monomethylhydrazine gyromitrin)	6–12 h	Nausea, vomiting, bloody diarrhea, abdominal pain, vertigo, convulsion, coma, liver failure, hemolysis	*Gyromitra* spp.
Hepatorenal failure (amatoxins, phallotoxins)	6–24 h	Nausea, vomiting, abdominal pain, diarrhea; then jaundice, liver and kidney failure, coma, death	*Amanita phalloides, Amanita verna, Amanita virosa, Galerina autumnalis, Galerina marginata*
Tubulointerstitial nephritis (orellanine)	36 h–14 days	Thirst, nausea, vomiting, flank pain, chills, oliguria	*Cortinarius orellanus, Cortinarius speciosissimus*
Rhabdomyolytic	24–72 h	Fatigue, muscle weakness, myalgia, rhabdomyolysis, renal failure	*Tricholoma equestre, Russula submigricans*

Tetrodotoxin poisoning results from consumption of improperly prepared pufferfish, manifest as paresthesias, vomiting, diarrhea, abdominal pain, ascending paralysis, and respiratory failure.

Nausea, vomiting, diarrhea, and paralysis within 18 to 36 hours

Foodborne botulism results from exposure to one of three distinct botulinum toxins, A, B, and E, produced when *Clostridium botulinum* spores germinate in food in an anaerobic environment. Gastrointestinal symptoms occur before the onset of neurologic symptoms in about 50% of patients with acute foodborne botulism. Descending paralysis begins with cranial nerve weakness manifested as dysphonia, dysphagia, diplopia, and blurred vision, followed by muscle weakness and respiratory insufficiency. Larger doses of toxin result in shorter incubation periods and more severe symptoms. Botulism can be differentiated from acute myasthenia gravis and Guillain–Barré syndrome (which may follow *C. jejuni* infection) by botulism's normal cerebrospinal fluid protein, the descending nature of the paralysis, absence of sensory symptoms, normal nerve conduction studies, and typical electromyographic findings of increase in the action potential with rapid repetitive stimulation. Confirmation is based on detection of toxin in food or in serum or stool of patients by mouse toxicity assay or of *C. botulinum* spores in the stool by selective culture.

Mushroom poisoning syndromes

Syndromes of food poisoning from mushrooms fall into at least 10 major categories, outlined in Table 50.3. Parasympathetic syndromes, delirium, disulfiram (Antabuse)-like symptoms, hallucinations, or gastroenteritis may occur after a short incubation period. The more serious syndromes of monomethylhydrazine poisoning, hepatorenal failure from amatoxin-containing mushrooms, delayed myopathy and rhabdomyolysis, and tubulointerstitial nephritis develop after longer incubation periods and may not be suspected initially. If available, specimens of the mushrooms should be examined promptly by a mycologist or poison control expert to

confirm the diagnosis. Toxins can be detected in gastric contents, blood, or urine by thin-layer chromatography.

THERAPY

Nonspecific therapy

Most food poisoning syndromes are self-limited, and for the majority of episodes, nonspecific supportive therapy is all that is required. Exceptions include botulism, listeriosis, some enteric infections in infants and compromised hosts, and some types of mushroom poisoning.

The mainstay of treatment is fluid and electrolyte replacement to prevent and treat dehydration. The first step is to assess the degree of volume depletion by examining the skin turgor, mucous membranes, vital signs, and mental status. Measuring postural changes in pulse and blood pressure is also helpful in quantifying the volume loss. Slightly dry mucous membranes and thirst indicate mild dehydration (3% to 5% deficit, or 50 to 60 mL/kg); loss of skin turgor, very dry mucous membranes, postural pulse increases, and sunken eyes indicate moderate dehydration (6% to 9%); and the additional presence of weak pulse, postural hypotension, cold extremities, or depressed consciousness indicates severe volume depletion, above 10%.

Most children and adults with diarrhea can be treated successfully with oral rehydration. This therapy is possible because of the coupled transport of glucose with water and sodium even in severely damaged small bowel. Diarrheal stool contains significant concentrations of sodium, potassium, and bicarbonate, and fluid therapy should replace these losses.

One liter of the World Health Organization's currently recommended replacement solution contains 75 mmol of sodium, 13.5 g of glucose, 20 mmol of potassium, 65 mmol of chloride, and 10 mmol of citrate (as a bicarbonate source). Commercial solutions such as Rehydralyte and Pedialyte have a slightly lower sodium concentration, but they are convenient and readily available, although expensive. A homemade approximation of the oral solution can be made by adding a pinch of salt, a pinch of baking soda, and a spoonful of sugar or honey to an 8-oz glass of fruit juice. For patients with altered consciousness or uncontrolled vomiting, intravenous rehydration with Ringer's lactate should be used initially. The estimated volume deficit should be replaced over 4 hours; after that, ongoing losses should be replaced. Gatorade and commercial soft drinks are poor choices because the low sodium content can lead to hyponatremia and the high osmolarity can exacerbate diarrhea.

Water intake should be allowed ad lib, and solid food can be introduced as soon as it is tolerated. Some patients will develop lactose intolerance after severe or protracted diarrhea, and dairy products should be avoided if they appear to exacerbate symptoms.

Antiemetics may be useful for severe or prolonged vomiting. Ondansetron (Zofran) can be used off-label, 4 to 8 mg orally or intravenously. Alternatively, promethazine (Phenergan), 12.5 to 25 mg PO, IM, IV, or PR, and prochlorperazine (Compazine), 5 to 10 mg orally or intramuscularly (IM), 25 mg rectally, or 2.5 to 10 mg IV could be used. Antidiarrheals should be used cautiously, especially in children. Pepto-Bismol 30 mL (2 tab) orally every 30 to 60 minutes (maximum 8 doses/24 hours) may be reasonable if an antidiarrheal is used because it has been shown to bind some enterotoxins. It generally should be avoided in children under 12 because of the salicylate content.

Specific therapy

Specific therapies for food poisoning are outlined in Table 50.4. Gastric emptying and administration of activated charcoal and cathartics (unless diarrhea is already present) are important for virtually all cases of mushroom poisoning. If vomiting has not occurred spontaneously in patients with botulism or ciguatera, the remaining food should be removed from the gut. In botulism, paralytic shellfish poisoning, and ciguatera, death from respiratory failure is the major risk, and monitoring the vital capacity can be lifesaving.

Equine-derived heptavalent antitoxin, which binds botulism toxin types A–G, has been recently approved for the treatment of patients 12 months and older. It is available in the United States through contacting the state health department's emergency line, and they will contact the CDC (770–488–7100) for release of antitoxin. It may prevent further paralysis but does not reverse established symptoms. To be effective, it should be administered early. Dosage and a protocol for administration of a skin test are listed in the package insert. Human-derived botulism immune globulin (BabyBIG) is licensed for treatment of infant botulism caused by toxin types A or B. It can be obtained from the California

Table 50.4 Specific treatment for food poisoning syndromes

Syndrome	First-line treatment	Comment
Staphylococcus aureus, Bacillus cereus, Clostridium perfringens, Norwalk virus	Fluid replacement, antiemetics (e.g., ondansetron [Zofran], promethazine [Phenergan], prochlorperazine [Compazine])	Oral rehydration is usually adequate if vomiting can be controlled.
Bacterial gastroenteritis	Fluid replacement; antimicrobials helpful for some syndromes	See chapters on specific organisms and Chapter 49, Gastroenteritis, for specific antimicrobial therapy
Clostridium botulinum	Gastric empying, cathartics if food is still in gastrointestinal tract; respiratory support, polyvalent antitoxin[a]	Antitoxin should be given as soon as possible
Cyclospora	Trimethoprim–sulfamethoxazole (160 mg trimethoprim component bid for 7 days)	If not treated, symptoms may be protracted and relapsing
Histamine (scombroid)	Antihistamine (e.g., diphenhydramine 25–50 mg PO, IM, or IV)	H_2 receptor antagonists (cimetidine) have been helpful for refractory symptoms
Ciguatera	Activated charcoal only if there is no vomiting and it has been $<$1 hour post ingestion; analgesia, antiemetics, supportive measures; atropine for symptomatic bradycardia	Amitriptyline (25–50 mg/d) may help paresthesias; mannitol infusion has been used
Neurotoxic shellfish poisoning	Supportive therapy	
Paralytic shellfish poisoning	Supportive therapy, monitor vital capacity	
Haff disease	IV hydration	Mannitol and bicarbonate have also been used to protect renal tubules
Muscarine-containing mushrooms	Gastric emptying, activated charcoal, cathartics; atropine 0.01–0.02 mg/kg IV up to 1 mg	Titrate atropine to drying of secretions; alternatively glycopyrrolate can be used.
Muscimol- and ibotenic acid-containing mushrooms	Gastric emptying, activated charcoal, cathartics; supportive measures	Benzodiazepines can be used for agitation
Hallucinogen-containing mushrooms	Reassurance, quiet room; benzodiazepines for severe agitation	
Monomethylhydrazine-containing mushrooms (*Gyromitra* spp.)	Gastric emptying, activated charcoal, cathartics; for delirium, pyridoxine, 25 mg/kg IV	For methemoglobinemia, methylene blue 1–2 mg/kg (1% solution 0.1–0.2 mL/kg) over 5 min
Amatoxin-containing mushrooms	Gastric emptying, activated charcoal; correction of fluid and electrolytes; monitoring glucose, liver, and renal function	IV silibinin[b] has been shown to decrease mortality. High-dose penicillin G can be used if silibinin is not available. *N*-acetylcysteine may help prevent liver cell death. Hemodialysis or liver transplantation may be necessary
Orellanine-containing mushrooms	Gastric emptying, activated charcoal, cathartics; cautious correction of fluid and electrolyte problems	Hemodialysis is often necessary

[a] Available through State Health Departments, or the Centers for Disease Control and Prevention (770–488–7100, 24 hours per day).
[b] (Legalon® SIL) is available directly from the principal investigator of an open NIH clinical trial (NCT00915681) by calling 1-866-520-4412.

Department of Public Health (510–231–7600 or www.infantbotulism.org).

In ciguatera poisoning, analgesia and avoidance of unpleasant stimuli such as warm baths are usually adequate. Anecdotal reports in the literature suggest that amitriptyline, 25 to 50 mg/day orally or gabapentin may be useful for dysesthesias. Intravenous mannitol has been reported to be effective for severe neurologic manifestations, but a single randomized control trial did not show a benefit. For histamine fish poisoning, conventional antihistamines, such as diphenhydramine, 25 to 50 mg PO, IM, or IV, are helpful. Epinephrine or albuterol should be given for bronchospasm. Intravenous cimetidine can be tried for refractory symptoms.

Atropine is a specific antidote for poisoning from muscarine-containing mushrooms, but the

dosage (0.01 to 0.02 mg/kg up to a maximum of 1 mg) should be titrated to control excess respiratory secretions and bradycardia rather than other symptoms. Alternatively glycopyrrolate can be used.

Specific treatment is usually not necessary for poisoning caused by ibotenic acid-containing or muscimol-containing mushrooms. Benzodiazepines can be used to control combativeness, agitation, muscular overactivity, and seizures. Cardiac and blood pressure monitoring are necessary because hypotension and bradycardia can result.

For poisoning caused by monomethylhydrazine-containing mushrooms, pyridoxine, 25 mg/kg IV, should be given; the dose can be repeated as needed to control seizures. The methemoglobin level should be measured if possible. If there is symptomatic methemoglobinemia with central cyanosis, methylene blue, 1 to 2 mg/kg or 0.1 to 0.2 mL/kg of a 1% solution, should be given over 5 minutes.

The high fatality rate associated with poisoning by *Amanita phalloides* and related amatoxin-containing mushrooms makes it a special concern. Toxin removal should be attempted with activated charcoal and should be continued until 4 days following ingestion because of the extensive enterohepatic cycling. During the initial phase, gastrointestinal symptoms may cause hypotension. This first stage often is followed by a stage of apparent improvement, but hepatic transaminases usually are elevated by 24 to 48 hours. Fulminant hepatic necrosis and acute renal failure begin after 48 to 96 hours. Supportive treatment consists of careful fluid replacement and monitoring of serum glucose and renal and liver function tests. Intravenous silibinin dihemisuccinate (Legalon® SIL) has been shown to decrease mortality in amatoxin mushroom poisonings. High-dose penicillin G can be used if silibinin is not available, but is not as effective, and it does not have additional benefit when used in conjunction with silibinin (and actually has higher mortality than silibinin used alone). *N*-acetylcysteine can be used as an antioxidant to help prevent liver cell death. Liver transplant has been successful in some cases. Assistance from the regional poison control center should always be sought for help with mushroom identification and for the latest treatment information.

REPORTING

Reporting of suspected foodborne outbreaks to local or state health departments is an important part of management because epidemiologic investigation can clearly establish the responsible food and may prevent many additional cases.

SUGGESTED READING

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51. Antibiotic-associated diarrhea

John G. Bartlett

Diarrhea is a relatively common complication of antibiotic use. Nearly all agents with an antibacterial spectrum of activity have been implicated, but ampicillin and clindamycin are perhaps the most frequent ones. The great majority of cases are enigmatic ("dysbiosis") or caused by *Clostridium difficile*. Rare causes are *Klebsiella* or *Staphylococcus aureus* enterocolitis.

DIAGNOSTIC STUDIES

Clostridium difficile-associated diarrhea should be suspected in any patient who has diarrhea in association with antibiotic exposure. The most common inducing agents are clindamycin, oral quinolones, and cephalosporins, primarily second- and third-generation cephalosporins.

The usual method to identify cases of diarrhea caused by *C. difficile* is the molecular test (PCR) for the toxin B gene or the older and less sensitive enzyme-immunoassay (EIA) for the toxin. The advantage of the PCR test is sensitivity and speed of the results, and it is relatively inexpensive; however, carriers will give false-positive tests. Many labs restrict testing to diarrheal stools and no more than one/week/patient. The EIA test is relatively specific and provides results within 2 to 3 hours, but is only about 60% to 80% sensitive so there are many false-negative results. In general, physicians need to be aware of the characteristic clinical findings and the test that was performed for proper interpretation. Most patients are over 65 years old, and develop symptoms during or shortly after the typical antibiotics symptoms occur in the context of medical care; diarrhea is the most prominent symptom and there may be a unique and offensive odor to the stool. Endoscopy or imaging are infrequently needed, but, if done, a result showing pseudomembranous colitis is nearly diagnostic of *C. difficile* infection (CDI). Laboratory findings that correlate with prognosis are the magnitude of leukocytosis, lactate level, and renal dysfunction.

Table 51.1 Treatment of *Clostridium difficile* diarrhea and colitis

Nonspecific measures: discontinue implicated antibiotic; if continued antibiotic treatment is necessary, use an alternative agent to the one responsible for inducing *C. difficile* and avoid the use of fluoroquinolones and cephalosporins
Provide supportive measures
Avoid antiperistaltic agents and agents that reduce gastric acid
Vancomycin: 125 mg PO QID × 10–14 days or
Metronidazole: 500 mg PO 500 mg TID or 250 mg QID for 10 days or
Fidaxomicin: 200 mg PO BID × 10 days
Severe disease: vancomycin 500 mg PO QID plus metronidazole 500 mg IV q8h

CLOSTRIDIUM DIFFICILE: TREATMENT

The first principle of treatment is discontinuation of the implicated antimicrobial agent. Supportive measures include rehydration with fluid and electrolyte restoration, and avoidance of antiperistaltic agents such as loperamide, diphenoxylate with atropine (Lomotil), or narcotics, and rehydration with fluid and electrolyte restoration.

If the condition being treated requires continued antibiotic treatment, the CDI-inducing agent and other antibiotics that are associated with high rates of CDI should be avoided, particularly cephalosporins and fluoroquinolones; the recommendation is to change to an agent that is unlikely to cause CDI, such as sulfonamides, tetracycline, aminoglycosides, vancomycin, macrolides, narrow-spectrum β-lactams, and urinary antiseptics.

Antibiotic treatment directed against *C. difficile* is readily available and highly effective using oral vancomycin (125 mg four times a day) or metronidazole (500 mg thrice daily or 250 mg

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Table 51.2 Management of relapsing *Clostridium difficile* diarrhea or colitis

Metronidazole or vancomycin PO × 10 days for the first relapse; an alternative is fidaxomicin 200 mg PO BID × 7 days
For subsequent relapses: vancomycin 125 mg PO × 10 days followed by vancomycin 125 mg PO BID × 1 week then 125 mg QD × 1 week and then 125 mg QOD × 4–6 weeks
Patients with multiple relapses are best treated with stool transplants by a qualified provider
Other treatments include probiotics and intravenous immunoglobulin (IVIG) but neither have well-verified benefit

four times a day for about 10 days) (Table 51.1). Response is usually seen within 24 to 48 hours with reduced diarrhea that resolves over 4 to 5 days. Overall response rates are generally reported at 90% to 95%. Vancomycin has ideal pharmacokinetic properties because it is poorly absorbed with oral administration, so colonic levels are several-hundred fold higher than the highest minimum inhibitory concentration ever measured for *C. difficile*. All strains are sensitive. This is a disease where the putative agent is entirely restricted to the intestinal lumen so tissue levels are not relevant to therapy. The disadvantages of vancomycin treatment are the relatively high rate of relapses (20% to 30%) and occasional poor response to the drug that is usually due to erroneous diagnosis or ileus. Fidaxomicin is probably the best drug with response rates similar to those of oral vancomycin for the initial episode, but there is a substantial reduction in the risk of relapse giving this agent a higher "global cure rate." The main limitation of fidaxomicin is price. Metronidazole does not have good pharmacokinetic properties because it is almost completely absorbed in the stomach with oral administration but some gets there by enterohepatic circulation and some presumably by transport across the inflamed colon. Most studies show that metronidazole is comparable to vancomycin in response rates except in patients who are severely ill.

Relapses of CDI occur only with antibiotic treatment. The usual presentation is recurrence of the initial symptoms, usually at 3 to 10 days after discontinuation of metronidazole, vancomycin, or fidaxomicin. Patients generally respond to readministration of either agent, but up to 50% of patients will have another bout of CDI. This rate is cut in half by use of fidaxomicin, presumably because it has less impact on the normal colonic flora which is ultimately the source of this disease (Table 51.2).

Clostridium difficile-associated diarrhea is now largely a nosocomial infection. It is assumed that this is generally acquired all within the healthcare system, but recent studies show that most patients are actually colonized at the time of admission, which complicates traditional methods of infection control. Infection control recommendations to control spread include: isolating patients, especially those with severe diarrhea or incontinence; enforcing handwashing with soap or detergent; and replacing electronic thermometers. With CDI outbreaks, it may be necessary to restrict use of selected antimicrobials. Transmission patterns based on whole gene sequencing show that antibiotic control in susceptible hosts is probably more important than infection control for preventing CDI, although both are important.

NAP-1 STRAIN

This strain was rare in the early 2000s, but it became an epidemic strain in Europe, and North America including Quebec about 2005. The unique features of this strain are that it may be somewhat more virulent compared to other strains; more importantly, it is resistant to quinolones, so extensive use of that class beginning in 1988 is thought to account for the high incidence of NAP-1 in North America and Europe.

Complications include severe disease with toxic megacolon that is refractory to medical management and requires surgery. The traditional standard surgical procedure was colectomy, but more recently there has been the use of a diverting colostomy with diverting ileostomy with reduced mortality rates and colon preservation.

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52. Sexually transmitted enteric infections

Thomas C. Quinn

INTRODUCTION

A wide variety of microbial pathogens may be transmitted sexually by the oral–anal or genital–anal routes. Sexually transmitted enteric infections may involve multiple sites of the gastrointestinal tract, resulting in proctitis, proctocolitis, and enteritis. These infections occur primarily in men who have sex with men (MSM) and heterosexual women who engage in anal–rectal intercourse or in sexual practices that allow for fecal–oral transmission. Anorectal infections with syphilis, gonorrhea, condyloma acuminata (human papillomavirus, HPV), lymphogranuloma venereum (LGV), and granuloma inguinale (donovanosis) have been recognized for many years. Over the past 2 decades, other sexually transmitted pathogens such as herpes simplex virus (HSV) and *Chlamydia trachomatis* have also been recognized as causing anorectal infection. Enteric pathogens traditionally associated with food or waterborne acquisition but that also may be transmitted sexually include *Giardia lamblia, Entamoeba histolytica, Campylobacter, Shigella*, and *Salmonella*. In patients with acquired immunodeficiency syndrome (AIDS), other opportunistic infections, including *Candida, Microsporida, Cryptosporidium, Isospora, Cyclospora, Mycobacterium avium* complex, and cytomegalovirus (CMV), may also cause intestinal disorders.

Depending on the pathogen and the location of the infection, symptoms and clinical manifestations vary widely. Perianal lesions are usually caused by syphilis, HSV, granuloma inguinale, chancroid, and condyloma acuminata. Rectal infections cause inflammation of the rectal mucosa, commonly referred to as proctitis. Symptoms include constipation, tenesmus, rectal discomfort or pain, hematochezia, and a mucopurulent rectal discharge. Proctitis can be caused by gonorrhea, chlamydia, syphilis, and HSV. Proctocolitis involves inflammation extending from the rectum to the colon, and in addition to the organisms causing proctitis, other enteric pathogens such as *Shigella, Salmonella, Campylobacter, E. histolytica*, and CMV may be involved. Enteritis is an inflammatory illness of the duodenum, jejunum, and/or ileum. Sigmoidoscopy results are often normal, and symptoms consist of diarrhea, abdominal pain, bloating, cramps, and nausea. Additional symptoms may include fever, weight loss, myalgias, flatulence, urgency, and, in severe cases, melena. Sexually transmitted pathogens usually associated with enteritis include *Shigella, Salmonella, Campylobacter, Giardia*, CMV, and, potentially, *Cryptosporidium, Isospora*, and *Microsporida*.

The large number of infectious agents that cause enteric and anorectal infections necessitate a systematic approach to the management of these conditions. While obtaining the medical history, the clinician should attempt to differentiate between proctitis, proctocolitis, and enteritis and should assess the constellation of symptoms that suggest one or another likely infectious cause. The history should be used to investigate types of sexual practices and possible exposure to the pathogens known to cause intestinal infections. Examination should include inspection of the anus, digital rectal examination, and anoscopy to identify general mucosal abnormalities. Initial laboratory tests should include a Gram stain of any rectal exudate obtained with the use of an anoscope. The demonstration of leukocytes provides objective evidence of the presence of an infectious or inflammatory disorder. Cultures for gonorrhea should be obtained from the rectum, urethra, and pharynx, and, if possible, rectal culture for chlamydia should be performed. Serologic tests for syphilis should be performed in all cases. Dark-field examination of any ulcerations and a rapid plasma reagin test should be performed. Cultures for HSV should be performed if ulcerative lesions are present. If proctocolitis is present, additional stool cultures for *Campylobacter, Salmonella*, and *Shigella* should be obtained, and stool examination for *E. histolytica* is indicated. For human immunodeficiency virus (HIV)-positive

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patients, other pathogens, including *Microsporida*, CMV, atypical *Mycobacteria, Cryptosporidium*, and *Isospora*, should be screened for by stool examination and cultured. Specific information on clinical presentation, diagnosis, and therapy is provided in other chapters on gastroenteritis, intestinal protozoa, and individual enteric pathogens.

GONOCOCCAL PROCTITIS

Rectal infection with *Neisseria gonorrhoeae* occurs predominantly among homosexual men and women engaging in anal–rectal intercourse. In many cases of women, the patient has no history of rectal intercourse and the infection is thought to have resulted from contiguous spread of infected secretions from the vagina. Symptoms, when present, develop approximately 5 to 7 days after exposure. Symptoms are usually mild and include constipation, anorectal discomfort, tenesmus, and a mucopurulent rectal discharge that may cause secondary skin irritation, resulting in rectal itching and perirectal erythema. Although asymptomatic or mild local disease is common, complications such as fistulas, abscesses, strictures, and disseminated gonococcal infection may occur.

Findings of rectal gonorrhea during anoscopy are nonspecific and limited to the distal rectum. The most common finding is the presence of mucopus in the rectum. The rectal mucosa may appear completely normal or demonstrate generalized erythema with local areas of easily induced bleeding, primarily near the anal–rectal junction. Diagnosis is usually made by Gram stain and culture of material obtained by swabbing the mucosa of the rectal area. The sensitivity of Gram stain of rectal exudate for identification of gram-negative intracellular diplococci is approximately 80% when obtained through an anoscope versus 53% for blindly inserted swabs. Cultures inoculated on selective media provide the definitive diagnosis; however, the precise sensitivity of a single rectal culture for gonorrhea may be no greater than 80%. DNA detection assays are now widely available for detection of gonorrhea in urogenital specimens and appear to be equally sensitive as culture.

Due to increasing antibiotic resistance of gonorrhea to cefixime and fluoroquinolones, the Centers for Disease Control and Prevention (CDC) recommends for treatment of uncomplicated urogenital, anorectal, and pharyngeal gonorrhea, combination therapy with a single intramuscular dose of ceftriaxone 250 mg plus either a single dose of azithromycin 1 g orally or doxycycline 100 mg orally twice daily for 7 days. Clinicians who diagnose gonorrhea in a patient with persistent infection after treatment (treatment failure) with the recommended combination therapy regimen should culture relevant clinical specimens and perform antimicrobial susceptibility testing of *N. gonorrhoeae* isolates. When ceftriaxone cannot be used for treatment of urogenital or rectal gonorrhea, two alternative options are available: cefixime 400 mg orally plus either azithromycin 1 g orally or doxycycline 100 mg twice daily orally for 7 days, or azithromycin 2 g orally in a single dose if ceftriaxone cannot be given because of severe allergy. If a patient with gonorrhea is treated with an alternative regimen, the patient should return 1 week after treatment for a test-of-cure at the infected anatomic site. For all patients with gonorrhea, every effort should be made to ensure that the patients' sex partners from the preceding 60 days are evaluated and treated for *N. gonorrhoeae* with a recommended regimen. If there is continued evidence of proctitis, further evaluation for other agents such as chlamydia, syphilis, enteric bacterial pathogens, and HSV should be considered.

CHLAMYDIA PROCTITIS

Rectal infection with LGV and non-LGV immunotypes of *C. trachomatis* has been well documented. LGV infections are endemic in tropical countries, but they have also been increasing in frequency among MSM in the United States and Europe. LGV infections usually cause a severe proctocolitis characterized by severe anorectal pain, bloody mucopurulent discharge, and tenesmus. Inguinal adenopathy, which is characteristic of genital LGV, is often present. Sigmoidoscopy typically reveals diffuse friability with discrete ulcerations in the rectum that occasionally extend to the descending colon. Strictures and fistulas may become prominent and can be easily misdiagnosed clinically as Crohn's disease or carcinoma. Histologically, rectal LGV may be confused with Crohn's disease because giant cells, crypt abscesses, and granulomas may be present.

The non-LGV immunotypes of *C. trachomatis* are less invasive than LGV and cause a mild proctitis characterized by rectal discharge, tenesmus, and anorectal pain. Many infected individuals may be asymptomatic and can be diagnosed only by routine cultures. However, even in

asymptomatic cases, abnormal numbers of fecal leukocytes are usually present. Sigmoidoscopy results may be normal or may reveal mild inflammatory changes with small erosions or follicles in the lower 10 cm of the rectum.

Rectal *C. trachomatis* infection can be diagnosed by nucleic acid amplified tests (NAATs) and nucleic acid hybridization tests, although they are not Food and Drug Administration (FDA) cleared for use with rectal or oropharyngeal swab specimens. Since chlamydia culture is not widely available for this purpose, NAATs have demonstrated improved sensitivity and specificity compared with culture for the detection of *C. trachomatis* at rectal sites and at oropharyngeal sites. Some laboratories have met Clinical Laboratory Improvement Amendment (CLIA) requirements and have validated NAAT testing on rectal swab specimens for *C. trachomatis*. Serology is useful for the diagnosis of LGV with a complement fixation titer of >1:64. Azithromycin, tetracycline, and doxycycline are the drugs of choice for infection with *C. trachomatis*. Azithromycin, 1.0 g as a single dose, is effective for urethritis and cervicitis and has been recommended for uncomplicated rectal infections. Doxycyline, 100 mg twice a day for 7 days, is effective, except for treating LGV infection, which should be treated for 3 weeks with doxycycline 100 mg orally twice a day. Patients should be followed carefully with repeat sigmoidoscopy, particularly when there is any question about the differential diagnosis of LGV versus inflammatory bowel disease.

ANORECTAL SYPHILIS

Treponema pallidum can be seen in its early infectious stages, with a primary anorectal lesion appearing 2 to 6 weeks after exposure to rectal intercourse. However, clinicians often fail to recognize anorectal chancres, and consequently, syphilis in MSM is diagnosed in a secondary or early latent stage much more often than in the primary stage. Careful perianal examination can reveal unsuspected perianal chancres, but digital rectal examination and anoscopy may be required to detect asymptomatic chancres higher in the anal canal or rectum. When anorectal syphilis causes symptoms, it is often misdiagnosed as a traumatic lesion, fissure, or hemorrhoiditis. When symptoms are present, they include mild anal pain or discomfort, constipation, rectal bleeding, and occasionally a rectal discharge. Primary anorectal syphilis may appear as a single or multiple, mirror-image perianal ulcer ("kissing chancres"). It can also present as an ulcerated mass typically located on the anterior wall of the rectum. Inguinal adenopathy with rubbery, nonsuppurative, painless nodes may be associated with anorectal syphilis; it helps distinguish it from fissures. Secondary syphilis may cause discrete polyps, smooth lobulated masses, mucosal alterations, and nonspecific mucosal erythema or bleeding. In secondary syphilis, condyloma lata may be found near or within the anal canal. These are smooth, warty masses and should be differentiated from the more highly keratinized condyloma acuminata.

Diagnosis of anorectal syphilis is based on serology, perirectal and digital rectal examination, and anoscopy. Detection of motile treponemes by dark-field examination is useful for evaluation of perianal and anal lesions but may be less specific for rectal lesions because pathogenic treponemes can be found in the intestine. Biopsies of rectal lesions or masses should be processed for silver staining if syphilis is suspected. Serologic diagnosis of syphilis is based on the presence of antibodies to non-treponemal and treponemal antigens. A positive Venereal Disease Research Laboratory (VDRL) test or rapid plasma reagin (RPR) test must be confirmed by a positive specific test such as the fluorescent treponemal antibody absorption test (FTA-ABS) or the microhemagglutination assay (MHA). Some clinical laboratories and blood banks have begun to screen samples using treponemal tests, typically by enzyme immunoassay. Persons with a positive treponemal screening test should have a standard non-treponemal test with titer performed reflexively by the laboratory to guide patient management decisions. For most HIV-infected persons, serologic tests are accurate and reliable for the diagnosis of syphilis and for following a patient's response to treatment. However, atypical syphilis serologic test results (i.e., unusually high, unusually low, or fluctuating titers) can occur in HIV-infected persons. When serologic tests do not correspond with clinical findings suggestive of early syphilis, use of other tests (e.g., biopsy and dark-field microscopy) should be considered.

Treatment for anorectal syphilis is standard treatment for early syphilis and consists of benzathine penicillin, 2.4 million U IM. Penicillin-allergic patients may be treated with a 14-day course of doxycycline, 100 mg twice daily, or tetracycline, 500 mg four times a day for 14 days.

SHIGELLA, *SALMONELLA*, AND *CAMPYLOBACTER* INFECTIONS

Shigellosis presents with an abrupt onset of diarrhea, fever, nausea, and cramps. Diarrhea is usually watery but may contain mucus or blood. Sigmoidoscopy usually reveals an inflamed mucosa with friability not limited to the distal rectum, and histologic examination shows diffuse inflammation with bacteria scattered throughout the submucosa. *Shigella sonnei* and *Shigella flexneri* account for most of the *Shigella* infections in the United States. Diagnosis is made by culturing the organism from the stool on selective media. Treatment is usually supportive with fluid replacement, and antimotility agents should be avoided. Antibiotics are useful in the management of shigellosis because use of appropriate therapy has reportedly shortened the period of fecal excretion and limited the clinical course. However, some authorities believe that antibiotic therapy should be reserved for the severely ill only or the immunocompromised patient because the infection is typically self-limited and resistance has been common. HIV-infected patients who develop *Shigella* infections may require prolonged treatment or suppressive therapy similar to those infected with salmonella. Antibiotic therapy should be chosen according to the sensitivity pattern of the *Shigella* species isolated. Ciprofloxacin, 500 mg twice a day for 7 days, is usually effective unless resistance is evident.

Campylobacter jejuni and *Campylobacter*-like organisms such as *Helicobacter cinaedi* and *Helicobacter fennelliae* have also been associated with proctocolitis in homosexual men. Clinical manifestations of infections resulting from all *Campylobacter* species appear nearly identical. There is often a prodrome with fever, headache, myalgia, and malaise 12 to 24 hours before the onset of intestinal symptoms. The most common symptoms are diarrhea, malaise, fever, and abdominal pain. Abdominal pain is usually cramping and may be associated with 10 or more bowel movements per day. *Campylobacter enteritis* is often self-limiting with gradual improvement in symptoms over several days. Illnesses lasting longer than 1 week occur in approximately 10% to 20% of patients seeking medical attention, and relapses are often seen in HIV-infected patients. Fecal leukocytes are uniformly present, and diagnosis is confirmed by isolation of the organisms on selective media in a microaerophilic atmosphere. Therapy consists of fluid and electrolyte replacement and antibiotic treatment. Ciprofloxacin 500 mg twice a day for 7 days or azithromycin 500 mg once daily for 3 days has been used for treatment successfully, but resistance to these antibiotics has also been increasing within recent years, and antibiotic susceptibility should be reviewed.

Salmonella infections of the intestinal tract are primarily caused by *S. typhimurium* and *S. enteritidis*. Salmonella has been reported among homosexual male partners, suggesting sexual transmission, and salmonella bacteremia in an HIV-infected individual is now diagnostic of AIDS. Clinical presentation often depends on the host immune status. In an immunocompetent person, salmonellosis is usually self-limited and causes gastroenteritis. No antibiotic therapy is recommended because symptoms fade within days, and antibiotics have been associated with prolonged salmonella intestinal carriage. In HIV-infected individuals, salmonella infections may cause severe invasive disease and often result in bacteremia with widespread infection. The fluoroquinolones are effective drugs of choice for *Salmonella* infections in immunocompromised individuals. Despite adequate therapy for bacteremia, virtually all HIV-infected patients may suffer recurrent salmonella septicemia. Ciprofloxacin, 500 to 750 mg twice daily, has been effective in suppressing recurrences in such patients.

PARASITIC INFECTIONS

Homosexual men engaging in sexual activities involving fecal contamination such as oral–anal sex are at increased risk for a number of parasitic infections, including *Giardia lamblia, Iodamoeba butschlii, Dientamoeba fragilis, Enterobius vermicularis, Cryptosporidium, Isospora*, and microsporidia. Of these infections, *Giardia* and *E. histolytica* appear to be the most common sexually transmitted parasitic infections. *Giardia lamblia* is associated with symptoms of enteritis, and *E. histolytica* may cause proctocolitis. Most *E. histolytica* infections are asymptomatic and less than 10% of those infected develop invasive disease with amebic dysentery or liver abscess. Most *E. histolytica* strains isolated from homosexual men are the nonpathogenic strains that are not usually associated with gastrointestinal symptoms. However, when symptoms are present, they may vary from mild diarrhea to fulminant bloody dysentery. These symptoms may wax and wane for weeks to months.

Diagnosis is based on demonstration of *E. histolytica* in the stool in a wet mount of a swab or in biopsy of rectal mucosal lesions. Occasionally,

multiple fresh stool examinations are necessary to demonstrate the cysts or trophozoites or *E. histolytica*. For noninvasive disease limited to the lumen only, paromomycin 25 to 30 mg/kg/day in three doses for 7 days is the regimen of choice. Invasive intestinal disease should be treated with metronidazole, 750 mg orally three times daily for 7 to 10 days.

Giardia lamblia also appears to be sexually transmitted through oral–anal contact. Giardiasis is typically an infection of the small intestine, and symptoms vary from mild abdominal discomfort to diarrhea, abdominal cramps, bloating, and nausea. Multiple stool examinations may be necessary to document infection with *G. lamblia*. When stool examination is negative, sampling of the jejunal mucus by the Enterotest or small-bowel biopsy may be necessary to confirm the diagnosis. Metronidazole 250 mg three times a day for 7 days is recommended. Alternative regimens include tinidazole, 2 g only single dose, or paromomycin, 10 mg/kg orally three times per day for 5 to 10 days.

Although sexual transmission of *Cryptosporidium, Isospora belli*, and *Microsporida* are commonly seen in HIV-infected homosexual men, evidence for sexual transmission is limited. These protozoa primarily infect the small bowel and cause nonspecific watery diarrhea, abdominal cramping, and bloating. Diagnosis is established by a modified acid-fast stain or fluoramine stain of the stool or by concentration and identification of the organism by the sugar-flotation method. A commercially available fluorescein monoclonal antibody assay increases the sensitivity for detection of *Cryptosporidium*. Treatment of *Cryptosporidium* or *Isospora* infections in immunocompetent patients with self-limited diarrhea is rarely required. Among HIV-infected individuals, treatment should be directed toward symptomatic treatment of the diarrhea with rehydration and repletion of electrolyte losses by either oral or intravenous route. Although several antibiotics have been used, including paromomycin and azithromycin, chronic infection and relapses are common. The most effective therapy currently is a reversal of immunosuppression with the use of highly active antiretroviral therapy. It is common for patients with severe diarrhea from *Cryptosporidium* and *Microsporida* to clear their infections by taking combination antiretroviral agents with reduction in the viral load below detectable limits. Successful treatment of the infection presumably results from a subsequent rise in CD4 count and restoration of immune competence sufficient to clear the intestinal infection.

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53. Acute appendicitis

Bian Wu and John Maa

BACKGROUND AND EPIDEMIOLOGY

Acute appendicitis is one of the most common surgical emergencies, with a lifetime incidence of approximately 7%. It can occur in males and females of all ages, but is most common in older children and young adults. The diagnosis is often delayed in younger children and the elderly due to atypical presentations.

PATHOGENESIS

The pathophysiology of acute appendicitis begins with obstruction of the appendicular lumen. The obstruction is commonly caused by a fecalith (impacted stool) in adults and lymphoid hyperplasia in children, but can also result from foreign bodies (undigested seeds), infections (especially parasitic), and tumors (most commonly adenocarcinoma, followed by carcinoid tumors). Luminal obstruction leads to accumulation of distal secretions and increased intraluminal pressure, which results in impairment of venous outflow and, subsequently, arterial inflow. The resulting ischemia yields bacterial translocation, mucosal necrosis, and, eventually, perforation. The natural progression and types of acute appendicitis are described in **Table 53.1** (simple acute, suppurative, gangrenous, perforated, associated with abscess). The organisms most typically associated with gangrenous or perforated appendicitis are *Escherichia coli*, *Peptostreptococcus*, *Bacillus fragilis*, and various species of *Pseudomonas*, with most cases being polymicrobial.

Table 53.1 Types of acute appendicitis

Type	Characteristics
Simple acute	Mild hyperemia, edema, appendiceal dilation, no serosal exudate
Suppurative	Edematous, congested vessels, fibrinopurulent exudate; peritoneal fluid increased, clear or turbid; may be walled off by omentum, adjacent bowel or mesentery
Gangrenous	Similar to suppurative plus areas of gangrene, microperforations, increased and purulent peritoneal fluid
Perforated	Obvious defect in wall of appendix; thick and purulent peritoneal fluid; may be associated with ileus or bowel obstruction
Abscess	Appendix may be sloughed; abscess at site of perforation: right iliac fossa, retrocecal, or pelvic; may present rectally; thick, malodorous pus

DIAGNOSIS

A classic presentation of acute appendicitis includes periumbilical pain that migrates to the right lower quadrant, representing a progression from visceral pain to parietal pain that may occur within a few hours or a few days. Physical examination often reveals point tenderness at McBurney's point, located two-thirds the distance from the umbilicus to the right anterior superior iliac spine. Worsening or diffuse abdominal pain or tenderness are concerning for perforation and peritonitis, as are fevers greater than 38.5°C (101.3°F). Occasionally a palpable mass may be felt in the right lower quadrant, suggestive of a walled-off abscess.

Onset of pain is classically followed by anorexia and nausea, and vomiting may occur. Absence of anorexia and repeated episodes of emesis suggest an alternate diagnosis. Importantly, the classic symptoms of acute appendicitis have limited sensitivity due to variant locations of the appendix and inflammatory irritation of nearby organs. A retrocecal appendicitis may present as flank or back pain, whereas an inflamed appendix in the pelvis may present as dysuria or be confused with testicular or gynecologic diseases. Inflammation of adjacent bowel may cause either an ileus or diarrhea, especially in cases of gross perforation or abscess.

The recent advances in ultrasonography and computed tomography (CT) have markedly improved the accurate diagnosis of appendicitis,

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especially in "atypical" cases. Ultrasound is non-invasive and an excellent way to evaluate young children for whom avoidance of radiation is desirable. However, the usefulness of ultrasound is technician-dependent and often limited by patient habitus (ultrasound waves penetrate poorly through fat). CT, optimally with IV and PO contrast, yields excellent sensitivity and specificity, but is costly and carries the risk of radiation and contrast exposure. Many diseases may mimic acute appendicitis and it is essential to combine history, physical exam, laboratory values, and imaging studies with clinical experience and judgment to minimize the rate of misdiagnosis.

TREATMENT

The mainstay of treatment for simple acute appendicitis is prompt surgical removal of the appendix. To prevent progression leading to perforation, it is important to achieve timely and proper source control. While some evidence supports using antibiotics alone to treat simple acute appendicitis, it is our opinion that appendectomy remains the standard of care. Antibiotics alone carry a significant risk of primary failure leading to perforation as well as disease recurrence, and the now widespread use of laparoscopic appendectomy results in lower rates of surgical complications and shorter hospital stays than were achieved with open appendectomy.

Similarly, surgery remains the standard of care for suppurative, gangrenous, and perforated appendicitis. The exception to urgent surgical intervention for acute appendicitis is perforated appendicitis associated with a contained abscess. In such cases, percutaneous drainage together with antibiotics and interval laparoscopic appendectomy in 6 weeks may be the best treatment strategy, to avoid injury to the small bowel and colon. Antibiotic selection should be tailored to the polymicrobial nature of the disease. Typically, an antipseudomonal β-lactamase is used, such as meropenem, cefepime, or piperacillin/taxobactam. In cases of β-lactamase allergy, combinations such as ciprofloxacin and metronidazole can be used. The most common bacteria that lead to a postoperative infection after appendectomy are: (1) *Bacteroides*, (2) *Klebsiella*, (3) *Enterobacter*, and (4) *E. coli*, although many of these infections are polymicrobial. Gram-positive cocci are less frequently isolated.

Laparoscopic appendectomy is generally recommended over open appendectomy because it results in less postoperative pain, shorter hospital stays, and a faster return to normal activities. The risk of wound infections is lower with laparoscopic surgery than with open surgery (odds ratio 0.43 with 95% confidence interval 0.34–0.54), but the risk of intra-abdominal abscesses is higher (odds ratio 1.87 with 95% confidence interval 1.19–2.93). This higher risk may be due to the more limited ability to perform peritoneal lavage with laparoscopic surgery as compared to open surgery. In fact, studies suggest there is no advantage to irrigation of the peritoneal cavity over suction alone during laparoscopic appendectomy for perforated appendicitis. Thus, open surgery may be preferred for patients with grossly perforated appendicitis. Laparoscopic surgery use is also limited in some parts of the world by the availability of laparoscopic equipment and surgeons trained in minimally invasive techniques.

PERIOPERATIVE MANAGEMENT

During workup for possible acute appendicitis, patients should be kept NPO. Once the diagnosis is made, a general surgeon should be consulted and the operation arranged. Since patients are typically volume depleted (as evidenced by tachycardia, low urine output, elevated creatinine, hemoconcentration), aggressive fluid resuscitation with an isotonic solution should be started, and electrolytes repleted. Should there be signs of perforation or frank peritonitis (as evidenced by worsening diffuse pain, rebound or involuntary guarding on exam, very high fever, findings on CT scan), the patient's operation should be further expedited.

A broad-spectrum antibiotic should be given prior to skin incision and is typically not continued postoperatively, except in cases with gross perforation. Preoperative preparation of the skin is best performed with a chlorhexidine–alcohol scrub. Postoperatively, patients undergoing laparoscopic appendectomy can typically be started on a clear liquid diet immediately and advanced to a regular diet the following morning. Patients with gross perforation and a likely associated ileus are typically kept NPO immediately postoperatively. The diet is then advanced slowly depending on the length of surgery and associated intra-abdominal inflammation or contamination. Patients should begin walking immediately postoperatively to prevent complications such as pneumonia or deep venous thrombosis.

Table 53.2 Types of postoperative infection

Type	Characteristics	Management
Superficial surgical site infection (SSI)	Cellulitis +/− infected subcutaneous fluid collection	PO or IV antibiotics +/− open skin at bedside to drain fluid followed by packing the wound with gauze
Deep surgical site infection (SSI)	Infection involving the abdominal fascia (may be associated with fascial dehiscence)	IV antibiotics +/− operative debridement
Organ space infection	Intra-abdominal abscess or gross postoperative perforation/peritonitis	IV antibiotics and percutaneous drainage or operative exploration and washout
Pylephlebitis	Infection and thrombophlebitis within the portal venous system	Intravenous antibiotics +/− systemic heparinization

POSTOPERATIVE COMPLICATIONS

Postoperative infections remain the major source of morbidity associated with acute appendicitis. Gross perforation of the acutely inflamed appendix changes the wound classification from clean-contaminated to dirty, with an associated increased risk of postoperative infection from around 10% to 40%. Classification of postoperative infections is dependent on the depth: superficial surgical site infection (SSI), deep SSI, and organ space infection (Table 53.2). While superficial SSIs can typically be managed with a short course of antibiotics with or without bedside opening of the superficial wound, deep SSIs require longer courses of antibiotics and possible return to the operating room for debridement. Organ space infections typically necessitate percutaneous drainage or operative exploration and washout, as well as an extended course of antibiotics.

To minimize the risk of superficial SSIs in cases of perforated appendicitis, the traditional approach after open appendectomy has been to close the fascia, but not the skin edges, to allow for healing by secondary intention or delayed primary closure. This is not typically performed after laparoscopic appendectomy. Laparoscopic appendectomy is associated with a lower risk of superficial and deep SSI, but a higher risk of organ space infection compared to open appendectomy. To minimize the risk of deep SSIs and organ space infections, a Jackson Pratt drain may be left in the abdomen after either open or laparoscopic appendectomy.

For cases of non-perforated appendicitis, postoperative antibiotics do not alter the incidence of superficial SSIs, deep SSIs, or organ space SSIs, but do correlate with higher rates of *Clostridium difficile* infection and urinary tract infection, as well as longer hospital stays. On the other hand, antibiotics play an important role in the postoperative management of perforated appendicitis. Patients with severe sepsis or septic shock in the postoperative period necessitate immediate transfer to the ICU and goal-directed therapy (blood cultures, IV antibiotics, IV fluids, and possible vasopressors). These patients often require return to the operating room for source control.

The presence of a postoperative hematoma significantly increases the risk of both superficial and organ space infections, thus meticulous intraoperative hemostasis is essential. Pyephlebitis (infection and thrombosis within the portal venous system) may occur with any intra-abdominal infection, but is now rare with the use of perioperative antibiotics. Other rare postoperative complications include stump appendicitis (related to incomplete resection of the appendix), cecal fistula (related to loss of seal at the resected appendicular orifice resulting in an organ space infection), and wound dehiscence (associated with deep surgical site infection).

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54. Diverticulitis

Ronald L. Nichols and James R. Korndorffer Jr

Diverticulosis coli is an anatomic abnormality of mucosal outpouchings in the colonic wall. Colonic diverticuli are often asymptomatic and the prevalence varies greatly with such factors as geographic location, dietary habits, race, and age. In the United States, the incidence has been noted to increase with age, with up to a third of the population over the age 60 being affected and over two-thirds of the population over 80 being affected.

The diagnosis of diverticulosis coli is often made incidentally in otherwise asymptomatic patients at the time of routine surveillance endoscopy. However, unless a stricture is present, most of these patients require only counseling about the need for prophylactic measures such as a fiber-rich diet, adequate fluid consumption, and the prevention of constipation. Discussion of the risk of possible infectious (up to 25% risk) or hemorrhagic complications of the disease should also be undertaken.

Clinically symptomatic diverticulosis commonly presents as acute inflammation or as lower gastrointestinal hemorrhage. While rare when compared to the frequency of diverticulosis in the population, clinically significant diverticular disease and its complications continue to tax the diagnostic and therapeutic skills of physicians. Physical findings range from diffuse slight abdominal tenderness to shock secondary to either massive hemorrhage or overwhelming sepsis. Even when clinical manifestations of diverticulosis occur, emergent surgical intervention is necessary in only a minority of patients. During such life-threatening emergencies, the physician must be prepared to resuscitate the patient quickly and proceed to surgical intervention without benefit of a definite diagnosis. These patients may have massive, or recurrent, gastrointestinal bleeding, but more commonly have generalized peritonitis that has developed after diverticular perforation.

DIAGNOSIS OF INFECTION

In patients with signs of abdominal infection, including fever and abdominal pain and tenderness, usually in the left lower quadrant, it is often possible to make a presumptive diagnosis of acute diverticulitis on the basis of history, physical examination, and initial laboratory tests. This allows for the initiation of resuscitative measures, including empiric antibiotic therapy. Although further diagnostic radiographic procedures can be delayed for up to 2 days, if the patient continues to show signs of improvement, it is best to perform them as soon as possible to confirm the presumptive diagnosis.

Although ultrasonography is an effective and relatively inexpensive method of evaluating the abdomen and pelvis, particularly for imaging abscesses and their relationship to adnexal structures, most consider computed tomography (CT) to be superior, and safer than contrast enema studies. For those that still prefer the contrast enema for colonic imaging, water-soluble contrast materials are preferred to barium to avoid barium peritonitis in case of perforation or leakage.

Once diverticulitis has been documented radiographically, further clinical decisions depend on the resolution of signs and symptoms of infection. If they resolve completely and the patient is stable, endoscopic examination of the entire colon is required to evaluate for neoplastic disease or complications such as stricture. Colonoscopy is best performed approximately 6 weeks after symptoms of acute diverticulitis have subsided so that enough time passes for resolution of any partial obstruction secondary to inflammatory changes in the bowel wall.

MANAGEMENT OF DIVERTICULITIS

The greatest number of complications in colonic diverticular disease result from infection. They range from localized short segments of

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diverticulitis, to abscesses and/or fistulas, to free perforation with generalized peritonitis and overwhelming intra-abdominal sepsis (Figure 54.1). While the cause of the diverticular formation has been established as increased intraluminal pressure, the cause of perforation is not clear. Some authorities postulate that a surge in intraluminal pressure is often the cause, and others suggest ulceration, ischemia, and foreign-body perforation.

Peridiverticulitis

When ulceration or ischemia is not accompanied by free communication with the peritoneal cavity, penetration of mixed bacterial flora into the wall initiates peridiverticular infection.

Patients with localized peridiverticular disease usually complain of abdominal pain localized to the left lower quadrant. In some cases, however, a redundant sigmoid colon may have sufficient mobility to produce local symptoms in the right lower or right upper abdominal quadrant as well as in the midepigastrium. These patients are often febrile and have mild leukocytosis. However, they typically respond well to bowel rest, parenteral fluids, and antibiotic therapy. Nasogastric tube insertion is usually unnecessary unless obstructive signs and symptoms are present.

It is important that patients take nothing by mouth to abolish the gastrocolic reflex. Morphine sulfate should not be administered because it can increase intracolonic pressure. Most patients require a 3- to 5-day course of appropriate parenteral antimicrobials (Table 54.1). If they continue to improve, with normalization of the white blood cell (WBC) count, temperature, and abdominal examination, we discontinue their parenteral antibiotics and advance them to a regular diet that is devoid of poorly digestible foods (e.g., whole corn).

Patients must be followed carefully after resolution of abdominal symptoms. If no disease other than diverticulosis is found on follow-up endoscopy, each patient should follow a fiber-supplemented diet with a generous consumption of fluids.

We do not recommend surgery after uncomplicated diverticulitis in otherwise healthy patients. Rather, we recommend medical therapy and the decision for elective surgery after resolution should be made on a case-by-case basis. Some factors which may influence the decision to proceed with elective colon resection include, frequency of episodes, age and immune status of the patient. Such resection can be performed by an open laparotomy technique or by laparoscopic technique if the equipment and expertise is available.

Although the medical approach rarely fails to control the signs and symptoms of peridiverticulitis, surgical resection may become necessary if the infection does not resolve with prolonged parenteral antibiotic therapy. Occasionally, a major complication such as liver abscess or bacteremia develops and requires colonic resection. However, patients with very limited symptoms and no signs of systemic sepsis may respond to oral regimens of antibiotics aimed at covering these colonic aerobes and anaerobes (Table 54.2).

Pericolic disease

If the peridiverticular process fails to respond to antibiotic therapy or the patient presents in a late stage of the infectious process, an abscess may be present. A pericolic abscess can often be demonstrated by CT or possibly ultrasound. If these studies reveal a small cavity and the patient is improving, continuation of medical therapy and antibiotics is warranted. However, in patients that are not improving or have a larger abscess cavity, percutaneous drainage may be a useful adjunct.

Patients with a history of an episode of complicated diverticulitis should be advised to undergo elective colon resection. Decompressing the purulent contents of an abscess via CT-guided percutaneous catheter placement gains time to improve the patient's status with volume replacement, parenteral hyperalimentation, and appropriate antibiotic therapy. Once the abscess cavity has been resolved by catheter drainage, it is possible to prepare the bowel for elective resection of the diseased colon with primary anastomosis. Our approach to preoperative colon preparation is shown in Table 54.3. Some authors currently do not recommend the use of mechanical cleansing before administration of the oral antibiotics.

Collections not accessible to percutaneous techniques or those associated with peritonitis are best treated with urgent surgical intervention. There are two essential operative goals. The first is to resect the inflamed colon and control the associated septic complications; we believe surgical resection of the infectious source is superior to simple diversion of colonic contents (colostomy) and drainage. The second goal is to restore intestinal continuity. Although this may require a second procedure in some cases, we believe it

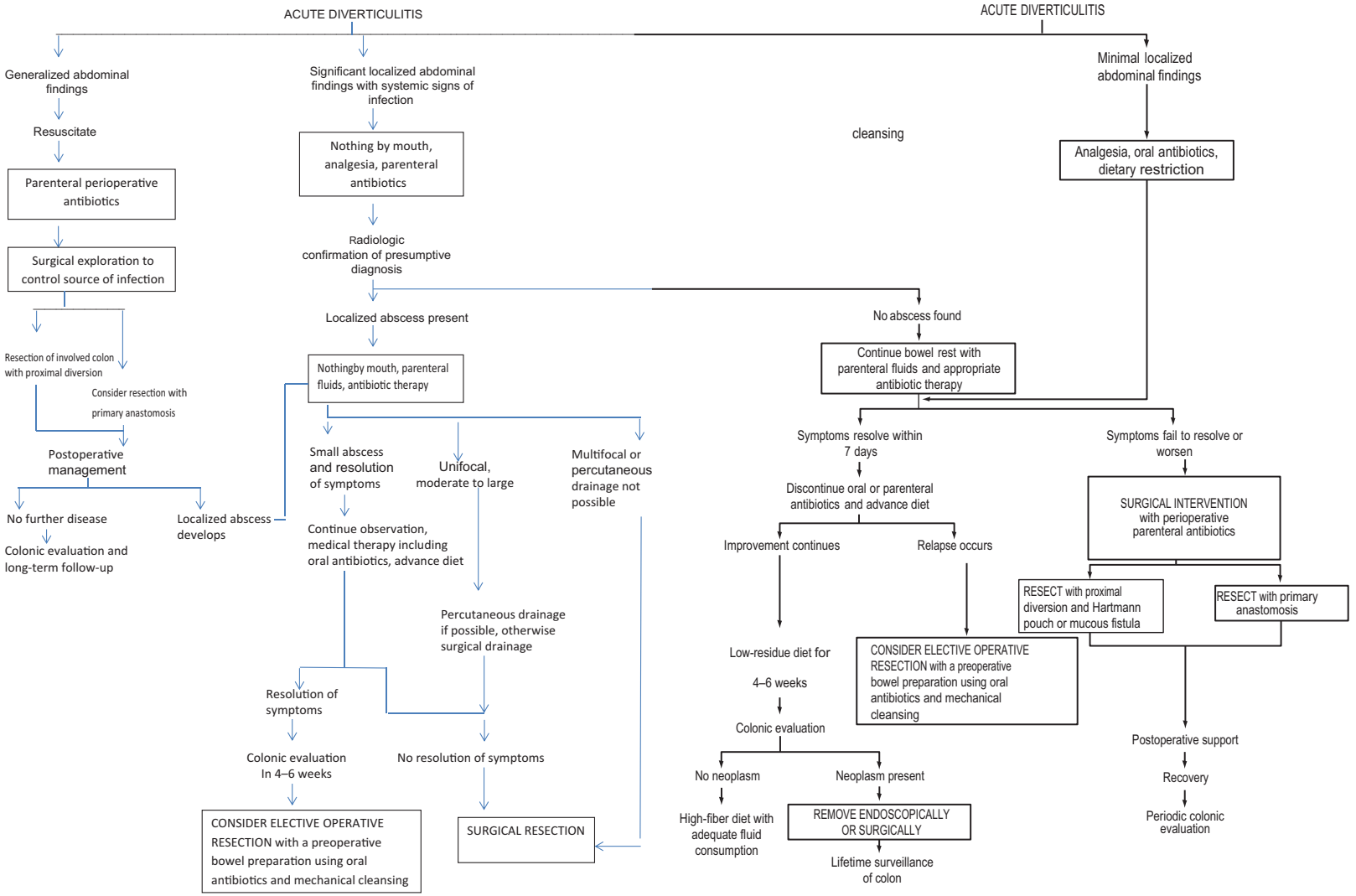

Figure 54.1 Algorithm for the workup and treatment of acute diverticulitis.

Table 54.1 Intravenous antibiotics for coverage of the aerobic and anaerobic human colonic microflora

Drug	Dosage	Frequency
COMBINATION THERAPY		
Aerobic coverage[a]		
Amikacin	15–20 mg/kg/d	q8–12h
Aztreonam	1–2 g	q6–8h
Ceftriaxone	1–2 g	12–24h
Ciprofloxacin	400 mg	ql2h
Gentamicin	5–7 mg/kg/d	q8h
Tobramycin	5–7 mg/kg/d	q8h
Anaerobic coverage[b]		
Clindamycin	600–900 mg	q8h
Metronidazole	500 mg	q8–12h
AEROBIC–ANAEROBIC COVERAGE (SINGLE-DRUG THERAPY)		
Ampicillin–sulbactam	1.5–3 g	q6h
Cefotetan	1–2 g	q8–12h
Cefoxitin	1–2 g	q6h
Ertapenem	1 g	q24h
Imipenem–cilastatin	500 mg	q6h
Meropenem	1 g	q8h
Piperacillin–tazobactam	3.375–4.5 g	q6h
Ticarcillin–clavulanate	3.1 g	q6h
Tigecyline	100 mg (initial dose) then 50 mg	q12h

[a] To be combined with a drug exhibiting anaerobic activity.
[b] To be combined with a drug exhibiting aerobic activity.

Table 54.3 Suggested approach to preoperative preparation for elective colon resection

Two days before surgery (at home)
Low-residue or liquid diet
One day before surgery (at home or in hospital if necessary)
Admit in morning (if necessary and allowed)
1. Continue clear liquid diet, IV fluids as needed
2. Whole-gut lavage with polyethylene glycol, 1 L/h PO starting at 8 a.m. until diarrhea is clear (no longer than 3–4 h)
No enemas
All patients receive 1 g of neomycin PO and 1 g of erythromycin base PO at 1 p.m., 2 p.m., and 11 p.m.
Day of surgery
Operation at 8 a.m.
A single dose of antibiotic with broad-spectrum aerobic/anaerobic activity given IV by anesthesia personnel in the operating room just before incision; repeat dosage if operation lasts more than 2 h

can be accomplished safely during the same operation (single-stage procedure) in most patients. This is particularly true in individuals who are not hemodynamically compromised, who have localized diverticulitis, or who have diverticulitis with an associated mesocolonic abscess amenable

Table 54.2 Oral antibiotic regimens for treatment of a mild episode of acute diverticulitis

Antibiotic	Dosage (mg)	Frequency-duration
Ciprofloxacin	500	BID
Ciprofloxacin and metronidazole	500 500	BID BID
TMP–SMX DS and metronidazole	800 500	BID BID
Amoxicillin-clavulanic acid	250–500	TID
Doxycycline	100	q24h

Abbreviations: BID = twice a day.
TID = three times a day.
TMS–SMX DS = trimethoprim–sulfamethoxazole (Bactrim) double strength.

to en bloc resection and with no intra-abdominal spillage of purulent material.

Another somewhat controversial technique is resection of the involved colon, usually the sigmoid, intraoperative lavage, and primary anastomosis. This procedure requires a team effort to keep control of either the proximal or distal colon during lavage, preventing gross peritoneal fecal contamination with its accompanying disastrous effects.

In summary, if urgent surgery is necessary for localized diverticulitis, we try to remove the inflamed colon, most often performing a primary anastomosis. If this is inadvisable because of hemodynamic instability or gross evidence of peritoneal contamination, we do an end colostomy with a distal pouch provided no distal obstruction is present. Diversion alone is rarely done as it has shown to result in a high mortality rate.

Generalized intra-abdominal sepsis

The cause of generalized abdominal findings suggesting intra-abdominal sepsis is often unknown before exploratory laparotomy. These patients require prompt fluid resuscitation and empiric antibiotic coverage with an agent or combination of agents that will control both aerobic and anaerobic enteric organisms (see Table 54.1). If there is evidence of perforation or if the patient is in shock, laparotomy as soon as the patient is stable is often necessary. Laparotomy often reveals fibrinous exudate, free pus, or abscesses throughout the abdominal cavity (Figure 54.2). If we find diverticulitis, we resect the involved segment and perform a proximal colostomy. Under these conditions, we do not consider performing a primary anastomosis. We prefer to leave a closed distal pouch, but only if there is no distal lesion

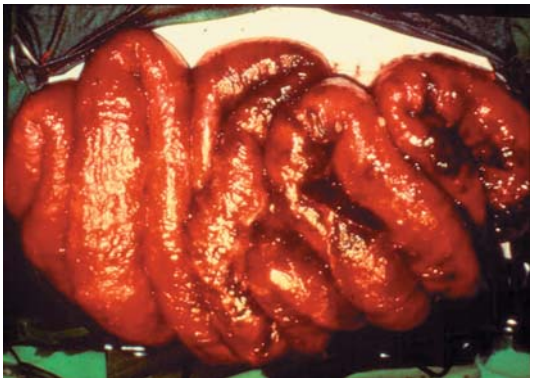

Figure 54.2 Generalized peritonitis occurring after free perforation of a sigmoid diverticulum. Open midline incision reveals erythematous distended small intestine.

present. Such a lesion could produce a blind-loop syndrome and leakage of the distal pouch, or could require another operation for its removal.

After resection, we copiously irrigate the abdominal cavity with normal saline. We strongly believe that if gross peritonitis is present, the skin wound should not be closed tightly if at all. Patients who have undergone such surgery usually require careful monitoring in an intensive care unit and appropriate antibiotic coverage.

Many of these patients develop secondary intra-abdominal or pelvic abscesses, which are detectable with CT or ultrasound. If percutaneous drainage is not successful a repeat laparotomy will likely be necessary. Many of these patients will also have prolonged ileus and therefore require parenteral hyperalimentation to meet the extraordinary metabolic demands of controlling intra-abdominal sepsis. Of course, enteral nutrition should be resumed as soon as possible. See also Chapter 55, Abdominal abscess.

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55. Abdominal abscess

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Intra-abdominal infections generally occur after entry of enteric organisms into the peritoneal cavity. An abscess is the body's way of attempting to contain an infection. Intraperitoneal and retroperitoneal abscesses can develop as a result of appendicitis, diverticulitis, necrotizing enterocolitis, pancreatitis, pelvic inflammatory disease, tubo-ovarian infection, surgery, or trauma. Given the vast number of microbes in our alimentary tract, any penetration of the wall of the gastrointestinal (GI) tract as a result of a vascular, traumatic, or iatrogenic event introduces these microbes into the abdomen. The concentration of microorganisms increases with distal progression down the GI tract. The morbidity of an intra-abdominal infection is 40%. The mortality is 20% in immunocompetent patients, and can be as high as 70% in the immunocompromised. This chapter explains types of peritonitis, locations of abscesses, diagnosis, treatment, common organisms associated with community-acquired and healthcare-associated infections, and suggested use of antimicrobials.

Abdominal abscess often follows or complicates peritonitis (see Chapter 57, Peritonitis). Primary peritonitis is an infection of the peritoneal cavity without an underlying violation of the intestinal wall; the most common cause of primary peritonitis is spontaneous bacterial peritonitis (SBP). The etiology of SBP is thought to be translocation of bacteria through the intestinal wall and into the abdomen. Clinical features of SBP may be subtle or absent, but usually SBP causes abdominal pain from infected ascites. The mainstay of treatment of primary peritonitis is antibiotics. Secondary peritonitis results from perforation of hollow viscera with spillage of intestinal contents, often from appendicitis, diverticulitis, or ulceration. The patient may initially present with severe abdominal pain, tenderness, rigid abdomen, or shock. The peritonitis can be focal or diffuse. If the spillage is small, the patient may not initially seek medical attention. Over the course of a few days the body will attempt to contain it, and an abscess may develop. If the abscess is less than 3 cm, the patient may only need antibiotics. An abscess 3 cm or greater usually needs drainage, and the percutaneous approach is preferred. Some abdominal abscesses progress to severe sepsis and shock, particularly when left untreated. Immunocompromised patients may have perforation with gross contamination of their abdomen, yet be relatively asymptomatic, making diagnosis more challenging. Tertiary peritonitis is a persistent or recurrent infection following treatment of primary or secondary peritonitis and is often found in patients with pre-existing comorbidities or who are immunocompromised.

Abdominal infection is designated uncomplicated or complicated. Uncomplicated infection usually involves one organ, as in acute (nonperforated) appendicitis, cholecystitis, or diverticulitis. Surgical resection is needed for many of these early, uncomplicated infections. Patients usually improve quickly and only need 24 hours or less of antibiotic coverage. Complicated infection extends beyond one organ into the peritoneal space. These infections can be florid fecal peritonitis from a perforated appendix or diverticulum and fecal contamination will often lead to an abscess.

Abscesses can form within the peritoneal lining, usually days after an intraperitoneal infection. Intraperitoneal abscesses commonly follow a perforated appendix or diverticulum, but also occur after tubo-ovarian infection, recent surgery (particularly of the colon), pyogenic liver abscess after biliary tract disease, or splenic abscess from trauma. Patients can also develop retroperitoneal abscesses, such as a pancreatic abscess. This can occur after pancreatitis which progresses through pancreatic necrosis and on to a definable collection. Retroperitoneal abscesses are usually found in one of four spaces: anterior retroperitoneum (lower esophagus, duodenum, pancreas, bile

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duct, splenic vein, appendix, ascending and descending colon, and rectosigmoid), posterior retroperitoneum (perinephric, around the ureters, gonadal vessels, aorta, and inferior vena cava), retrofascial (ileopsoas muscle and paraspinous muscles), and retroperitoneal pelvis (prevesical space, retrovesical presacral, and perirectal).

Routine history, physical exam, and laboratory studies are the initial workup of suspected intra-abdominal infection. Some patients may have an unreliable exam, such as those with obtunded mental status, recent analgesia, or immunosuppression. A plain film is useful in establishing "free air" (as a result of perforation of a hollow viscus), pneumatosis (as a result of ischemic bowel), dilated loops (as a result of *Clostridium difficile*), or obstruction as possible signs of abdominal infection. Ultrasound is useful in diagnosing abscess, but it is limited by the skill of the technician and the patient's body habitus. For patients who do not need an emergent operation, computed tomography (CT) is the best imaging modality to detect an abscess.

The cornerstones of treatment of an abscess are source control and antimicrobials. Initially, fluids are given, electrolyte derangements and coagulopathies corrected, and antibiotics started. Source control requires taking measures to eliminate a source of infection, control ongoing contamination, and restore premorbid anatomy and function. In recent years, there has been a shift from open abdominal drainage to percutaneous drainage. Interventional radiologists now approach many abscesses that previously would have been considered best approached by laparotomy. The results of percutaneous drainage are equal clinically and more cost-effective. Percutaneous drainage may result in significantly fewer physiologic alterations in patients and may eliminate or reduce the need for an open operation. An open operation may still be needed for poorly localized, loculated, complex, or diffuse fluid collections, necrotic tissue, or percutaneously inaccessible locations, such as the posterior subphrenic space or among loops of small bowel.

The CT scan findings should be discussed with a surgeon to avoid inappropriate abscess drainage in the presence of free hollow-organ perforation and peritonitis. There are some patients in whom drainage catheter placement is not appropriate, and laparotomy is the procedure of choice. Patients with diffuse peritonitis or a high clinical suspicion of a perforation should undergo surgery as soon as possible, continuing ongoing resuscitation in the operating room. Debridement is indicated in the case of intra-abdominal necrosis, such as infected necrotic pancreas. Open drainage of abdominal abscesses has been associated with enteric fistula formation, adult respiratory distress syndrome, renal failure, and liver failure. Some surgeons leave the abdomen open if source control is uncertain. In some cases, closing the abdomen is not prudent, particularly when the bowel is left in discontinuity or is too dilated to allow closure of the surgical wound, as forcing the abdomen closed can cause abdominal compartment syndrome. Instead, the abdomen can be packed open with a vacuum-assisted device. A second-look operation may be scheduled at the surgeon's discretion.

Table 55.1 Pathogens in abdominal abscess

Community-acquired intra-abdominal infection		Healthcare-associated intra-abdominal infection
Aerobes	**Anaerobes**	
Escherichia coli	*Bacteroides*	*Staphylococcus epidermidis/aureus*
Klebsiella pneumoniae	*Clostridium*	*Pseudomonas aeruginosa*
Proteus mirabilis	*Peptostreptococcus*	*Enterococcus*
Streptococcus	*Fusobacterium*	*Enterobacter*
Enterococcus	*Prevotella*	

Antimicrobial treatment is an adjunct to source control. The correct antimicrobial agent started early has been shown to significantly improve outcomes. While cultures from the abscess are necessary, blood cultures are not always needed in the initial workup of patients with suspected intra-abdominal infection. However, in patients who appear toxic or immunocompromised, knowledge of appropriate coverage for potential bacteremia may be helpful in determining antimicrobial therapy. Infections are divided into community-acquired or healthcare-associated (**Table 55.1**). This distinction is important in determining which bacteria are the likely source and which antimicrobial to choose for initial coverage. All intra-abdominal infections show prevalence of gram positives (*Streptococcus* species, *Enterococcus faecalis*), gram negatives (*Escherichia coli*, *Klebsiella* species, and *Pseudomonas aeruginosa*) and anaerobes (*Bacteroides* and *Clostridium*). Healthcare-associated infections are more likely to have more resistant flora, and those patients that do not respond to the initial empiric antimicrobials may have resistant *P. aeruginosa*, vancomycin-resistant

Table 55.2 Empiric regimens for treatment of abdominal abscess

Community-acquired intra-abdominal infection			Healthcare-associated intra-abdominal infection	
Antibiotic(s)	**Mild to moderate infection**	**Severe infection**	**Antibiotic(s)**	**By definition, likely resistant bacteria**
Single agent	Ertapenem Moxifloxacin Tigecycline Ticarcillin-clavulanic Cefoxitin	Imipenem-cilastin Meropenem Doripenem Piperacillin–tazobactam	*Single agent*	Imipenem-cilastin Meropenem Doripenem Piperacillin–tazobactam
Double agent	Cefazolin + metronidazole Cefuroxime + metronidazole Ceftriaxone + metronidazole Cefotaxime + metronidazole Ciprofloxacin + metronidazole Levofloxacin+ metronidazole	Cefepime + metronidazole Ceftazidime + metronidazole	*MRSA*	Add vancomycin Can add linezolid Can add daptomycin Can add quinupristin–dalfopristin Can add tigecycline
			VRE	Add linezolid Can add quinupristin–dalfopristin Can add daptomycin Can add ampicillin

Abbreviations: MRSA = Methicillin-resistant *Staphylococcus aureus*; VRE = vancomycin-resistant enterococcus.

enterococcus (VRE), or *Candida globrata* as their pathogen. The patients most likely to develop severe abdominal infections are those with a high Acute Physiology and Chronic Health Evaluation (APACHE) score, poor nutritional status, inability to achieve adequate source control, or immunosuppression.

The general consensus on antimicrobials is to "hit hard and early," meaning start broad-spectrum antibiotics immediately, and quickly narrow the antibiotics after cultures have returned. The choice of antibiotics depends on whether the infection is community-acquired or healthcare-associated. In some instances, an antifungal is needed. There are several antimicrobial choices available to treat intra-abdominal infections. Many can be treated with a single agent (Table 55.2). Methicillin-resistant *Staphylococcus aureus* (MRSA) is found in some intra-abdominal infections and should be treated with vancomycin. Linezolid, daptomycin, quinupristin–dalfopristin, and tigecycline also provide adequate coverage for MRSA. Empiric treatment of VRE is not recommended unless the patient is at very high risk for an infection due to this organism (such as a liver transplant patient with infection from the biliary tree) or is known to be colonized with VRE; this organism is usually sensitive to linezolid, quinupristin–dalfopristin, daptomycin, and ampicillin. Antifungal therapy is recommended if *Candida* is grown from intra-abdominal cultures. Fluconazole is appropriate for treatment of *Candida albicans*, but an echinocandin (caspofungin, micafungin) should be used for fluconazole-resistant *Candida*

Table 55.3 Treatment of *Candida*

Fungus	Antifungal
Candida albicans	Fluconazole
Resistant *Candida*, i.e, *globrata*	Caspofungin Micafungin

species such as *Candida globrata* or *Candida tropicalis* (Table 55.3). If the index of suspicion is high for fungal infection, such as in an immunocompromised patient or in the setting of a healthcare-associated infection, antifungal coverage should be started early, since fungal cultures often require prolonged incubation times. Antimicrobial therapy should be limited to 4 to 7 days, unless source control cannot be obtained. This is a change from previous recommendations which advised broad-spectrum antimicrobials for an empiric 14-day course. Once the patient has no fever for 24 to 48 hours, has a normal white blood cell count, and has clinically improved, the antimicrobial may be discontinued. In most cases, the antimicrobials can be stopped in 7 days or less. Probiotics can be started on patients receiving antimicrobial treatment for intra-abdominal infection.

Patients with inadequate source control, old age, higher level of organ dysfunction, or significant comorbidities are at a higher risk of treatment failure and death. Intra-abdominal infections are frequent and have significant morbidity and mortality. Patients benefit from early diagnosis with early start of antimicrobials

and source control. In most cases, a CT scan will identify the necessary cause of an intra-abdominal infection. There are several choices of antimicrobials, but treatment should start broad and then be tailored to the culture results. When patients improve, stop the antimicrobials to decrease the chance of creating multiresistant organisms. Most patients will do well with close coordination of care among specialists in surgery, radiology, critical care, and infectious disease.

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56. Splenic abscess

Ross M. Clark and Thomas R. Howdieshell

The diagnosis of splenic abscess is often overlooked because of its rarity and misleading clinical features, as well as the presence of predisposing conditions that obscure its clinical presentation. Hence, it is not surprising that splenic abscess is often diagnosed during postmortem examinations (0.2% to 0.7% incidence in various autopsy series), even in the era of antibiotics. Contributing factors to an apparent increase in the incidence of splenic abscess include advances in radiologic imaging, comfort with nonoperative management of blunt splenic trauma, and a greater number of patients who have cancer or are otherwise immunocompromised.

INCIDENCE AND PREDISPOSING FACTORS

Splenic abscesses occur more commonly in males (55% to 60% in several series), with the average age ranging from 25 to 54 years. Nelken and colleagues describe a bimodal distribution: patients younger than 40 years of age, generally immunosuppressed or drug addicts, who usually present with a multilocular abscess; and patients older than 70 years of age who are suffering from diabetes and/or a nonendocarditic septic focus and develop a unilocular abscess.

The primary predisposing causes of splenic abscess include metastatic hematogenous infection, contiguous disease processes extending to the spleen, splenic trauma, hematologic disorders (collagen vascular diseases, hemoglobinopathies, malignancy), and immunodeficiency states (acquired, congenital). The incidence of these predisposing causes or risk factors is shown in Table 56.1.

Table 56.1 Primary predisposing causes or risk factors for splenic abscess

Factors	Percentage
Infectious etiology	**68.8**
Endocarditis	15.3
Septic syndrome	11.9
Miscellaneous	11.9
Urinary infection	7.1
Otitis	3.3
Appendicitis	2.8
Pneumonia	2.8
Brucellosis	2.3
Lung abscess	2.3
Malaria	1.9
Diverticulitis	1.9
Amebiasis	0.95
Noninfectious etiology	**31.2**
Contiguous diseases	23.0
Trauma	16.7
Hemoglobinopathies	11.9

Metastatic hematogenous infections

Infective endocarditis is the most common condition predisposing a patient to splenic abscess (Table 56.1, Figure 56.1). Although the exact incidence is difficult to determine, several studies demonstrated the occurrence of splenic embolization in 31% to 44% of the patients with endocarditis. Histologic examination disclosed splenitis in at least 20% of patients. Splenic infarction occurred in 30% to 67% of patients with endocarditis during the pre-antibiotic era, and in 33% to 44% of these patients during the antibiotic era. In 1977, Pelletier and Petersdorf reported the incidence of splenic abscess in patients with subacute bacterial endocarditis to be approximately 2.4%. Mycotic aneurysms are seen angiographically within abscesses, but whether these predispose a patient to, or result from, splenic abscess remains uncertain.

In addition to endocarditis, a multitude of other infections have been reported as primary causes of splenic abscess (see Table 56.1). Miscellaneous infections include dental abscess, bacteremia after

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dental extraction, tonsillectomy, peritonsillar abscess, acute parotitis, bronchiectasis, perinephric abscess, decubitus ulcer, complicated infectious mononucleosis, tuberculosis, yellow fever, typhoid fever, diphtheria, cat scratch disease, and anthrax.

Conditions resulting in splenic ischemia and infarct have been implicated in the development of splenic abscess, probably from hematogenous spread of pathogens. Splenic abscess has been reported after splenic artery ligation in the course of liver transplantation surgery, division of the short gastric vessels during laparoscopic Nissen fundoplication, and accidental injection of the splenic artery during endoscopic procedures for gastric bleeding.

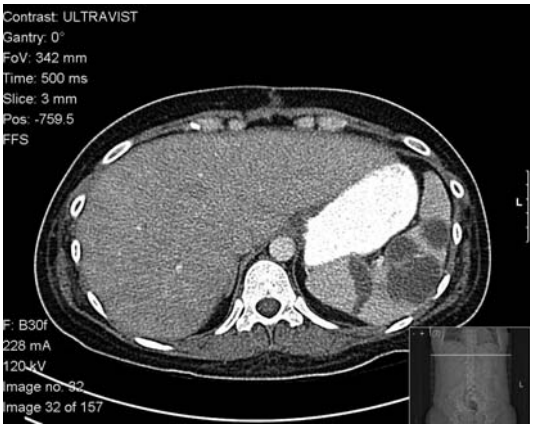


Figure 56.1 Multilocular splenic abscess in an intravenous drug abuse patient with bacterial endocarditis.

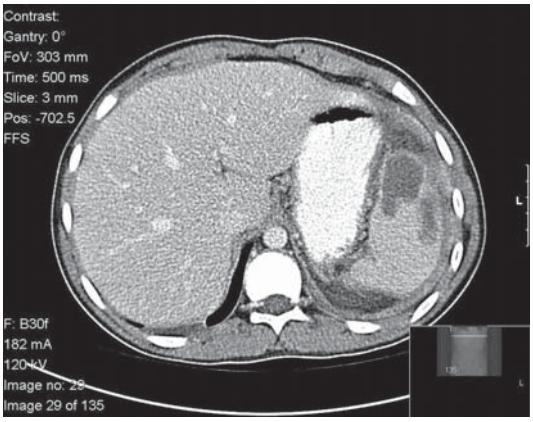
Contiguous infection

On occasion, splenic abscess can result from the direct extension of disease having its primary focus in adjacent organs. Contiguous extension from diverticulitis, pancreatic pseudocyst or carcinoma, gastric ulcer, carcinoma of the stomach, perihepatic abscess, perinephric and subphrenic abscess, and carcinoma of the descending colon have been reported. Splenic abscess has rarely been reported as an extraintestinal manifestation of inflammatory bowel disease.

Traumatic abscess

Traumatic abscess results from secondary infection and suppuration of contused parenchyma or of a hematoma arising from injury to splenic tissue. In a report by Phillips, the initial traumatic injury was not easily recognized or reported, and most patients developed signs and symptoms of splenic infection after a latent period of 2 weeks to 4 months after sustaining injuries to the left upper quadrant. Splenic abscess has been reported after operative repair of splenic injury (splenorrhaphy), and nonoperative management of blunt splenic injuries diagnosed by computed tomography (CT) scan (Figure 56.2). On occasion, radiologic procedures such as splenic artery embolization for hemorrhage control following traumatic injury, splenoportography for portocaval shunt evaluation, and percutaneous transluminal coronary angioplasty have been implicated as causes of splenic abscess, sometimes up to 4 months afterward.

A



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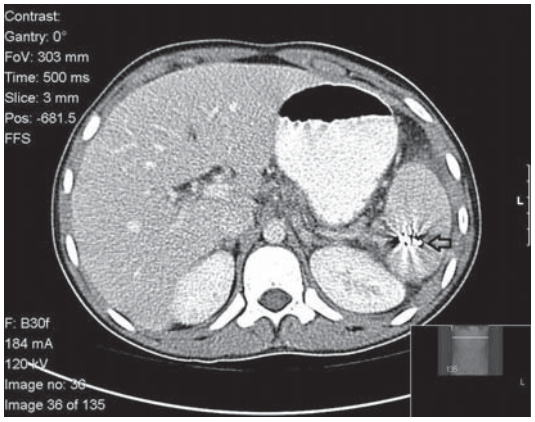

Figure 56.2 (A, B) Splenic abscess following nonoperative management of blunt splenic injury including splenic artery embolization. Note embolization coil (B, see arrow).

Hematologic disorders

Hemoglobinopathies accounted for approximately 12% of splenic abscesses reported by Alsono-Cohen. Patients with sickle cell disease have an increased risk of acquiring invasive bacterial infections as a result of hyposplenism, including functional defects in opsonization, phagocytic function, and cell-mediated immunity. If a patient with sickle cell disease and prior splenic infarcts develops a transient bacteremia from a central line infection or cholecystitis, bacteria may seed the infarcted regions with resultant abscess formation.

The spleen may also be a site of infection in patients with collagen vascular diseases. Splenic abscesses have been reported in patients with rheumatoid arthritis, systemic lupus erythematosus, myelodysplastic syndrome, and polyarteritis nodosa. Pathologic features of the spleen in these illnesses include capsulitis and small infarcts.

Immunodeficiency states

Splenic abscess has been reported complicating acquired immunodeficiency syndrome (AIDS), chemotherapy, cancer (leukemia, lymphoma), bone marrow and solid organ transplantation, long-term steroid use, monoclonal antibody immunosuppressive medications, and conditions such as diabetes mellitus and alcoholism.

DIAGNOSIS

History and physical examination

The signs and symptoms of a splenic abscess are often insidious, nonspecific, and related to the underlying disease. Table 56.2 characterizes the clinical findings in 227 patients. Fever is the most common symptom along with pain in the left hypochondrium or vague abdominal pain. Pain is probably caused by splenitis with capsular involvement. Abscesses located in the upper pole of the spleen tend to irritate the diaphragm, causing radiation of pain toward the left shoulder (Kehr's sign) and an elevated, immobile left hemidiaphragm. Splenic rupture also commonly manifests as left shoulder pain. An abscess located in the lower pole of the spleen more often irritates the peritoneal surface, resulting in peritonitis. A deep-seated abscess that does not involve the splenic capsule may be accompanied only by nonspecific symptoms of infection without pain or other localizing signs.

Table 56.2 Clinical findings in splenic abscess

Clinical feature	Percentage
Fever	92.5
Abdominal tenderness	60.1
Abdominal pain	57.5
Splenomegaly	56.0
Left upper quadrant pain	39.2
Pleuritic pain	15.8
Toxic syndrome	15.4
Vomiting	14.0

Laboratory findings

Leukocytosis is present in 70% to 80% of patients, but is a variable finding. In several series, the white cell count varied between 2400 and 41 000 cells/mm^3. In general, other serum laboratory studies were not helpful. Blood cultures were positive in 50% to 70% of patients. Of these positive blood cultures, 60% to 75% grew the same organisms as those subsequently isolated from the splenic abscess.

The infecting organisms and their incidence from a review of 189 patients of Nelken and others are reported in Table 56.3. *Candida* abscesses of the spleen are seen almost exclusively in neutropenic patients with the exception of disseminated candidiasis as a complication of abdominal surgery. Fungal abscesses due to *Candida* are also more likely to complicate the use of broad-spectrum antibiotics, indwelling central venous lines, total parenteral nutrition, systemic steroids, cytotoxic chemotherapy, malignancy, or immunosuppression after organ transplantation. Organisms responsible for AIDS-related splenic abscesses include *Salmonella, Mycobacterium avium-intracellulare, Mycobacterium tuberculosis*, *Candida, Aspergillus*, and *Pneumocystis jirovecii* (*carinii*). A novel *Klebsiella pneumoniae* strain with hypermucoviscous properties has been reported as the cause of hepatic and splenic abscesses in otherwise healthy hosts. In several series, approximately one-fourth of patients with a splenic abscess did not have an organism cultured from the abscess cavity, possibly related to the use of intravenous antibiotic therapy prior to abscess drainage.

Radiographic findings

The most common findings on chest radiography are an elevated left hemidiaphragm (31%), pleural effusion (28%), and left basilar pulmonary

Table 56.3 Infecting organisms and their incidence in splenic abscess

Organism	Percentage
Aerobic bacteria ($n = 90$)	**56**
All staphylococci	20
All *Salmonella*	15
Escherichia coli	15
Enterococcus	8
Salmonella typhi	7
Unspecified *Streptococcus*	6
Unspecified coliforms	6
Staphylococcus epidermidis	4
α-*Streptococcus*	4
Klebsiella	3
Enterobacter	2
Proteus	2
Pseudomonas aeruginosa	2
Shigella	2
Diphtheroids	2
Beta-hemolytic *Streptococcus*	1
Nonhemolytic *Streptococcus*	1
Fungi ($n = 41$)	**26**
Candida albicans	42
Candida tropicalis	21
Aspergillus	10
Blastomycosis	5
Aureobassidium pullulans	2
Anaerobic bacteria ($n = 28$)	**18**
Mixed	30
Bacteroides	23
Propionobacterium species	20
Clostridium	13
Streptococcus	10
Fusobacterium	4
Actinomyces	0

consolidation (18%). Plain abdominal films reveal an abnormal soft-tissue density or gas pattern in only 35% of patients. CT scanning, with a sensitivity of 96%, and an associated specificity between 90% and 95%, is currently the best diagnostic test for splenic abscess. CT scan may show a homogeneous low-density area, with or without rim enhancement; lucent areas within the spleen containing fluid levels of different densities; and intrasplenic gas formation. CT scan may also be useful for guiding percutaneous abscess drainage.

Ultrasonography has a sensitivity of 60% to 75% in the detection of splenic abscess. The ultrasound appearance of splenic abscess is characterized as a hypoechoic or nearly anechoic, ovoid- or round-shaped area in the spleen, with varying internal echogenicity, irregular wall, and mild to moderate distal acoustic enhancement. Ultrasonic examinations are not specific, and the findings are highly variable and may be difficult to interpret. However, ultrasonography is low cost, noninvasive, and readily repeatable to evaluate for interval change or resolution.

Differential diagnosis

The differential diagnosis should include intraparenchymal hematoma, splenic infarction, parasitic and nonparasitic splenic cysts, subphrenic abscess, pulmonary empyema, perinephric abscess, neoplasm, and leukemic infiltration. In a review of 3372 subphrenic abscesses, Ochsner and Graves found a primary lesion in the spleen in approximately 4% of the cases. Therefore, the possibility of coexistent splenic abscess should be considered in the presence of a subphrenic abscess. Pulmonary empyema as a complication of splenic abscess (4%) may also divert the clinician's attention from the primary lesion.

TREATMENT

There is no place for long-term medical management of a clinically overt splenic abscess. The mainstay of treatment consists of splenectomy and appropriate antibiotics, with a success rate of 86% to 94%. Mounting evidence has shown that percutaneous drainage plus effective antibiotics is a safe and efficacious therapy. Percutaneous drainage may be used if the patient has a unilocular abscess, is in unstable condition from a recent operation, has had multiple previous operations, or has significant risks for general anesthesia or standard surgical drainage. The catheter can be removed when the drainage is minimal and the cavity has decreased in size as evidenced by sinogram, ultrasound, or CT scan. If the patient does not improve clinically, splenectomy is recommended. Percutaneous drainage, with a reported success rate of 68% to 75%, is most likely to succeed when the abscess collection is unilocular, has a discrete wall, and has no internal septation. Abscesses containing thick, tenacious, necrotic debris are less likely to be successfully drained percutaneously, as are phlegmons, poorly defined cavities, microabscesses, multiple

abscesses, and abscesses originating from a contiguous process. Complications associated with percutaneous drainage include hemorrhage, pleural empyema, pneumothorax (transpleural catheterization), and fistula.

Broad-spectrum antibiotics should be initiated when a splenic abscess is diagnosed. This therapy should include agents effective against staphylococci, streptococci, and gram-negative bacteria. A semisynthetic penicillin or advanced-generation cephalosporin plus an aminoglycoside are recommended. If a contiguous abdominal process is suspected, anaerobic agents such as clindamycin or metronidazole should be added. In immunosuppressed patients, antifungal coverage such as fluconazole should be initiated early in the disease process. Some authors recommend continuing antibiotics for 2 to 3 weeks after splenectomy or discontinuation of percutaneous drainage.

The optimal management of fungal splenic abscess remains to be defined. Some authors have suggested prolonged courses of amphotericin B with a total dose ranging from 500 mg to 2 g. Others have suggested splenectomy in conjunction with amphotericin B for the treatment for fungal splenic abscess. The argument in support of splenectomy for fungal abscess is based primarily on reports of bacterial splenic abscess in which nonoperative therapy was associated with high mortality. However, because most cases of splenic candidiasis represent disseminated infection, splenectomy does not address the problem of *Candida* present in other tissues, most notably the liver. There are many reports of confirmed splenic fungal abscesses resolving with antifungal drugs alone. Several case reports and a recent multicenter randomized trial in patients without neutropenia or major immune deficiency indicate that fluconazole may be as efficacious as amphotericin B. Patients suspected of having a fungal abscess should have a specific diagnosis made by percutaneous aspiration of the liver or spleen or laparoscopic or open biopsy of the lesions.

Splenic abscess may rupture into the peritoneal cavity, thus causing acute peritonitis. A mortality rate of 50% has been reported in cases of splenic abscess rupture. A splenic abscess may also drain into the stomach, colon, or pleura. However, splenic abscesses most commonly produce repeated bacteremia, which ends in septic shock if not treated. Two-thirds of all splenic abscesses in adults are solitary, and one-third are multiple. In children, however, the opposite is true. Solitary abscesses generally are easier to diagnose and treat, and usually are caused by streptococci, staphylococci, or *Salmonella*. Multiple abscesses tend to be caused by gram-negative bacilli or *Candida*. The prognosis is clearly related to patient age, associated diseases, and development of multisystem organ failure.

With early diagnosis and treatment of splenic abscess, the mortality rate can be as low as 7%. Medical therapy appears appropriate for patients with mycobacterial, *P. jirovecii*, and fungal disease. Percutaneous drainage appears reasonable for patients with a singular, unilocular abscess without associated intra-abdominal disease. In patients in whom there is any question as to the accessibility, locularity, or singularity of the abscess, or if there is a question of intra-abdominal pathology, splenectomy remains the treatment of choice.

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57. Peritonitis

Linda A. Slavoski and Matthew E. Levison

Peritonitis is inflammation within the peritoneal cavity. This chapter considers infectious causes of peritonitis. Two major types include: (1) primary (spontaneous or idiopathic) and (2) secondary. When signs of peritonitis and sepsis persist or recur after treatment for secondary peritonitis, the clinical entity has been termed tertiary peritonitis. In comparison with patients with other forms of peritonitis, tertiary peritonitis has significantly longer intensive care unit (ICU) and hospital stays, higher organ dysfunction scores, and higher mortality rates (50% to 70%).

Intraperitoneal abscesses can result from (1) localization of the initially diffuse peritoneal inflammatory response to one or more dependent sites (i.e., the pelvis, the right or left subphrenic spaces, which are separated by the falciform ligament, and Morrison's pouch, which is the most posterior superior portion of the subhepatic space and is the lowest part of the paravertebral groove when the patient is recumbent) or (2) at the site of the intra-abdominal source of the infection (e.g., periappendiceal, pericholecystic, or peridiverticular abscess). For management of peritoneal catheter-related peritonitis, see Chapter 96, Dialysis-related infection.

PRIMARY PERITONITIS

Primary peritonitis, also called spontaneous bacterial peritonitis (SBP), is defined as infection within the peritoneal cavity without an evident intra-abdominal source. Primary peritonitis occurs at all ages: in children, in association with postnecrotic cirrhosis and with nephrotic syndrome, and in adults, with ascites from any cause, but most commonly alcoholic cirrhosis. Rarely, primary peritonitis occurs with no apparent underlying disease.

Primary peritonitis has been reported in 10% of all hospitalized patients with alcoholic cirrhosis and ascites. The risk of developing primary peritonitis is greater in patients with more advanced cirrhosis but also increases with coexisting gastrointestinal hemorrhage, previous primary peritonitis, use of proton pump inhibitors, or low protein levels in ascitic fluid (<1 g/dL), presumably because of decreased ascitic fluid opsonic activity.

Primary peritonitis is monomicrobial and only rarely involves anaerobes; if cultures reveal a polymicrobial or anaerobic infection, secondary peritonitis should be suspected. *Escherichia coli* is the most frequently isolated pathogen, followed by *Klebsiella* species and *Streptococcus pneumoniae*.

Cases with positive ascitic fluid culture but low leukocyte counts (<250 neutrophils/mm^3) and no clinical findings of peritonitis are designated as *monomicrobial nonneutrocytic bacterascites* (MMNNB). This may represent early colonization of the peritoneal cavity because some patients progress to SBP; in others it resolves spontaneously. Conversely, some patients have clinical evidence of peritonitis, elevated leukocyte counts (greater than or equal to 250 neutrophils/mm^3) in the ascitic fluid, but negative cultures, called *culture-negative neutrocytic ascites* (CNNA); blood cultures are positive in one-third of cases.

Polymicrobial nonneutrocytic bacterascites (PMNNB) is diagnosed when Gram stain or culture of peritoneal fluid demonstrates multiple organisms and there is less than 250 neutrophilic leukocytes/mm^3. This variant usually complicates puncture of the intestines during paracentesis, which occurs in less than 1% of paracenteses. Risk factors for this complication include ileus, intestinal adhesions, and inexperience of the operator. If the peritoneal fluid protein concentration is greater than 1 g/dL and the osponic activity of the fluid is adequate, PMNNB is reported to resolve spontaneously.

The route of infection in primary peritonitis may be hematogenous, lymphogenous, via transmural migration through the intact bowel wall, or, in women, from the vagina via the fallopian tubes. In addition, clearance of bacteria from

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blood is delayed in patients with cirrhosis due to decreased phagocytic activity within the reticuloendothelial system, impaired intracellular killing by neutrophils and monocytes, impaired opsonization, and low serum and ascitic complement levels.

The clinical features of primary peritonitis are variable. In children it is often confused with acute appendicitis. The most common sign is fever (often low grade), reported to occur in up to 80% of patients. Fever may be present without abdominal signs or symptoms, or the intraperitoneal infection may be clinically silent. Ascites predating the infection is almost always present. Other signs and symptoms include abdominal pain, nausea, vomiting, diarrhea, diffuse abdominal tenderness, rebound tenderness, and hypoactive to absent bowel sounds. Atypical signs such as hypothermia, hypotension, and unexplained decline in renal function may be present, as well as unexplained encephalopathy, hepatorenal syndrome, and variceal bleeding in cirrhotic patients. Because peritonitis may be clinically inapparent in a patient with ascites and decompensated liver disease, routine paracentesis is necessary in every hospitalized cirrhotic patient with ascites, especially if febrile, to disclose its presence.

The diagnosis of primary peritonitis requires exclusion of intra-abdominal sources of infection, usually by contrast-enhanced computed tomography (CT). Examination of the ascitic fluid is required. The ascitic fluid leukocyte count is generally greater than 250 polymorphonuclear leukocytes/mm^3. Gram stain of the fluid is commonly negative because of the low bacterial density. The diagnostic yield of ascitic fluid culture is enhanced by culturing a large volume (e.g., 10 to 20 mL). Blood cultures should also be obtained because concurrent bacteremia is present in up to 75% of these patients.

Primary peritonitis is managed medically unless secondary peritonitis is suspected, in which case either exploratory laparotomy or laparoscopy is done. Because the Gram stain is often negative in primary peritonitis, the initial choice of antimicrobial agents is empiric and is modified once results of cultures and susceptibility testing are available. Initial therapy should be directed against enteric gram-negative bacilli and gram-positive cocci. Acceptable regimens include the third-generation cephalosporins ceftriaxone and cefotaxime, the fourth-generation cephalosporin cefepime, or one of the newer generation of fluoroquinolones (e.g., levofloxacin or moxifloxacin) that have improved activity against *S. pneumoniae*, including those strains that are relatively penicillin resistant, or β-lactam antibiotic-β-lactamase inhibitor combinations (e.g., ticarcillin–clavulanate or piperacillin–tazobactam).

Fluoroquinolones should not be used for treatment of primary peritonitis if used previously to prevent primary peritonitis, because of the likelihood of a fluoroquinolone-resistant pathogen. If peritonitis develops during hospitalization or in a community where antibiotic-resistant *E. coli* or *Klebsiella pneumoniae* (e.g., extended-spectrum β-lactamase [ESBL]-producing strains) are prevalent, broader-spectrum antimicrobial therapy should be used, such as a carbapenem (e.g., ertapenem, imipenem, meropenem, or doripenem).

Streptococcus pneumoniae and group A streptococci are best treated with high-dose penicillin G, ceftriaxone, or cefotaxime. Methicillin-sensitive *Staphylococcus aureus* is best treated with a penicillinase-resistant penicillin (nafcillin) or with a first-generation cephalosporin (cefazolin). If the strain is methicillin resistant or the patient is allergic to penicillin, vancomycin is used. If *Pseudomonas aeruginosa* is isolated, an aminoglycoside can be given in combination with an antipseudomonal penicillin or cephalosporin, aztreonam, or imipenem or meropenem, or, to avoid the nephrotoxicity and ototoxicity of aminoglycosides, ciprofloxacin combined with another antipseudomonal agent should be used if results of susceptibility testing permit. Intraperitoneal antimicrobial administration is not beneficial.

A clinical response should be evident by 48 to 72 hours with appropriate antimicrobial therapy. Failure to respond should prompt an examination for an alternative or additional diagnosis. Antimicrobial therapy should be continued for 10 to 14 days if improvement is noted; however, shorter-course (5 day) therapy is efficacious if rapid clinical improvement occurs. Treatment of primary peritonitis is ultimately successful in up to 85% of cirrhotic patients, but because of the underlying liver condition, the overall mortality has been reported as high as 95% in some series. Those patients with the poorest prognosis were found to have renal insufficiency, hypothermia, hyperbilirubinemia, and hypoalbuminemia.

Patients with peritoneal fluid neutrophil counts less than 250 cells/mm^3 (MMNNB) and signs or symptoms of infection (temperature greater than 100°F or abdominal pain or tenderness) should receive empiric antibiotic therapy for primary peritonitis, while awaiting results of cultures, because symptomatic patients with MMNNB variant are prone to primary peritonitis even

though at time of the paracentesis it is not known whether the cultures will yield bacteria. Because only 15% of asymptomatic patients with MMNNB progress to primary peritonitis, asymptomatic patients with the MMNB variant usually do not need antibiotics and observation is appropriate. In these asymptomatic patients the paracentesis should be repeated as soon as the first culture yields bacteria. Antibiotics are initiated only if signs or symptoms of infection develop or if the second paracentesis demonstrates neutrocytic ascites.

If the peritoneal neutrophil count was at least 250/mm^3, but the peritoneal Gram stain and culture were negative (i.e., CNNA variant of primary peritonitis), antimicrobial therapy should be continued, because CNNA has clinical, prognostic, and therapeutic characteristics similar to that of primary peritonitis, although other possible causes of neutrocytic ascites such as peritoneal carcinomatosis, pancreatitis, and tuberculous peritonitis must be ruled out.

Cirrhotic patients who have had an upper gastrointestinal bleed, ascitic fluid protein <1.5 g/dL, or recurrent primary peritonitis are at high risk of primary peritonitis and may benefit from antibiotic prophylaxis with norfloxacin (400 mg daily), ciprofloxacin (750 mg once a week), or trimethoprim–sulfamethoxazole (one double-strength tablet once daily for 5 days each week). Prophylaxis may be an option in patients awaiting liver transplantation but may not otherwise prolong survival in patients with end-stage liver disease. Indeed long-term antibiotic use may increase risk of secondary infection with resistant pathogens.

Occasionally, peritonitis may be caused by *Mycobacterium tuberculosis*, usually from hematogenous dissemination from remote foci of tuberculous infection or extension of infection in mesenteric lymph nodes, intestine, or fallopian tubes or ovaries. The diagnosis of tuberculous peritonitis can usually be confirmed by histologic examination and culture of a peritoneal biopsy specimen and fluid. Diagnosis of *Coccidioides immitis* peritonitis can be made by wet mount of ascitic fluid, histology, and culture of the peritoneal biopsy specimen and fluid.

SECONDARY PERITONITIS

Secondary peritonitis is associated with a predisposing intra-abdominal lesion. Numerous intra-abdominal processes may give rise to secondary peritonitis; a partial list includes perforation of a peptic ulcer; traumatic perforation of the uterus, urinary bladder, stomach, or small or large bowel; appendicitis; pancreatitis; diverticulitis; bowel infarction; cholecystitis; biliary sepsis; and female genital tract infection such as septic abortion, postoperative uterine infection, endometritis, or salpingitis.

Secondary peritonitis is usually an endogenously acquired polymicrobial infection. On average, about five bacterial species are isolated, including both obligate and facultative anaerobes. The species of organisms vary with the primary source of the infection. Community-acquired peritonitis secondary to a breach in the integrity of the stomach and duodenum in the absence of obstruction usually involves mouth flora, i.e., mainly β-lactam-susceptible gram-positive cocci and anaerobic gram-negative bacilli, such as *Prevotella melaninogenica* (formerly a member of the *Bacteroides melaninogenicus* group), and *Candida* species. Community-acquired peritonitis from a breach in the integrity of the lower small bowel or colon, or a breach of more proximal portions of the gastrointestinal tract when obstruction is present, involves colonic flora with *E. coli*, *Bacteroides fragilis*, enterococci, other *Bacteroides* species, *Fusobacterium*, *Clostridium perfringens*, other clostridia, *Peptostreptococcus*, and *Eubacterium*. Similar organisms (*E. coli*, enterococci, *Clostridium*, and *B. fragilis*) are also responsible for peritonitis complicating cholecystitis and biliary sepsis. Concomitant bacteremia occurs in 20% to 30% of patients, most frequently from *E. coli* and *B. fragilis*. In patients who acquire their infection in the hospital, antibiotic-resistant organisms such as *Enterobacter*, *Serratia*, *Acinetobacter*, vancomycin-resistant enterococci, and *P. aeruginosa* are frequently isolated.

The presenting symptoms are similar to those of primary peritonitis. The rapidity of onset and initial location and extent of peritoneal involvement vary with the inciting event; for example, sudden massive intraperitoneal spillage of gastric contents secondary to traumatic injury produces severe epigastric pain that, within minutes, spreads to involve the entire abdomen. In contrast, the spread of pain from a lesion such as a ruptured appendix or colonic diverticulum is more gradual and limited as the inflammatory process usually has time to wall off.

Pain is the predominant symptom. Pain and abdominal tenderness to palpation are usually maximal over the organ in which the process originated (e.g., epigastrium for a ruptured peptic ulcer, right upper quadrant for cholecystitis, right

lower quadrant for appendicitis, and left lower quadrant for diverticulitis). Other findings include fever, nausea, vomiting, and abdominal distension. The patient often lies motionless with the legs drawn up to the chest; any motion is likely to exacerbate the abdominal pain. Blood pressure is usually normal early but may fall with onset of septic shock, and there may be tachypnea and tachycardia. Direct and rebound abdominal tenderness and abdominal wall rigidity are often present. Bowel sounds are absent. Rectal and vaginal examinations, and in women in whom an ectopic pregnancy is suspected, a urinary beta-human chorionic gonadotropin (β-HCG) determination, are necessary.

Often, the diagnostic evaluation must be brief because of the patient's critical condition. Laboratory studies include a complete blood count, serum chemistry profile, liver profile, and amylase and lipase determinations. Appropriate cultures should be done promptly (e.g., blood), although culture of peritoneal fluid is often delayed until the time of laparotomy. Chest radiographs should be obtained to exclude chest conditions that might simulate an intra-abdominal process. Plain radiographs of the abdomen may also be helpful, sometimes revealing free air or fluid, bowel distension, ileus, or bowel wall edema. However, CT of the abdomen and pelvis with contrast is most helpful to localize the infection and indicate its probable source.

Antimicrobial therapy is initiated early to control bacteremia and minimize the local spread of infection. Patients with hemodynamic, respiratory, renal, and other critical organ system dysfunction require immediate appropriate supportive therapy. Surgery is often necessary to drain purulent material that contains bacteria, and excessive levels of proinflammatory cytokines and adjuvants (e.g., fecal matter, food, blood, bile, barium) that would enhance the virulence of peritoneal infection; debride devitalized tissues that foster anaerobic conditions; and control continued peritoneal contamination with bacteria and adjuvants by removing the initiating process (e.g., cholecystitis, appendicitis, and diverticulitis). Optimal management also includes bowel decompression (e.g., by proximal colostomy for perforation, diverticulitis, or colonic carcinoma). Proper timing and adequacy of surgical source control is paramount. To reduce the bacterial load and inflammatory exudate, a lavage of the abdominal cavity is performed, with particular attention to areas prone to abscess formation (e.g., paracolic gutters, subphrenic area).

Some patients, who are too severely ill and unstable from septic shock or coagulopathy to have a definitive procedure at the initial operation, are resuscitated and stabilized in an ICU setting for 24 to 36 hours and returned to the operating room in a series of re-explorations for additional debridement of necrotic tissue and foreign matter, drainage of residual infectious foci, and source control. Swelling of the bowel, retroperitoneum, and abdominal wall may preclude abdominal closure after surgery. Temporary closure of the abdomen to prevent herniation and contamination of the abdominal contents can be achieved using gauze and large, impermeable, self-adhesive membrane dressings, mesh with or without zipper- or Velcro-like closure devices, or vacuum-assisted closure devices. Advantages of this management strategy include avoidance of abdominal compartment syndrome and easy access for re-exploration. The disadvantages include significant disruption of respiratory mechanics and potential contamination of the abdomen with nosocomial pathogens.

Percutaneous catheter drainage guided by CT scan or ultrasonography may in some cases decrease the need for surgical therapy or delay surgery until the acute process and sepsis are resolved and a definitive procedure can be performed under elective circumstances. Where possible, percutaneous catheter drainage of abscesses and other well-localized fluid collections is preferable to surgical drainage if there is no evidence of uncontrolled perforation.

Antibiotic therapy should begin as soon as blood cultures are obtained but often before peritoneal fluid can be obtained for culture. Initial therapy is often empirical and must have broad-spectrum activity against the suspected pathogens. Peritoneal fluid cultures can be obtained at the time of paracentesis, percutaneous drainage of an intraperitoneal abscess, or laparotomy.

The spectrum of initial empiric antimicrobial coverage for community-acquired acute stomach and proximal jejunum perforations, in the absence of acid-reducing therapy or malignancy, should include aerobic gram-positive cocci and oral anaerobes. The spectrum of empiric antimicrobial coverage for community-acquired (1) distal small bowel-, appendiceal, and colon-derived infection, (2) more proximal gastrointestinal perforations in the presence of obstruction or paralytic ileus, and (3) biliary-derived infection if a biliary-enteric anastamosis is present should include facultative gram-negative bacilli, especially *E. coli*, and enteric streptococci, and obligate

Table 57.1 Empiric regimens for secondary peritonitis[a]

Single agent
1. β-lactam–β-lactamase inhibitor (piperacillin–tazobactam[b,c])
2. Moxifloxacin[b,c,d,e,f]
3. Carbapenem (imipenem[b,c], meropenem[c], doripenem[c], or ertapenem[g])[d]
4. Tigecycline[b,f,h]
Combinations
5. Cefazolin, cefuroxime, ceftriaxone, or cefotaxime plus metronidazole
6. A third- or fourth-generation cephalosporin (ceftazidime[c] or cefepime[c]) plus metronidazole
7. Levofloxacin[d,e,f] or ciprofloxacin[c,d,e,f] plus metronidazole
8. Aztreonam[c,f,i] plus vancomycin plus metronidazole[b]

[a] These regimens should be adjusted based on the results of culture and susceptibility testing.

[b] Empiric regimens with activity against *Enterococcus faecalis* are preferred for severe or nosocomial infections.

[c] Antipseudomonal

[d] The carbapenems and often fluoroquinolones, but not third-generation cephalosporins or β-lactam–β-lactamase inhibitor combinations, are active against ampC β-lactamase-producing and extended-spectrum β-lactamase (ESBL)-producing aerobic–facultative gram-negative bacilli.

[e] Fluoroquinolones are not recommended for use in patients who have received a fluoroquinolone in the past 3 months or in locales that have high rates (>10%) of fluoroquinolone-resistant *E. coli*.

[f] Tigecycline or fluoroquinolone- or aztreonam-containing regimens can be used in penicillin-allergic patients.

[g] Ertapenem does not cover *P. aeruginosa*.

[h] Tigecycline has shown increased risk of death compared to other drugs when used to treat a variety of serious infections, including complicated intra-abdominal infections.

[i] Aztreonam lacks activity against anaerobes and gram-positive cocci and must be combined with vancomycin and metronidazole.

anaerobic gram-negative bacilli, especially *B. fragilis* (see Table 57.1).

Inclusion of enterococcal coverage is somewhat controversial. It is prudent to include empiric antienterococcal therapy in an attempt to improve outcome in high-risk patients and in patients with cardiac valvular lesions that place them at high risk for a bad outcome of endocarditis (e.g., prior endocarditis, prosthetic cardiac valves, or complex cyanotic heart disease) (see Table 57.1).

Empiric therapy directed against vancomycin-resistant *Enterococcus* (VRE) *faecium* is not recommended unless the patient is at high risk for an infection due to this organism, such as a liver transplant recipient with an intra-abdominal infection from the hepatobiliary tree or a patient known to be colonized with VRE. Antibiotics active against VRE *faecium* include tigecycline, daptomycin, linezolid, and quinupristin–dalfopristin. For the more penicillin-susceptible VRE *faecalis*, ampicillin, linezolid, or daptomycin is appropriate (*E. faecalis* is inherently streptogramin resistant).

Similarly, treatment of *Candida* is controversial. Isolation of *Candida* from blood cultures or as the sole organism within residual or recurrent intra-abdominal infection, or as the predominant organism on Gram staining of peritoneal exudate, requires additional antifungal therapy for patients with severe community-acquired or healthcare-associated infection with either fluconazole or an echinocandin (caspofungin, micafungin, or anidulafungin) for fluconazole-resistant *Candida* species such as *Candida glabrata* and *Candida krusei*. Use of fluconazole for non-albicans *Candida* should be based on in vitro susceptibility testing. For the critically ill patient, therefore, initial therapy with an echinocandin instead of a triazole is recommended. Because of toxicity, amphotericin B is not recommended as initial therapy.

Because a significant proportion of *B. fragilis* is now resistant to clindamycin, cefoxitin, and cefotetan, and aminoglycosides have significant nephrotoxicity and ototoxicity, these drugs can no longer be recommended for empiric coverage now that more reliable and less toxic agents are available. For example, although *B. fragilis*, as well as many *Prevotella melaninogenica* are resistant to ampicillin, ticarcillin, and piperacillin, these organisms are sensitive to the β-lactam–β-lactamase inhibitor combinations piperacillin–tazobactam, and ticarcillin–clavulanate, as well as the carbapenems, the fluoroquinolone moxifloxacin, tigecycline, and metronidazole. All these antimicrobial agents, except metronidazole, will also be active against most *E. coli* and therefore can be used as single-drug therapy (see Table 57.1). Ampicillin–sulbactam is no longer recommended for use because of high rates of resistance to this agent among community-acquired *E. coli*.

Because nosocomial intraperitoneal infections are caused by more resistant flora, broader-spectrum empiric regimens are appropriate, as well as for more severe community-acquired infection or infection in immunocompromised patients (Table 57.1). Acute Physiology and Chronic Health Evaluation II (APACHE II) score >15, advanced age, low albumin levels, poor nutritional status, and concurrent malignancy increase risk for a more severe infection.

Local susceptibility profiles should be reviewed and empiric regimens modified accordingly. Empiric regimens should also be modified once results of susceptibility testing are available.

However, empiric antimicrobial therapy directed against anaerobes should be maintained, even if anaerobes are not recovered, because of the unreliability of clinical anaerobic methodology.

The duration of antimicrobial therapy after adequate surgery is usually 5 to 10 days but depends on control of the source of the infection, severity of infection, clinical response to therapy, and normalization of the white blood cell count. Only a short course of antimicrobial therapy (about 24 hours) is required for sterile peritonitis that occurs around an infected but resected intra-abdominal organ, such as an appendix or gallbladder. Once the patient can tolerate oral therapy, antimicrobial agents can be given orally rather than intravenously, if oral agents are available that have antimicrobial activity equivalent to that of the intravenous regimen.

The main therapy for any intraperitoneal abscess is early and adequate drainage. Effective management depends on accurate localization of the abscess and discrimination between single and multiple abscesses. In recent years, successful therapy has been accomplished using percutaneous catheter drainage as an alternative to surgery. This method has become possible with the use of refined imaging techniques, especially ultrasonography and CT. The general requirements for CT- or ultrasound-guided percutaneous catheter drainage include (1) an abscess that can be adequately approached; (2) an abscess that is unilocular; (3) an abscess that is not vascular and the patient has no coagulopathy; (4) joint radiologic and surgical evaluation, with surgical backup for any complication or failure; and (5) the possibility of dependent drainage via the percutaneously placed catheter. CT also allows detection of an unsuspected additional intra-abdominal problem that would otherwise require surgical intervention. Percutaneous catheter drainage can be used as an initial approach in a patient too unstable to withstand immediate surgery. Definitive surgery can then be postponed until the patient is in better condition.

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58. Whipple's disease

Amirkaveh Mojtahed and Payam Afshar

In 1907, Dr. George H. Whipple, a pathologist at Johns Hopkins Hospital, described the first case of "intestinal lipodystrophy" in a 36-year-old male physician with symptoms of chronic diarrhea, abdominal pain, weight loss, and chronic cough. The patient succumbed to his death after 5 years of his disease. Universally fatal prior to the advent of antibiotics, the condition now known as Whipple's disease has accumulated case reports and case series with a recent prospective study in the management of the disease. This rare disease masquerades as a multisystem condition of symptoms that are nonspecific, rendering the diagnosis inaccessible unless included in the differential diagnosis. Based on the most recent prospective study, the disease is well managed with appropriate attention to diagnosis and antibiotic therapy.

After the initial case report by Dr. Whipple, progress was made towards establishing the means of diagnosis and treatment. In 1949, periodic acid–Schiff (PAS) staining helped identify the red appearance of glycoproteins within intestinal macrophages. Shortly afterwards, the first microscopic identification of a bacteria-like organism led to the first successful treatment of Whipple's disease with chloramphenicol. Electron microscopy and the advancement of histologic staining helped further characterize the infectious entity as a gram-positive bacterium. In 1992, polymerase chain reaction (PCR) was used to identify the ribosomal RNA of the organism, classifying it as an actinomycete. Genomic sequencing of the organism in 2003 has brought us to the current classification of this rod-shaped, gram-positive actinomycete as *Tropheryma whipplei*.

Whipple's disease is a multisystem chronic disease that is exceedingly rare with an approximated incidence of 1 per 1 000 000 population, with a middle-aged White male predilection. The pathogenesis of *T. whipplei* is important for the explanation of the population at risk and the multisystem nature of the disease. Occupations at risk include farmers, due to soil and animal contact, as well as sewage plant workers. The mode of transmission of the disease is not known but is speculated to be oral–fecal, with shed from the gastrointestinal tract. Curiously, no reports of human-to-human transmission have been made and humans are the only carriers of *T. whipplei* to manifest clinical disease. Fluorescence *in situ* hybridization (FISH) has been instrumental in characterizing this as a metabolically active organism of the intestinal mucosa. The bacteria reside deep in the lamina propria of the intestinal tract where they replicate in the macrophages of the asymptomatic host. Apoptosis of the macrophage initiates the cascade that leads to the multisystem pathology of Whipple's disease, via invasion from the intestinal lymphatics and eventual hematogenous spread to distant tissues.

The nonspecific clinical presentation of the condition creates confusion for the clinician and latency in the diagnosis that can span for many years. Whipple's disease is primarily a disease of the gastrointestinal tract with extraintestinal symptoms of arthralgia, fever, and neurologic syndromes. The classic presentation of prodromal arthralgias followed by gastrointestinal complaints of diarrhea and abdominal pain, which may be delayed for years, should lead to the inclusion of Whipple's disease in the differential diagnosis. The gastrointestinal symptoms may result in malabsorption, malnutrition, hypoalbuminemia with abdominal lymphadenopathy and eventual anasarca. The seronegative arthralgia can mimic other rheumatologic conditions with a migratory pattern and joint destruction that is unresponsive to immunosuppression. The ominous neurologic manifestations usually occur in conjunction with the gastrointestinal disorder or as disease relapse due to inadequate blood–brain barrier penetration of the antibiotic. These are variable and may include cognitive impairment, psychiatric disorder, sensorimotor impairment, and cranial nerve abnormalities, the most notable

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and pathognomonic being oculomasticatory myorhythmia or oculofacial myorhythmia. The overall incidence of central nervous system (CNS) Whipple's disease is approximated at 10% to 40% but may be underestimated due to underreporting. The rare cardiac manifestations of Whipple's disease include blood culture-negative endocarditis, constrictive pericarditis, myocarditis, coronary arteritis, and congestive heart failure. Mucocutaneous Whipple's pathology includes reports of hyperpigmentation of the skin, vasculitic rash, and hemorrhagic gingivitis. Lastly, pulmonary complaints of chronic cough with the appearance of pulmonary nodules and endobronchial lesions that resemble sarcoidosis of the lungs have been reported.

The diagnosis of Whipple's disease should be led by the clinician's suspicion and supported by affected tissue sampling. Duodenal biopsies are most commonly the method of diagnosis. Experts recommend at least five mucosal biopsies of the most distal segment of the duodenum to avoid sampling error. Endoscopic findings commonly reveal lymphangiectasia with widening of intestinal villi or white plaques denoting lipid deposition. Routine hematoxylin and eosin staining of the intestinal biopsies identifies the foamy cytoplasm of the macrophage while PAS stain enhances the appearance of cytoplasmic granules that represent the glycoprotein component of the *T. whipplei* bacterial cell wall. Due to nonspecific PAS-positivity, real-time PCR should be used to confirm the diagnosis. FISH can be used in conjunction with PCR for confirmation but is not necessary. Patients with the diagnosis of Whipple's disease should undergo cerebrospinal fluid (CSF) analysis with PCR to exclude CNS involvement, as neurologic damage may be irreversible and absence of symptoms is not a reliable marker to rule out cerebral infection. If initially positive, repeat lumbar puncture with PCR should be performed to ensure bacterial eradication. Patients with symptoms beyond the gastrointestinal tract should have appropriate tissue sampling (synovial fluid, cardiac valve, lymph nodes, skin, etc.) based on clinical presentation.

Appropriate treatment of Whipple's disease with antibiotics is essential to avoid the inevitable mortality of the condition. In addition, it is imperative that the chosen antibiotic has blood–brain barrier penetration and can obtain high CSF levels. In the era of antibiotics, tetracycline had long been the therapy of choice, yet relapse rates up to 35% and the poor response to retreatment in patients with CNS involvement has led to other therapies. Recently, the only prospective, randomized study to examine therapy compared the efficacy of bactericidal ceftriaxone versus meropenem, followed by oral trimethoprim–sulfamethoxazole for 12 months with a 3-year observance for remission. Based on this long-term follow-up, all 40 patients achieved remission. Penicillin G followed by doxycycline is also a valid therapeutic option (Table 58.1). Clinical response to therapy should occur within 1 to 3 weeks with follow-up studies to include duodenal histology and PCR in patients with gastrointestinal manifestation and CSF analysis with PCR in patients with CNS involvement.

TROPICAL SPRUE

Tropical sprue (TS) is an acquired malabsorptive and likely infectious disease of unknown etiology that affects locals and travelers who reside in the tropics. Residence in the tropics for longer than a month with chronic diarrhea and nutritional deficiencies are the usual symptomatic hallmarks. Endemic areas include south Asia, Caribbean, Central America, and northern South America while sparing Africa and the Middle East. Most often it is a disease of local inhabitants; however, long-term visitors are also at risk. TS, initially described as a disease of low socioeconomic population, can also affect those with access to medical care, adequate hygiene, and nutritional diet. In North America and Europe, TS should be suspected in the long-term traveler after exclusion of common causes of chronic diarrhea and malabsorption.

Several theories for infectious mechanisms exist, but a specific organism has not been implicated. Patients with TS frequently report a preceding acute infectious diarrheal illness. This finding, in addition to a possible mechanism of small bowel injury explained by an overgrowth of aerobic coliform bacteria with resolution of symptoms after antibiotics, justifies an alternative nomenclature of TS: post-infective tropical malabsorption.

Patients suffer from chronic diarrhea related to malabsorption of fatty acids and carbohydrates, as well as bile salt-induced diarrhea from terminal ileal (TI) involvement. Loss of brush border enzymes (e.g. lactase), impaired fat absorption leading to steatorrhea, and nutrient deficiencies of primarily folate, vitamin D, and, as the disease progresses, B_{12} are commonly seen in TS. Macrocytic anemia from nutrient deficiency is commonly seen. Steatorrhea also leads to loss of fat-soluble

Table 58.1 Treatment of Whipple's disease

Induction therapy	
Penicillin G	2 million units intravenous every 4 hours for 14 days
Ceftriaxone	2 g intravenous daily for 14 days
Meropenem (if penicillin allergy)	1 g intravenous three times daily for 14 days
Maintenance therapy	
Trimethoprim–sulfamethoxazole (TMP–SMX)	160/800 mg twice daily for 12 months
Doxycycline (if sulfa allergy), plus Hydroxychloroquine	100 mg once daily oral, plus 200 mg three times daily for 12 months

vitamin absorption with subsequent vitamin deficiency clinical sequelae.

Diagnosis is by exclusion of close mimics, particularly celiac sprue (CS). The incidence of TS has decreased as the serum testing for CS has improved suggesting many of these cases were not TS. Infectious diarrheal illnesses such as entamoebiasis, AIDS enteropathy, Whipple's disease, giardiasis, isosporiasis, and cryptosporidiosis must be excluded. Mucosal scalloping, a common feature of CS, can be present on endoscopy while biopsies of any region of the small bowel can show partial villous atrophy and intraepithelial lymphocytes. Duodenal biopsies are of highest yield as the ileum is affected in later stages. Similar biopsy changes are present in tropical enteropathy, a subclinical variant; however, without overt symptoms of TS. A thorough workup is indicated but the diagnosis can also be confirmed by response to treatment.

Three to six months of tetracycline 250 mg four times a day with folate is the first-line treatment regimen. In several case series, initial folate (1 to 5 mg/day) has been shown to resolve symptoms. B_{12} should also be replaced subcutaneously if deficient. Cholestyramine may reduce diarrheal frequency if TI is involved. Recurrence or relapse can occur in 20% of cases requiring repeat treatment. If tetracycline is contraindicated in the patient, sulfonamide antibiotics can be used, based on a single study.

SMALL INTESTINAL BACTERIAL OVERGROWTH

Small intestinal bacterial overgrowth (SIBO) is an entity resulting from increased numbers of bacteria residing in the small bowel. Patients can experience bloating, dyspepsia, abdominal pain, diarrhea, and weight loss. Symptoms are linked to excessive bacterial fermentation of carbohydrates and proteins. Deficiencies of B_{12} and fat-soluble vitamins are considered but rarely present.

Patients at risk generally have altered gut motility or physiology. Risk factors include prior surgeries such as gastrectomy or ileocecal resection, diverticula, fistulas, hypochlorydia, liver disease, chronic pancreatitis, immunodeficiencies, and motility disorders associated with diabetes, scleroderma, and intestinal pseudo-obstruction. There is suggestion that irritable bowel syndrome is linked to SIBO but this remains uncertain.

The gold standard for diagnosis is a jejunal aspirate with greater than 10^5 bacteria, but its role as gold standard is in doubt. Lactulose breath testing, with an abnormal gas profile suggesting increased bacterial burden in the small bowel, is often more clinically feasible.

Treatment is primarily antibiotics, management of nutritional deficiencies and eliminating medications that reduce transit time. A trial of lactose-free, high-fat, low-carbohydrate, and low-fiber diet may also improve symptoms. A well-tested therapy is the use of nonabsorbable antibiotics such as rifaximin 550 mg PO q8h for 10–14 days. Treatment with absorbable antibiotics is less desirable due to resistance and side effects. Recurrence is expected in patients with anatomic or motility disorders. Prokinetic agents may help such patients. Probiotics have not proved effective.

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PART VIII

Clinical syndromes: genitourinary tract

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59. Urethritis and dysuria

George Pappas, Ioannis A. Bliziotis, and Matthew E. Falagas

The term urethritis refers to inflammation of the urethra, which can be attributed both to infectious and noninfectious processes. The urethral canal essentially represents the first site of the body to be exposed to a variety of sexually transmitted pathogens, and the interaction of these pathogens with the epithelial cells of the urethra gives rise to the syndrome's symptoms.

Dysuria refers to the experience of pain or burning sensation or discomfort in urination, and is a subjective symptom related to varying pathology of the urinary tract. The urethra being the terminal pathway of urine flow, its inflammation most often accounts for experience of dysuria.

ETIOLOGY

Traditionally urethritis has been divided into gonococcal urethritis (GU) and nongonococcal urethritis (NGU). *Neisseria gonorrhoeae* as a cause of urethritis has been recognized since ancient years, and in fact its name represents a description, in Greek, of the syndrome's symptoms as defined by Galen: "gono" referring to semen, which was supposed to be the main constituent of the urethral discharge, and "rrhea" a term for flow. Descriptions of urethritis exist in the Old Testament, in the Book of Leviticus, in ancient Chinese documents, and in the Hippocratic Corpus.

NGU has been often considered synonymous to *Chlamydia trachomatis* infection, although a continuously increasing number of pathogens are also implicated (Table 59.1). *Chlamydia trachomatis* is generally thought of as the commonest cause of NGU, especially in younger patients, although some studies suggest that *Ureaplasma urealyticum*, biovar 2, may be a more prevalent cause of infection. Numerous other pathogens have been associated with NGU: *Mycoplasma genitalium* as a cause of urethritis was recognized in the early 1980s; its etiologic role as a sexually transmitted pathogen has been confirmed recently. *Trichomonas vaginalis* is invariably isolated in clinical series of urethritis. *Gardnerella vaginalis* has also been considered a frequent cause of urethritis in certain series. Herpes simplex virus (HSV) is also a potent cause, both as HSV-1 and HSV-2. More rare causes include adenoviruses, lymphogranuloma venereum (*Chlamydia trachomatis* serotypes L1, L2, L3), mycobacteria, and syphilis, as well as gram-negative pathogens (e.g. *Escherichia coli* in cases of strictures or cystitis). Even rarer causes include other viral infections, cytomegalovirus (CMV) in immunocompromised patients, streptococcal species (especially *Streptococcus pyogenes*), *Neisseria meningitidis*, fungi, and anaerobes such as *Bacteroides* species.

Table 59.1 Etiology and relative frequency of infectious urethritis

Pathogen	Reported frequency in cases of urethritis
Neisseria gonorrhoeae	12%–34%
Chlamydia trachomatis	15%–55% of NGU
Mycoplasma genitalium	3%–38% of NGU
Ureaplasma urealyticum	6%–60% of NGU
Trichomonas vaginalis	<5% of NGU
Gardnerella vaginalis	12% of NGU in a single study
Mycoplasma hominis	Rare, frequency vaguely defined
Herpes simplex virus	Rare
Gram-negative bacteria	Rare
Adenoviruses	Rare
Other: mycobacteria, syphilis, lymphogranuloma venereum, streptococci, *Neisseria meningitidis*, anaerobes, fungi	Very rare/isolated reports

Abbreviation: NGU = nongonococcal urethritis.

EPIDEMIOLOGY

The global annual incidence of urethritis is enormous: An estimated 62 million cases of GU and 89 million cases of NGU occur annually. In the

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United States alone, approximately five million annual cases are reported, the great majority of which is NGU. The incidence of GU has been declining in the United States since 2000, while inverse trends have been observed for NGU. The latter are accompanied though by a declining incidence of chlamydial NGU and may actually reflect the increasing recognition of other etiologies of NGU or the effect of chlamydial control programs. A steady increase of the total urethritis cases reported in males has been observed in France in recent years. The increasing availability of sophisticated diagnostic techniques in developing countries has also helped underline the magnitude of the problem.

There seems to be no racial predilection for the incidence of the syndrome but certain socioeconomic factors may apply, urethritis being more common in low-income populations. Gender predilection seems also not to exist, although the difference in the syndrome's clinical presentation between males and females may account for a larger percentage of female cases that are asymptomatic and thus not reported; on the other hand, while male urethritis is a distinct syndrome, female disease is often misdiagnosed in the context of, or coexists undiagnosed with, inflammation of other sites of the female urogenital tract, most importantly cervicitis. Due to urethritis being a sexually transmitted disease, the age group of 20 to 24 years predominates in reported cases. The use of condoms has been inversely related to the incidence of urethritis. Other risk factors include the use of spermicides (which, however, may predispose to chemical urethritis only), the number of sexual partners, homosexuality in males, unprotected anal sex for heterosexual males, and history of other sexually transmitted diseases.

CLINICAL MANIFESTATIONS

The disease is often asymptomatic, particularly so in female patients and in cases of chlamydial etiology. Up to 75% of women with chlamydial urethritis experience no symptoms. Gonococcal urethritis exhibits a shorter incubation period than NGU and a more abrupt onset, and is usually symptomatic. Incubation period lies between a few days, for gonococcal disease, and up to 2 weeks for the nongonococcal one. Urethral discharge, dysuria, and urethral pruritus are the cardinal symptoms: Discharge is a product of the polymorphonuclear cell influx in the region as part of the immune response and epithelial cell apoptosis, is usually mucopurulent, most often observed at the morning, may be blood-tinged, and is a result of the inflammatory interplay following entry of the pathogen: this inflammatory response is more pronounced in cases of gonococcal compared to chlamydial urethritis and in males compared to females. Occasionally, in women with gonococcal infection symptoms can result from endocervical infection, such as altered vaginal discharge or intermenstrual bleeding and menorrhagia. Other causes of NGU such as *M. genitalium* tend also to cause symptomatic disease whereas *Trichomonas* infection in males can range from asymptomatic to more severe clinically than GU.

DIAGNOSIS

The diagnosis of urethritis is based on the presence of relevant clinical symptoms accompanied by laboratory findings: Gram stain microscopy of urethral secretions that exhibits five or more white blood cells (WBCs) per oil-immersion field, or a positive WBC esterase test of first-void urine, or a first-void urine sample exhibiting 10 or more WBCs per high-power field. The latter though has been considered inadequate by various studies reporting that 12% of chlamydial infections and 5% of gonococcal ones may be undiagnosed by this criterion.

Gram stain microscopy allows for initial etiologic workup, since the observation of gram-negative intracellular diplococci may allow for a rapid diagnosis of gonococcal urethritis, with a sensitivity and specificity of >95% and >99% respectively in symptomatic men. However, microscopy has poor sensitivity (around 50%) in urethral samples of asymptomatic men and urethral and cervical samples of females. Thus, absence of pathologic findings on a Gram smear does not rule out gonococcal infection, especially in the later situations. Cultures may allow for isolation of the specific pathogen and evaluation of its antimicrobial susceptibility. Due to the increase in worldwide prevalence of cephalosporin-resistant strains of *N. gonorrhoeae*, cultures and susceptibility testing have become useful for new cases of urethritis and essential for cases with recurrence after treatment for GU.

Molecular diagnostic methods have been increasingly applied to urethritis diagnosis, nucleic acid amplification tests (NAAT) being the most popular choices, since they can be performed with urine specimens as well as urethral samples. These assays have shown exquisite

Table 59.2. Diagnostic tools for pathogens involved in urethritis

Pathogen	Diagnostic tools	Comments
Neisseria gonorrhoeae	Gram stain Culture NAHT NAAT	Culture and NAHT require urethral swab specimens, whereas NAAT can be performed on urine specimens. Culture allows identification of resistant strains
Chlamydia trachomatis	Culture Direct immunofluorescence Enzyme immunoassays NAHT NAAT	NAHT require urethral swab specimens, whereas NAAT can be performed on urine samples/in females addition of cervical samples increases sensitivity NAAT more sensitive and 100% specific
Mycoplasma genitalium	NAAT	NAAT can be performed on urine samples/in females addition of cervical samples increases sensitivity
Ureaplasma urealyticum, Mycoplasma hominis	Culture	Cultures need specialized media, not performed in everyday practice Urethral swabs preferred to urine samples
Trichomonas vaginalis	Wet preparation Culture NAAT	Wet preparation is 60% sensitive, often negative in males Anaerobic culture of urethral swab or first-void urine, 95% sensitive NAAT is considered superior to cultures (97% sensitivity and 98% specificity), but needs multiple samples in males

Abbreviations: NAAT = nucleic acid amplification tests, NAHT = nucleic acid hybridization tests.

sensitivity and specificity both for gonococci and *Chlamydia*, but lack the ability to identify resistant strains of gonococcus. Other NAAT exist for less common pathogens, such as *M. genitalium*, but their standard application in clinical practice has been under dispute. Other diagnostic tests for NGU include a wet preparation for *Trichomonas* diagnosis and a potassium hydroxide (KOH) preparation for fungal infections. Table 59.2 summarizes current diagnostic facilities for each pathogen and specific data about each assay's sensitivity and specificity. After confirmation of GU or NGU diagnosis, especially in cases of high-risk populations or GU recurrence, it is advisable to test for other sexually transmitted diseases, including human immunodeficiency virus (HIV) and syphilis, and, in female patients, pregnancy should be ruled out before specific antibiotic recommendations.

COMPLICATIONS

The importance of urethritis as a medical entity lies not in the severity of the syndrome per se, but in its potential complications: these complications may be rare in male patients, but do include formation of strictures or abscesses, prostatitis, epididymitis, infertility, disseminated gonococcal infection, and proctitis. In female patients complications are more common, and may lead to pelvic inflammatory disease, which may be of considerable severity. Females with GU and NGU can become infertile due to symptomatic or asymptomatic infection of the upper genital tract, which may cause direct damage to the uterus or fallopian tubes. Disseminated gonococcal infection can also follow urethritis in females. In pregnant women, chlamydial infection can lead to transmission of the pathogen to neonates leading to ophthalmia neonatum. Another important parameter of urethritis is that local inflammation results in disruption of the integrity of the epithelial barrier, thus urethritis confers an increased risk for HIV transmission. Finally, Reiter syndrome is another complication of GU and NGU. It is characterized by the coexistence of arthritis, urethritis, and conjunctivitis or uveitis due to an autoimmune process after gastrointestinal or genitourinary infections.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes traumatic urethritis, occurring after catheterization, chemical urethritis, noninfectious prostatitis, other infections of the lower urinary tract, and autoimmune urethritis of Reiter syndrome. Dysuria should be differentiated from frequency or urgency, which point to other diagnoses. It is reported that dysuria may be aggravated by alcohol consumption, or during menstruation in females. There are no systemic symptoms such as fever, and presence of such symptoms should orientate the diagnosis elsewhere. Since dysuria may be attributed to infectious processes of the whole genitourinary tract, including prostatitis or even pyelonephritis, but also to noninfectious causes of flow obstruction (including anatomical malformations, neoplasms, or even hormonal causes such as endometriosis, and neurogenic and psychogenic conditions), the significance of this subjective

symptom is mainly in localizing the clinician's interest in the genitourinary tract.

A high number of WBCs in urine, termed pyuria, can be observed both in urethritis and other lower urinary tract infections, including cystitis. Pyuria with a negative urinary culture (with $\leq 10^2$ common uropathogenic bacteria/mL of urine) is termed "sterile pyuria". NGU is among the most common causes of sterile pyuria, which include among others tuberculosis of the urinary tract, prostatitis, nephrolithiasis, interstitial cystitis, and urinary tract malignancies.

TREATMENT

Table 59.3 summarizes the suggested antibiotic regimens used in the treatment of urethritis, in accordance to guidelines from Europe and the USA. Many cases of urethritis resolve spontaneously, or evolve, in cases of NGU, into asymptomatic infection. Nevertheless, antibiotic treatment of urethritis should always follow the diagnosis to prevent complications and further transmission of the pathogen.

Another important aspect regarding treatment is that gonococcal and chlamydial infection frequently coexist; thus, a diagnosis of gonococcal infection through a Gram smear showing gram-negative intracellular diplococci will warrant treatment of both gonococcal and chlamydial disease. This observation has further raised questions regarding the utility of sophisticated diagnostic assays when Gram smear shows gonococcal disease: it simply is cheaper to treat both for GU and chlamydial urethritis than confirm or exclude chlamydial disease through further testing.

Various antibiotics have been effective in the treatment of different forms of urethritis. Regimens for gonococcal disease include third-generation cephalosporins administered as a single dose. Ceftriaxone exhibits higher blood microbicidal levels and for a more sustained period than cefixime and should be considered as the optimal regimen (Table 59.3). Oral cephalosporins have proven inferior to ceftriaxone, and gonococcal resistance to cefixime is increasing; thus it is no longer considered a first-line therapy. Other cephalosporins have not proven advantageous compared to the aforementioned regimens. Recent European guidelines recommend an increase in the single dose of ceftriaxone to 500 mg because of resistance.

Azithromycin is efficacious against both gonococci as well as *Chlamydia*; it is thus considered

Table 59.3 Optimal treatment of urethritis and alternative approaches[a]

Gonococcal urethritis
(*all therapies in conjunction with therapy against* Chlamydia: *azithromycin 1 g orally in a single dose or doxycycline 100 mg orally twice daily for 7 days*)
- First-line regimen:
  Ceftriaxone, 250 mg intramuscularly, single dose
- Second-line, alternative regimens[b]:
  Cefixime, 400 mg orally, single dose
  Azithromycin, 2g orally, single dose (regimen for patients with cephalosporin allergy, no additional treatment for *Chlamydia* needed)
- Alternative regimens of inferior, or unproven efficacy[b]:
  Spectinomycin, 2 g intramuscularly, single dose, or
  Ceftizoxime, 500 mg intramuscularly, single dose, or
  Cefoxitin, 2 g intramuscularly, single dose, plus probenecid, or
  Cefotaxime, 500 mg intramuscularly, single dose,
  Cefpodoxime, 200 mg orally, single dose, or
  Cefuroxime axetil, 1 g orally, single dose

Chlamydial infection
- Azithromycin, 1 g orally, single dose, or
- Doxycycline, 100 mg orally, twice daily for 7 days
- Alternative regimens
  Erythromycin base, 500 mg orally, four times daily, for 7 days, or
  Erythromycin ethylsuccinate, 800 mg orally, four times daily, for 7 days, or
  Ofloxacin, 300 mg orally, twice daily for 7 days, or
  Levofloxacin, 500 mg orally, once daily, for 7 days

Mycoplasma genitalium infection
- Azithromycin, 1 g orally, single dose, or
- Doxycycline, 100 mg orally, twice daily for 7 days (possibility of resistant strains)

Ureaplasma urealyticum infection
- Azithromycin, 1g orally, single dose, or
- Doxycycline, 100 mg orally, twice daily for 7 days (possibility of resistant strain), or
- Quinolones, as used for *Chlamydia trachomatis* infection

Mycoplasma hominis infection
- Doxycycline, 100 mg orally, twice daily for 7 days (possibility of resistant strain), or
- Quinolones, as used for *Chlamydia trachomatis* infection, or
- Clindamycin, dose varying

Trichomonas vaginalis infection
- Metronidazole, 2 g orally, single dose, or
- Tinidazole, 2 g orally, single dose

Pregnancy
- Azithromycin, 1 g orally, single dose, or
- Amoxicillin, 500 mg orally, three times daily, for 7 days
- Alternatively: any erythromycin regimen, apart from erythromycin estolate

[a] Major recommendations from Workowski and Berman, 2006 and Centers for Disease Control and Prevention, 2012.
[b] The patient should return in 1 week for a test-of-cure at the site of infection.

sufficient monotherapy at high doses in cases of established cephalosporin allergy (Table 59.3). Similarly, according to some authors azithromycin should also be the preferred empirical therapy for *Chlamydia* when GU is diagnosed (thus used together with a cephalosporin), since tetracycline resistance is increasing among gonococcal isolates whereas azithromycin is efficacious against both microbes. Spectinomycin, although of exquisite microbiologic efficacy (>98%), is expensive and needs parenteral administration. Quinolones were viewed as potential single-dose monotherapy candidates that could treat both gonococcal and chlamydial infection, but the increasing rates of gonococcal resistance to these agents worldwide made them unsuitable for therapy of GU. On the other hand, ciprofloxacin's efficacy against *Chlamydia* is doubtful.

For chlamydial infection, azithromycin and doxycycline have proven equally successful, with microbial cure rates of 97% and 98%, respectively. Azithromycin is superior in terms of compliance since it can be directly administered upon diagnosis, but doxycycline is of considerably lower cost. Azithromycin may be superior though regarding treatment of *M. genitalium* infections. There is no difference in the percentage or severity of adverse events between the two antibiotic classes. None of the various alternatives has proven superior, although not all of them have been evaluated in randomized trials. Erythromycin is marred by low compliance due to frequent gastrointestinal adverse events.

There is increasing concern regarding emergence of resistance to azithromycin by *M. genitalium*, since recent studies have underlined therapeutic failures in cases of urethritis treated with azithromycin. These studies have shown a potent role for moxifloxacin in such cases. *Ureaplasma urealyticum* follows the susceptibility patterns of *Chlamydia*, although the risk of tetracycline resistance is significant. *Mycoplasma hominis* is resistant to azithromycin and macrolides, but sensitive to tetracyclines, quinolones, and clindamycin.

In pregnancy, gonococcal infection can be treated with the usual cephalosporin regimens, and azithromycin can be considered a safe regimen for chlamydial infection. In addition, amoxicillin can also be administered safely and efficaciously in these patients.

Patients should be advised to abstain from sexual practices for the following week post treatment initiation, and previous sexual contacts should be traced and tested, extending to a period of 6 weeks prior to diagnosis. If the patient reports no contacts during this period, then the last sexual partner should be notified and tested. Alternatively, sexual partners can be treated on the responsibility of the patients, a practice that has been supported inconsistently as effective. Test of cure is not advisable for patients that become asymptomatic after therapy. However, this follow-up testing for microbiologic eradication is suggested for all pregnant women at 3 weeks after treatment completion and for all patients with gonococcal infection that initially received second-line treatment or alternative regimens.

Of note, there is an increased prevalence of gonococcal infections in patients with a recent previous gonococcal infection, and a similar risk exists for a new chlamydial infection after an initial one in female patients, with reinfection possessing greater potential for complications. Therefore, asymptomatic patients should be retested 3 to 12 months after treatment, although this test is distinct from a test seeking evidence of microbiologic eradication.

Recurrence of urethritis may be attributed to noncompliance with the initial treatment, initial infection by resistant strains (of great importance in GU, which should be excluded by culture upon recurrence), or re-exposure to a non-treated partner. Examples of recurrence in NGU include undiagnosed *Trichomonas* infection, which should be treated with metronidazole or tinidazole, infection by a *U. urealyticum* strain resistant to tetracycline, which should be treated with azithromycin, or *M. genitalium* resistant to tetracycline (or on rare occasions to azithromycin). Another common diagnosis in male patients may be chronic nonbacterial prostatitis, which in a significant percentage is accompanied by sterile urethral inflammation.

PREVENTION

Prevention through screening has been often advocated: US Preventive Services Task Force supports the annual screening for chlamydial infection in sexually active females aged 24 years or younger, and in older females who belong to certain risk groups (multiple partners, sex workers, etc.). Screening for gonococcal infection should also be advocated to the aforementioned high-risk groups of patients in addition to patients with a history of gonococcal infection or other sexually transmitted disease. On the other hand, some European authorities recommend

screening for *Chlamydia* only in high-risk groups. Similarly, routine screening for *Chlamydia* in pregnancy during first visit has not been universally acceptable from a cost-effectiveness point-of-view; however, all women undergoing termination of pregnancy should be tested for chlamydial infection due to the risk of ascending infection. The active research in the field of development of a *Chlamydia* vaccine may offer further prospects in the future for control of urethritis incidence; until then though public health policies should be vigorously implemented.

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60. Vaginitis and cervicitis

Sebastian Faro

INTRODUCTION

Vaginitis and cervicitis are undoubtedly linked in many instances, to some degree. When considering cervicitis as a discrete entity, the most common causes are infections due to *Chlamydia trachomatis* and *Neisseria gonorrheae*. Other causes of cervicitis are human papillomavirus (HPV) and infrequently considered are herpes simplex virus (HSV), *Mycoplasma*, and *Ureaplasma*. The two latter bacteria are commonly found colonizing the lower genital tract in sexually active women and their role in the disease of female pelvic organs is not well understood. However, recent data have implicated the mycoplasmas and ureaplasmas in both obstetric and gynecologic pelvic infections. Other causes of cervicitis have been documented throughout the world, e.g., *Mycobacterium tuberculosis*, *Schistosoma haematobium*, Epstein–Barr virus, amoebiasis, and cytomegalovirus, but are uncommon in the United States. However, when taking a history it is important to determine if there has been recent travel outside the United States, especially to parts of the world where these diseases are prevalent. The patient's past travel experience or her sexual partner's travel experience are important when evaluating the patient with vaginitis and cervicitis. The patient's travel experience can be significant when administering empirical antimicrobial treatment, especially when treating suspected gonococcal cervicitis. *N. gonorrhoeae* acquired from Asia tends to be resistant to the antibiotics commonly administered in the United States to treat gonococcal infection. Therefore, all patients being evaluated for vaginitis should be evaluated for the coexistence of cervicitis.

Vaginitis can be divided into two broad categories: infectious and noninfectious, and either can lead to cervicitis. The most common noninfectious cause of vaginitis is bacterial vaginosis (BV) which has been shown not to be simply an alteration in the indigenous vaginal microbiota. Gram-negative bacteria, especially the obligate anaerobic bacteria, make up a large portion of the vaginal microbiota. The gram-negative bacteria cell wall contains lipopolysaccharide (LPS), which is known to stimulate the cytokine cascade and the proinflammatory response syndrome. Patients with a predominance of gram-negative bacteria, and therefore an increase in the LPS content, in the vagina, have an increased vaginal concentration of tumor necrosis factor-α (TNF-α). This finding suggests that BV is not simply an alteration in the indigenous vaginal microbiota but perhaps should be considered as a subclinical infection. Therefore, in some cases it is difficult to distinguish between vaginitis and vaginosis, e.g., in the patient with BV and trichomoniasis. Patients may have both vaginitis and cervicitis of the same etiology or of different etiologies, e.g., *Trichomonas* can cause both vaginitis and cervicitis, whereas a patient with BV can also have chlamydial cervicitis. It is possible for the patient with BV to have a complex cervicitis involving BV bacteria plus *C. trachomatis* and *N. gonorrhoeae*. These potential situations underscore the need for the physician to consider the possibility of coexisting conditions in order to initiate appropriate treatment.

Many women with vaginitis are asymptomatic and do not seek treatment until they develop symptoms. Women examined for conditions other than vaginitis or even having a well-woman examination can be found to have an abnormal vaginal discharge, which should be evaluated. This is especially important because most chlamydial and gonococcal infections are asymptomatic. Vaginitis can often cause significant health problems and negatively impact the patient's quality of life, such as disruption of personal relationships, ability to attend work and social activities. Pregnant patients who have vaginitis and cervicitis can experience premature preterm rupture of amniotic membranes, premature delivery, and postpartum endometritis. Patients with vaginitis and cervicitis who undergo pelvic surgery are at

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Table 60.1 Bacteria of the indigenous vaginal microbiota

Lactobacillus crispatus	*Escherichia coli*	*Atopobium vaginae*
L. jensenii	*Enterobacter aerogenes*	*Bacteroides fragilis*
L. gasseri	*E. agglomerans*	*Bifidobacterium*
L. vaginalis	*E. cloacae*	*Prevotella bivia*
L. iners	*Klebsiella oxytoca*	*Fusobacterium*
Staphylococcus aureus	*K. pneumoniae*	*Mobiluncus*
S. epidermidis	*Morganella morganii*	*Megasphaera*
Streptococcus agalactiae	*Gardnerella vaginalis*	*Sneathia*
S. pyogenes	*Peptococcus*	*Peptostreptococcus*

Note: E. agglomerans is now known as *Pantoea agglomerans*.

risk for post operative pelvic infection. BV has also been associated with complex pelvic inflammatory disease. Therefore, a simple evaluation of the vagina and cervicitis can lead to proper management, resolution of vaginitis and cervicitis, and improve the patient's quality of life.

INDIGENOUS VAGINAL MICROBIOTA

The indigenous vaginal microbiota is complex and not well understood, especially the possible relationships between the bacteria of the vaginal microbiota, as well as the indigenous bacteria and the host. However, the use of molecular microbiologic techniques, such as polymerase chain reaction (PCR) analysis, has enabled a better understanding and shed new insight in understanding the make-up of the indigenous microbiota (Table 60.1). Molecular techniques have revealed the presence of bacteria that have not been found using classical microbiologic culture techniques. The microflora consists of a vast array of facultative and obligate anaerobic bacteria, and new genera and species are being found as part of the indigenous vaginal microbiota. The indigenous vaginal bacteria can be divided into four categories based on which bacterium or bacteria are dominant (Table 60.2). A "healthy vaginal microbiota" is dominated by *Lactobacillus*; however, not all species of *Lactobacillus* are effective in maintaining a "healthy vaginal microbiota." Species of *Lactobacillus* that are important in maintaining a "healthy vaginal microbiota" are those that produce adequate levels of lactic acid, hydrogen peroxide (H_2O_2), and a bacteriocin termed lactocin. These three factors, and there are likely other factors which are unknown at this time, appear

Table 60.2 Categories of the indigenous vaginal microflora

1. Healthy vaginal microflora – *Lactobacillus* dominant
2. Aerobic vaginal microflora – dominated by facultative anaerobes
3. Bacterial vaginosis – dominated by obligate anaerobes
4. Lactobacillosis – overgrowth of *Lactobacillus*

to be significant in maintaining the vaginal environment that is favorable for the growth of *Lactobacillus*. These same factors are hostile to the growth of gram-negative and gram-positive facultative and obligate anaerobic bacteria.

Lactobacillus crispatus, L. jensenii, and *L. gasseri* are the three most common species found in the vagina of women with a "healthy vaginal microflora." Patients with *L. iners*, even in the presence of *L. jensenii* and/or *L. gasseri* appear to have an unstable microflora and are likely to develop "aerobic vaginitis (AVF)" or BV. The direction in which the vaginal microflora will drift and eventually become established appears to be dependent upon whether or not *Gardnerella vaginalis* is present as a member of the indigenous vaginal microbiota.

One mechanism provided by *Lactobacillus crispatus, L. jensenii*, and *L. gasseri* is the production of lactic acid. Lactic acid results in maintaining the vaginal pH < 4.5. This acidic pH favors the growth of *Lactobacillus* and inhibits the growth of facultative and obligate anaerobic bacteria. When lactobacilli are dominant this results in a ratio of lactobacilli to pathogenic bacteria of 1000:1. The concentration of lactobacilli is $\geq 10^6$ bacteria/mL of vaginal fluid. This ratio of lactobacilli to pathogenic bacteria is important when considering a surgical procedure on a patient whose vaginal microflora is dominated either by a gram-positive or gram-negative facultative anaerobe or by obligate anaerobes, i.e. when pathogenic bacteria predominate. When the vaginal microflora is disrupted in such a way, especially in the patient undergoing pelvic surgery, transvaginal ovum retrieval, cesarean section, or who has preterm premature rupture of amniotic membranes leading to delivery of a premature fetus, all such patients are at significant risk for the development of a postoperative infection. Therefore, patients undergoing pelvic surgery who have a *Lactobacillus*-dominant indigenous vaginal microflora are likely to derive benefit from surgical antibiotic prophylaxis because of their risk of infection.

A second mechanism is the production of H_2O_2 by many species of *Lactobacillus*, especially *L. crispatus, L. jensenii*, and *L. gasseri*; most strains

of *L. iners* do not produce H_2O_2. Hydrogen peroxide is toxic to obligate anaerobes because they do not produce catalase. Hydrogen peroxide can be converted to super oxide, which can disrupt DNA. Thus, the production of lactic acid and H_2O_2 appears to work in concert with a third factor, bacteriocin, which is a low-molecular-weight protein that has antibacterial properties. The bacteriocin produced by *Lactobacillus*, known as Lactocin, has been demonstrated to inhibit the growth of *Gardnerella* and *Prevotella* as well as other bacteria.

The cause of an alteration in the indigenous vaginal microflora is unknown. However, one change in the vaginal environment that appears to be instrumental in the disruption of a *Lactobacillus*-dominant indigenous vaginal microflora is a change in the vaginal pH. When the pH rises, growth of *Lactobacillus* slows and when pH is between 4.5 and 5, this appears to be a transitional zone. If *G. vaginalis* is present the microflora is destined to develop into BV. If *Gardnerella* is not present then it may well develop into "aerobic vaginitis." This is an important concept to understand because when the gram-negative bacteria are dominant there is an increase in TNF-α in the vagina. Thus, an inflammatory state is created and conditions such as BV are associated with increased risk of an infection in the upper genitalia tract as well as an increased risk of contracting sexually transmitted diseases, e.g., HIV. This inflammatory response involves the endocervical epithelium, making this tissue more receptive to contracting sexually transmitted organisms. In addition, patients with an altered vaginal microflora, e.g., BV, are at increased risk of developing a postoperative pelvic infection when undergoing pelvic surgery.

BACTERIAL VAGINOSIS

BV can be defined as a vaginal microflora that is dominated by obligate anaerobic bacteria. The diagnosis can be established easily with very little cost to the patient and consuming no more than 5 minutes of the physician's time. The clinical criteria are rather easy to determine (Table 60.3) and differentiate the most common types of vaginitis or vaginosis, and can assist in determining proper management. The patient should be reevaluated 1 to 2 weeks after completing treatment to determine if the pH has returned to the acidic range (pH $>$ 3.8 to $\leqq$ 4.5) and if large bacilli are present. If the pH $\geq$ 5 and microscopic examination of the vaginal discharge does not reveal

Table 60.3 Diagnosis of an altered vaginal microflora

	Healthy	Aerobic vaginitis	Bacterial vaginosis
Bacteria	Lactobacillus	Facultative anaerobes	Obligate anaerobes
Discharge color	White to slate-gray	Dirty-gray to purulent	Dirty-gray
Odor	None	None	Fish-like (Foul)
Microscopic analysis			
Squamous cells	Cytoplasmic membrane easily identified		Clue cells present
	Nucleus easily identified		Nucleus obscured
WBC	<5/hpf	<5/hpf	<5/hpf
Bacteria	Large bacilli	May be one morphotype or multiple morphotypes	Multiple morphotypes

Abbreviations: hpf = high-power field.

the presence of large bacilli, the patient's initial vaginitis or vaginosis can reoccur or a different type of vaginitis can evolve. This can occur if the patient is diagnosed with BV and treated with metronidazole or clindamycin. The antibiotic will suppress the anaerobic bacteria and may suppress lactobacilli, allowing the facultative anaerobes to flourish if the pH is not decreased to $<$ 5.

Mycoplasma and *Ureaplasma* are commonly found to be part of the indigenous vaginal microbiota in patients with a *Lactobacillus*-dominant vaginal microflora, aerobic vaginitis, or BV. *Mycoplasma* and *Ureaplasma* are found in approximately 60% of sexually active individuals. It is not understood how or if these bacteria have a role either in maintaining a healthy vaginal microflora or acting in concert with one or more of the pathogenic bacteria to create an environment that favors the growth of the pathogenic bacteria. Thus, there is much speculation regarding the potential role of *Mycoplasma* and *Ureaplasma*; however, other than nongonococcal and non-chlamydial urethritis, and perhaps cervicitis, treatment should not be initiated for these bacteria.

An organism that has gained significant attention is *L. iners*, which seems to be common in patients with an altered vaginal microflora. In addition, *L. iners* appears to rarely be present when *L. crispatus* is dominant. *L. iners* has been reported

Table 60.4 Treatments for bacterial vaginosis

Metronidazole 500 mg orally twice a day for 7 days, or
Metronidazole gel 0.75%, one full applicator (5 g) intravaginally hs × 7 days, or
Clindamycin cream 2%, one full applicator (5 g) intravaginally hs × 3 days, or
Tinidazole 2 g orally once daily for 2 days, or
Tinidazole 1 g orally once daily for 5 days, or
Clindamycin 300 mg orally twice a day for 7 days, or
Clindamycin ovules 100 mg intravaginally once at hs × 3 days

CDC MMWR, Sexually Transmitted Diseases Treatment Guidelines, December 17, 2010; 59: 1–110.

to be present when *L. jensenii* and *L. gasseri* are dominant. In this latter situation the vaginal microflora appears to be unstable and more easily undergoes shifts in the vaginal microbiota.

BV is made up of a variety of obligate anaerobes which can reach concentrations of $>10^8$ bacteria/mL of vaginal fluid, mainly pathogenic bacteria. Undoubtedly there are facultative anaerobes present but probably fewer than 10^5 bacteria/mL of vaginal fluid. This concentration of bacteria is important because this is an enormous inoculum and can initiate or contribute to significant infection.

Treatments of BV are not very adequate because of the high recurrence rates (Table 60.4). The typical treatments are all designed to suppress the growth of obligate anaerobic bacteria. Treatments may have a suppressive effect on lactobacilli and not suppress the facultative anaerobic bacteria. However, if the pH does not decrease (<4.5) lactobacilli will not grow and either the obligate anaerobic bacteria or facultative anaerobic bacteria will gain dominance. This is the reason that the patient should be re-evaluated within one to two weeks following treatment. The two key observations that are indicative of whether there was resolution or not are: (1) has the vaginal pH returned <4.5, and (2) are large bacilli present. If the pH $\geq$ 5 and no large bacilli are present then patient has not responded in a positive manner. Patients who fail to respond should be referred to a gynecologist who has an interest in vulvovaginal disease.

Patients with BV who have greater than 5 WBCs/40× magnifications (wet prep) should be considered to have an infection and should be evaluated for *Trichomonas vaginalis*, *Chlamydia trachomatis*, and *Neisseria gonorrhoeae*. BV is dominated by gram-negative obligate anaerobes and probably gram-negative facultative anaerobes. The cell wall of gram-negative bacteria contains LPS, the substance that initiates a proinflammatory response. It has been shown that patients with BV have an increased concentration of TNF-α in the vaginal milieu. The increase in TNF-α indicates that BV may not be a condition that initiates a classic inflammatory response, namely a significant increase in WBCs, but is associated with a possible upregulation of the cytokine cascade. This may be significant in patients who develop an infection, e.g., pelvic inflammatory disease, or who are having significant pelvic surgery, placing the patient at significant risk for developing a postoperative pelvic infection.

AEROBIC VAGINITIS

This condition may have a variety of presentations, bacteriologically; that is, dominance can be unimicrobial, e.g., *Streptococcus agalactiae* (group B streptococcus, GBS) or *Escherichia coli* or other unimicrobial vaginitis, or polymicrobial vaginitis. This condition does not resemble BV in that there are no clue cells, often noted as a purulent discharge indicating an inflammatory reaction, and either one bacterial morphotype, e.g., cocci in chains indicating dominance by streptococci or morphologically similar small rods, e.g. *E. coli*, or a variety of morphotypes indicating a polymicrobial condition. Typically the discharge is odorless. Many gynecologists do not advise obtaining a specimen for culture because whatever bacterium or bacteria is recovered is part of the normal vaginal microflora. However, obtaining a culture does assist: (1) in differentiating BV from aerobic vaginitis, (2) in determining which bacterium or bacteria is dominant, and (3) in determining if it is a mixed gram-positive and gram-negative vaginal microbiota. Without determining the microbiology, it would be difficult to administer appropriate treatment. The treatment most frequently administered, without bacteriologic data, is either metronidazole or clindamycin, neither of which is suitable for treating "aerobic vaginitis." Aerobic vaginitis like BV places the patient undergoing pelvic surgery at risk for the development of postoperative pelvic infection. This potential for infection resides in the fact that the inoculum in BV or aerobic vaginitis is extremely high with pathogenic bacteria achieving a concentration $\geq 10^6$ bacteria/mL of vaginal fluid.

Treatment for aerobic vaginitis has not been established. Again, a main factor in determining whether or not *Lactobacillus* is dominant is the vaginal pH. The pH of the vagina in patients with aerobic vaginitis is $\geq$ 5, similar to that seen in

Table 60.5 Treatment of aerobic vaginitis

Orally administer first-generation cephalosporin + intravaginal administered boric acid vaginal capsules (600 mg) twice a day for 14 days

patients with BV. This creates an environment that is unfavorable to the growth of *Lactobacillus* and favorable to the growth of pathogenic bacteria. Since there are no studies to guide treatment regimens, the author will give his recommendations based on logic. The evaluation should begin with determining if the patient's vagina contains appropriate species of *Lactobacillus*, i.e., *L. crispatus, L. jensenii*, and/or *L. gasseri*. If none of these species are present in the patient's vagina restoration of a healthy vaginal microbiota or a *Lactobacillus*-dominant microbiota will not be achieved. If the patient has one or more of these species of *Lactobacillus* present in the vagina, treatment can be instituted either with vaginal boric acid alone or in combination with an antibiotic such as oral first-generation cephalosporin (Table 60.5). Boric acid is administered intravaginally to lower the pH of the vagina and reduce or inhibit the growth of gram-positive and gram-negative pathogenic bacteria. First-generation cephalosporins have a broad spectrum of activity, being active against many gram-positive and gram-negative facultative anaerobic bacteria. Since there is a high concentration of pathogenic bacteria and an extremely low concentration of *Lactobacillus*, the pH of the vagina will be maintained in a range > 3.8 and < 4.5. In order for *Lactobacillus* to grow the pH must be < 4.5 and maintained long enough for *Lactobacillus* to gain a foothold and the growth of pathogenic bacteria to be suppressed. The patient should be re-evaluated within 2 to 3 weeks to determine if the vaginal microbiota has been restored to a *Lactobacillus*-dominant indigenous vaginal microflora.

TRICHOMONAS VAGINALIS VAGINITIS

Trichomonas vaginalis is a sexually transmitted flagellated protozoan that causes significant infection and is transmitted via sexual contact. Trichomoniasis can be symptomatic or asymptomatic and is frequently associated with other sexually transmitted infections (STIs). The clinical presentation can, initially, be mistaken as BV. The pelvic exam should be coupled with a microscopic examination of the vaginal discharge; if WBCs are present (>5 WBCs/40× magnification) and no flagellated protozoa are seen a specimen should be obtained either for culture or PCR analysis for the detection of *T. vaginalis*.

Trichomonas vaginitis typically presents with a copious discharge that is dirty gray to purulent, may or may not have a foul odor, and is often found coexisting with BV. If BV is initially the diagnosis and the microscopic examination reveals a typical picture of BV and WBCs are present, STIs such as *T. vaginalis*, *C. trachomatis*, or *N. gonorrhoeae* should be suspected. Approximately 25% of patients infected with *Trichomonas* have petechiae in the vaginal epithelium and or cervix. Microscopic analysis of the vaginal discharge reveals numerous WBCs, clue cells can be present if there is an overabundance of obligate anaerobic bacteria present, and the squamous epithelial cells are well estrogenized. If the clinical presentation is consistent with a possible *Trichomonas* infection but the protozoan is not identified a specimen should be sent for culture or PCR to determine whether or not the patient is infected with *T. vaginalis*. In general, if a patient has a vaginal discharge and complains of vaginal burning or itching or odor but no pathogen has been identified, a specimen should be submitted to the laboratory for the identification of *T. vaginalis* and *Candida*. US Food and Drug Administration (FDA)-approved tests for the identification of *T. vaginalis* are: OSOM Trichomonas Rapid Test (Genzyme Diagnostics, Cambridge Massachusetts), Affirm VP III (Becton Dickenson, San Jose California), Amplicor (Roche Diagnostic Corp.), APTIMA (ASR, Gen-Probe, Inc.).

The treatment of vaginal trichomoniasis is the administration of oral metronidazole (Table 60.6). Approximately 2% to 5% of the patients will be infected with a low-level resistant strain. Metronidazole intravaginal gel is less effective than orally administered metronidazole because it does not achieve adequate levels in the paravaginal and periurethral glands. It is estimated that metronidazole gel administered intravaginally is <50% effective. There is also a significant rate of reinfection; in one study 17% of treated patients were found to be reinfected. Therefore, the patient's sexual partner should be treated whether or not the partner is symptomatic. The patient should be evaluated within 2 weeks of completing therapy and probably 3 months after the completion of therapy. The patient and her sexual partner should be treated simultaneously and condoms should be used during sexual intercourse and until the first follow-up examination. This will permit evaluation and reduce the chance

Table 60.6 Treatment for *Trichomonas vaginalis* vaginitis

Initial treatment
Metronidazole 2 g orally in a single dose[a], or
Metronidazole 500 mg orally twice daily × 7 days[b]
Treatment for failures or reinfection
Metronidazole 500 mg orally three times a day[b], or
Metronidazole 2 g orally daily for 7 days[a], or
Tinidazole 2 g orally in a single dose[a], or
Tinidazole 500 mg orally daily for 7 days[b], or
Tinidazole 2 g orally daily for 7 days[a]

[a] CDC MMWR Sexually Transmitted Diseases Treatment Guidelines, 2010

[b] Author's recommendations to tinidazole consultation can be obtained and susceptibility testing of *T. vaginalis* isolates can be performed by the CDC (telephone 404–718–4141; http://www.cdc.gov/std).

of reinfection during this initial management of the female patient with vaginal *Trichomonas* infection. A patient suspected of having a resistant strain can be treated by increasing the dose of metronidazole or tinidazole (Table 60.6). Strains of *T. vaginalis* that have low-level resistance tend to respond to tinidazole.

VULVOVAGINAL CANDIDIASIS (VVC)

Vulvovaginal candidiasis (VVC) is a complex condition because approximately 20% of healthy, asymptomatic women have *Candida* as part of their indigenous vaginal microbiota. Therefore, the question that arises when treating women with symptomatic vulvovaginitis is can complete eradication of the yeast be achieved or should complete eradication be a realistic goal? Approximately 75% of women will experience at least one episode of VVC in their lifetime and 40% to 45% will experience two or more episodes in their lifetime. Approximately 10% to 20% will develop complicated VVC and require a detailed evaluation, and 5% will develop chronic or recurrent VVC.

The patient with VVC presents with pruritus of the vulva, external dysuria, pain, swelling of the vulva, and erythema. Signs of VVC are vulva edema, fissures, excoriations, and a vaginal discharge that is white with a consistency that ranges from liquid to pasty; the latter is often described as "cottage cheese-like." Although these signs and symptoms are highly indicative of the presence of VVC other conditions can present with similar signs and symptoms. The diagnosis can be established by performing a microscopic examination (wet prep) of the vaginal discharge and by mixing a second aliquot of the vaginal discharge with a drop or two of 10% potassium hydroxide (KOH). A wet prep must be examined microscopically (best under 40× magnification) to determine that there are no abnormalities of the vaginal discharge. Mixing 10% KOH with vaginal discharge will dissolve all constituents in the discharge except hyphae. Fungal hyphae contain chitin and chitin is resistant to strong alkali. The microscopic appearance of yeast cells are elliptical or pear-shaped cells; some of these yeast cells will have a short hypha projecting from one end of the cell (germ tube), or there will be long branching filaments (hyphae). Determining the vaginal pH can be useful, although a particular pH is not associated with VVC; however, a pH <5 is more commonly associated with VVC than a pH >5. However, candidiasis can also be present in patients with BV, aerobic vaginitis, and trichomoniasis. A patient presenting with clinical symptoms and signs of VVC, a pH <4.5, but for whom the microscopic examination of the vaginal discharge does not reveal candidiasis should have a specimen submitted for culture of yeast, as should the patient whose wet prep reveals the present of yeast. The yeast should be identified to species because nonalbicans species tend to be resistant to the usual antimycotic agents, both prescription and over-the-counter antifungal agents. Patients treated for VVC should be re-evaluated within 2 to 3 weeks following treatment to determine if the patient's signs and symptoms have resolved (clinical cure). If the patient's signs and symptoms have resolved, microscopic examination of the vaginal discharge is not necessary. It is important to remember that 10% to 20% of healthy asymptomatic women harbor *Candida*; because of this it is not possible to eradicate yeast from the vaginal microbiota in all patients. Therefore, isolation and culture of yeast from the vagina is used to determine the species of *Candida* found in the patient's vagina for purposes for enhancing treatment.

Microscopic examination of the vaginal discharge revealing hyphae does not establish the species of *Candida* but can differentiate between the hyphae-producing species of *Candida* and *Candida glabrata*. The latter species does not produce hyphae and presents as budding yeasts. *C. glabrata* is resistant to prescription and over-the-counter antimycotic agents. Treatment of *C. glabrata* can be attempted with standard antimycotic agents but the duration of treatment should be extended to 14 days. Standard treatments for *Candida albicans* range from a single dose to 7-day dosing (Table 60.7). If standard

Table 60.7 Treatment regimens for VVC

Prescription agents
Butoconazole 2% cream 5 g in a single dose intravaginal × 1 dose
Nystatin 100 000 unit vaginal tablet intravaginal, daily for 14 days
Terconazole 0.4% cream 5 g intravaginal for 7 days
Terconazole 0.8% cream 5 g intravaginal for 3 days
Terconazole 80 mg vaginal suppository daily for 3 days
Oral agents
Fluconazole 100 mg tablet administered in a single dose
Over-the-counter agents
Butoconazole 2% cream 5 g intravaginal for 3 days
Clotrimazole 1% cream 5 g intravaginal for 7–14 days
Clotrimazole 2% cream 5 g intravaginal for 3 days
Miconazole:
2% cream 5 g intravaginal for 7 days
4% cream 5 g intravaginal for 3 days
100 mg vaginal suppository daily for 7 days
200 mg vaginal suppository daily for 3 days
1200 mg vaginal suppository daily for 1 day
Tioconazole 6.5% ointment 5 g intravaginally in a single application

CDC Sexually Transmitted Diseases Treatment Guidelines 2010.

treatment fails to resolve VVC consider that the species is other than *C. albicans*. If the patient was compliant in administering intravaginal medication or taking a complete course of oral medication, the yeast should be isolated, identified to species and if a species other than *C. albicans* is present, alternative treatment should be administered (Table 60.7). If treatment with the typical prescription and over-the-counter antimycotic agents using prolonged dosing (14 days) fails, non-fluconazole azole drugs can be administered, e.g., boric acid gelatin capsules (600 mg) administered intravaginally daily for 2 weeks. The patient's vagina can be painted with gentian violet dye, weekly until the patient's symptoms have resolved. Another approach is to administer amphotericin B (10%) vaginal suppositories twice daily for 10 days. Patients with recurrent VVC should be screened for diabetes and HIV.

CERVICITIS

Cervicitis is not a simple condition but can be a rather complex condition that can be difficult to resolve. It is now known that some bacteria are capable of forming a biofilm on tissue, e.g., *N. gonorrhoeae* and *G. vaginalis*. The two most common causes of cervicitis are due to *C. trachomatis* and *N. gonorrhoeae*. One significant problem is treating the patient with cervicitis not due *to C. trachomatis* and *N. gonorrhoeae* because the etiology is often not known. Therefore, when a patient treated for cervicitis not caused by *C. trachomatis* or *N. gonorrhoeae* fails to achieve resolution the condition becomes chronic, and more invasive treatments are undertaken, e.g., cryosurgery or laser ablation. Other bacteria that may cause cervicitis are those bacteria associated with BV, e.g., *G. vaginalis* and *Mycoplasma genitalium*.

A biofilm is a complex matrix produced by bacteria and can contain a variety of bacteria. Biofilms have been associated with several recalcitrant infections involving *E. coli*, *Helicobacter pylori*, and *Pseudomonas aeruginosa*. Recently, *G. vaginalis* and *Atopobium vaginae*, two bacteria commonly associated with BV, have been shown to form a biofilm on the vaginal epithelium of women with BV. This finding could be significant in understanding why some patients with BV fail to respond to treatment and why some patients develop persistent cervicitis, even after cryosurgery or laser ablation. The matrix of biofilms forms a protective covering for the bacteria that dwell within the matrix so that antibiotics, WBCs, immunoglobulin, and antibodies are unable to penetrate the matrix and reach the bacteria.

Diagnosis

The diagnosis of cervicitis is based on the following findings:

1. Purulent or mucopurulent endocervical discharge, bleeding easily induced by gentle palpation of the endocervical epithelium with a cotton-tipped applicator
2. Cervical bleeding associated with sexual intercourse
3. Hypertrophy of the endocervical columnar epithelium associated with detectable or undetectable infection.

The diagnosis of cervicitis is often overlooked because it may be subtle. One indicator of cervicitis is the presence of >10 WBC/40× magnification in the absence of *T. vaginalis* vaginitis. An endocervical specimen should be obtained and submitted for the detection of *C. trachomatis* and *N. gonorrhoeae*. Specific tests for *M. genitalium*, *Ureaplasma urealyticum*, and *Ureaplasma parvum* are not commercially available. Patients found to have chronic cervicitis should also be evaluated for upper genital tract infection, i.e., endometritis and salpingitis. HSV can cause cervicitis but often it is not clinically apparent. In patients with cervicitis and risky sexual practices the workup should include testing for *C. trachomatis*, *N. gonorrhoeae*, and HSV. The data supporting

Table 60.8 Treatment for cervicitis

C. trachomatis
Azithromycin 1 g orally in a single dose, or
Doxycycline 100 mg twice a day orally for 7 days, or
Erythromycin base 500 mg orally four times a day for 7 days, or
Erythromycin ethylsuccinate 800 mg four times a day for 7 days, or
Levofloxacin 500 mg orally once a day for 7 days, or
Ofloxacin 300 mg orally twice a day for 7 days
N. gonorrhoeae
Ceftriaxone 250 mg IM in a single dose, or
Cefixime 400 mg orally in a single dose, or
Azithromycin 1 g orally in a single dose, or
Doxycycline 100 mg orally twice a day for 7 days

CDC Sexually Transmitted Diseases Treatment Guidelines 2010.

testing for herpes simplex as a cause for cervicitis are not available but (author's opinion) the workup should include all three microorganisms. Patients known to have contracted genital HSV, even though they do not have an acute outbreak, could be shedding virus asymptomatically and, therefore, an endocervical specimen submitted for HSV detection could be positive and responsible for chronic cervicitis.

Treatment

The treatment of cervicitis due to *C. trachomatis, N. gonorrhoeae*, and *H. simplex* requires two different approaches. *C. trachomatis* and *N. gonorrhoeae* are bacteria and can be treated with antibiotics. If either or both these bacteria are documented as the etiology of the patient's cervicitis, then the patient's sexual partner should be treated at the same time. The patient should be re-evaluated for bacteriologic eradication following treatment. Treatment of HSV does not result in eradication of the virus but can suppress the virus and result in resolution of the cervicitis. The sexual partner of a patient who has been found to be positive for HSV should be evaluated for acute HSV infection. If the sexual partner does not have evidence for present or past HSV infection, antiviral suppressive therapy should be administered to the patient that has a documented HSV infection. If treatment is initiated prior to having laboratory confirmation of the specific etiology, treatment should be instituted against *C. trachomatis* and *N. gonorrhoeae* (Table 60.8). It is preferred to initiate treatment when the tests for *C. trachomatis* and *N. gonorrhoeae* have confirmed the presence of these two sexually transmitted diseases (STDs). Treating the patient based on clinical findings will prevent spread of the infection to the sexual partner or partners. The patient should be advised to refrain from sexual contact until the tests results are known. If either *C. trachomatis* or *N. gonorrhoeae* or both has been detected the patient should be notified and advised that her sexual partner or partners should be informed and treated.

Quinolone resistance among *N. gonorrhoeae* strains is widely disseminated throughout the United States. Therefore in 2007, the Centers for Disease Control and Prevention (CDC) recommended that quinolones not be used to treat *N. gonorrhoeae* infections. Resistance develops rapidly to macrolides and therefore these agents should not be used empirically for the treatment of gonococcal cervicitis. Patients treated with quinolones or doxycycline or azithromycin should have: (1) confirmation of the presence of *C. trachomatis* and/or *N. gonorrhoeae*, (2) isolates of *N. gonorrhoeae* tested for resistance against cephalosporins, especially ceftriaxone and cefepime, doxycycline, levofloxacin, ofloxacin, and azithromycin. Resistance to cephalosporins has been rare in the United States but has been reported in Asia. The CDC reported that between 1987 and 2008 only four isolates have been resistant to ceftriaxone and 48 isolates have been found to have decreased susceptibility to cefepime. Therefore, patients treated for known gonococcal cervicitis should be asked about travel to the Middle East and Hawaii. They should also be queried about the travel of their sexual contact(s).

Follow-up

The CDC does not recommend follow-up test of cure for those patients treated with the recommended antibiotic regimens, except if the patient is pregnant. However, the author recommends that the patient indeed have follow-up and test-of-cure testing if the patient has one or more of the following:

1. an STD infection in the past,
2. a sexual partner who has had a previous STD,
3. multiple sexual partners, and
4. has not received ceftriaxone as part of the treatment regimen.

Since most recurrent infections occur secondary to reinfection, a detailed sexual history should be obtained to determine the risk of sexual behavior. In addition, patients found to have one or more STDs should be screened for syphilis, HIV, HSV, HPV, and hepatitis B and C.

SUMMARY

Patients with vaginitis should be evaluated for cervicitis. The presence of >5 WBCs/40× magnification in the vaginal discharge and the absence of a pathogen, e.g., *T. vaginalis*, suggests the presence of cervicitis. Cervicitis can be caused by a variety of microorganisms and some, such as *N. gonorrhoeae* and *G. vaginalis*, can produce a biofilm. The presence of a biofilm creates a problem for the physician treating the patient because the biofilm prevents antibiotics achieving adequate levels within the matrix to eradicate the bacteria. Biofilm typically contains more than one genus and this complicates the treatment of cervicitis. Clinical findings associated with cervicitis are hypertrophy of the endocervical columnar epithelium, which bleeds easily when touched, and the presence of endocervical mucopus. Inflammation of the cervix potentiates acquisition of STDs, especially HIV. Patients who have an STD, such as trichomoniasis, *C. trachomatis*, and *N. gonorrhoeae*, should have a complete evaluation for the possible existence of other STDs. In addition, the patient should be evaluated for HPV. Patients who are positive for the strains associated with cancer need to be educated about the potential for the development of cervical, vaginal, or vulva cancer. A plan of management should be presented to the patient, emphasizing prevention. Thus vaginitis and cervicitis are not minor conditions but can have far reaching effects on the patient's well being.

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61. Epididymo-orchitis

Suyin Chi and Thomas Fekete

INTRODUCTION

Infectious and inflammatory processes involving the contents of the scrotum are uncommon. They are usually easy for patients to identify because they cause symptoms of pain and swelling. However, most clinicians other than urologists are unfamiliar with the range of problems that can affect the testis and epididymis and rarely see boys or men with orchitis or epididymitis.

ANATOMY/DEFINITION

The epididymis is a tightly coiled tubular structure on the posterior aspect of the testes that connects the efferent ducts of each testis to the vas deferens. The three regions of the epididymis – the head, body, and tail – serve as sequential sites for sperm transport, maturation, and storage.

Epididymitis involves inflammation or infection of the epididymis, usually accompanied by pain and swelling. It is the most common cause of intrascrotal inflammation. Acute epididymitis is characterized by symptoms lasting for less than 6 weeks, whereas chronic epididymitis involves symptoms persisting for 3 months or longer. Orchitis, or inflammation of the testes, is less common than epididymitis, and rarely occurs in isolation except in cases of viral disease. However, infection of the epididymis can spread to the adjacent testis making it difficult to distinguish the clinical entities involving them, thus the term epididymo-orchitis is used to capture these combined inflammatory processes. In patients with acute epididymo-orchitis, inflammatory responses in adjacent structures, such as the seminal vesicles, can occur and can lead to abscess formation.

EPIDEMIOLOGY

Overall, studies suggest that acute epididymo-orchitis is relatively uncommon. A prospective Canadian study demonstrated that 0.9% of men who presented to outpatient urology clinics in 2004 had epididymitis, which was less common than prostatitis or interstitial cystitis.

Acute epididymo-orchitis tends to involve only one side at a time, with right and left being equally susceptible. Bilateral inflammation is exceedingly rare. The average age of patients in the prospective Canadian study was 41 years. Other studies report variable mean ages, but the incidence of epididymitis tends to peak in younger, sexually active men, with the majority of cases occurring between 20 and 39 years.

PREDISPOSING FACTORS

The exact pathogenesis of epididymitis has not been clearly elucidated. Epididymo-orchitis is usually associated with a sexually transmitted infection, urinary tract infection, or systemic infection. It is presumed that infecting organisms usually reach the epididymis via retrograde extension from the prostate or seminal vesicles, but hematogenous and lymphatic spread may also occur. It has been proposed that high voiding pressures may result in urethrovasal reflux. Acute epididymitis is rare in prepubescent boys and, when present, is usually associated with abnormalities of the urinary tract, including vesicoureteral reflux.

Urologic factors – including lower urinary tract obstruction from benign prostatic hyperplasia (BPH), prostate cancer, or urethral stricture – have been associated with epididymitis in older patients, and the presumption is that they lead to infection via the ascending route or by not permitting normal drainage of the proximal internal genital structures. Invasive prostate procedures, including biopsy, transurethral resection, brachytherapy, laser prostatectomy, and radical prostatectomy have been associated with epididymitis; reported rates are approximately 1% to 2%. No controlled studies have been conducted to evaluate the efficacy of prophylactic antibiotics

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for these procedures. Other mechanical insults such as direct trauma or pressure (e.g., from bicycle riding) have been associated with epididymitis even after vasectomy. Vasectomy itself has been associated with persistent tenderness and a nodular presence in the scrotum – presumably the result of sperm extravasation ("sperm granuloma").

ETIOLOGY

Infectious

In children below the age of sexual activity, the microbial flora of epididymitis is a mix of skin and urinary flora. Among sexually active adolescents and men less than 35 years old, acute epididymitis is likely associated with a sexually transmitted infection caused by *Chlamydia trachomatis* or *Neisseria gonorrhoeae*. Mycobacteria and ureaplasma are isolated more frequently in younger men with chlamydial epididymitis than in other infectious causes of epididymitis, although the role they play in acute epididymitis is unclear. Gram-negative enteric organisms tend to cause epididymitis in older men, although sexually transmitted infections are still common.

Many other less common infectious causes of acute epididymitis have been reported (see Table 61.1). Mumps, a paramyxovirus, is a well-known cause of orchitis, but epididymitis may develop as a complication. Although the overall incidence of mumps orchitis has fallen dramatically with the widespread use of the MMR vaccine, there have been reported outbreaks in the United Kingdom and United States since 2000. They often occurred in post-pubertal men in high density settings, such as college dorms and camps, where the virus can spread through direct contact and respiratory droplets. Up to 40% of post-pubertal men with mumps can develop unilateral or bilateral orchitis with some degree of testicular atrophy from inflammation and edema, although the risk of sterility is low. Men with a history of no vaccination or only having received a single dose of the vaccine were at higher risk of developing orchitis as a complication of mumps.

Mumps orchitis is a self-limited disease and the treatment is supportive with bed rest, scrotal support, and nonsteroidal anti-inflammatory drugs (NSAIDs). The role of steroids is unclear in preserving testicular function. Vaccination remains the best means to prevent infection, although it is not 100% effective. Chronic epididymo-orchitis has been described with infections causing granulomatous disease, such as tuberculosis and brucellosis, as well as noninfectious causes, such as medication and generalized inflammatory disorders. Tuberculosis epididymitis is rare and difficult to diagnose. Seeding of the epididymis may be due to hematogenous spread. Patients may present with a painful or painless scrotal mass or swelling. Urinalysis usually shows sterile pyuria, but secondary bacterial infection may be present. Diagnosis is made via identification of *Mycobacterium tuberculosis* from the urine. Because few organisms are present in the urine, direct smears are usually negative and sensitivity of cultures may be only 50%. The sensitivity of urinary polymerase chain reaction (PCR) has been reported as 84% to 97%, although this test is not widely available.

Table 61.1 Causes of acute epididymo-orchitis

Cause	Organism/disease
Sexually acquired	
Major	*Chlamydia trachomatis*
	Neisseria gonorrhoeae
Other	*Ureaplasma urealyticum*
	?Mycoplasma genitalium
Associated with bacteriuria	
Major	*Escherichia coli*
	Proteus spp.
	Klebsiella pneumoniae
	Pseudomonas aeruginosa
Other	*Haemophilus influenzae* type b
	Salmonella spp.
	Staphylococci
	Streptococci
Other infections	
Bacterial	*Mycobacterium tuberculosis*
	Brucella spp.
	Nocardia asteroides
Fungal	*Blastomyces dermatitidis*
	Histoplasma capsulatum
	Coccidioides immitis
	Candida albicans
	Candida glabrata
Viral	Mumps
	Mumps vaccine
	Cytomegalovirus (in HIV)
Parasitic	*Schistosoma haematobium*
	Wuchereria bancrofti filariasis
Noninfective causes	
	Amiodarone therapy
	Vasculitis
	Behçet's disease
	Polyarteritis nodosa
	Henoch–Schönlein purpura
	Sarcoidosis
Idiopathic	

BCG-induced tuberculous epididymitis, or BCGitis, is caused by therapy with bacille Calmette–Guérin used to treat bladder cancer. This attenuated strain of *Mycobacterium bovis* is instilled into the bladder to cause an inflammatory response against the tumor cells. In rare cases, it has been reported to cause granulomatous epididymo-orchitis. Patients develop necrotic areas in the epididymis that may spread to the testes, causing scrotal enlargement, with or without pain. Ultrasound reveals a heterogeneous, hypoechoic appearance of the epididymis.

Brucella is a relatively common cause of epididymo-orchitis in endemic areas, particularly in the Mediterranean and Middle Eastern countries and can occur in 2% to 20% of patients with brucellosis. Most patients have acute, febrile brucellosis when epididymo-orchitis occurs. Unilateral scrotal pain and swelling are the most common symptoms, but dysuria and urinary frequency can also be present. Leukocytosis is often absent. Patients may have a history of occupational contact with animals or consuming unpasteurized milk or cheese. Urinalysis and culture are often normal, and blood cultures for brucella are positive in about 50% of cases. Biopsy can reveal granulomatous orchitis. History and serologic testing for brucellosis may aid in diagnosis. Antibiotic therapy for brucellosis is usually effective.

Histoplasmosis has been reported as a very rare cause of granulomatous epididymo-orchitis. Scrotal swelling is often unilateral and may precede respiratory and systemic symptoms. Surgical intervention and systemic antifungal therapy may be treatment options.

Distinct etiologies of epididymo-orchitis have been reported in patients with human immunodeficiency virus (HIV) infection and in transplant recipients receiving immunomodulating drugs. Epididymo-orchitis with bacteremia has been caused by *Haemophilus influenzae* and *Elizabethkingia* (formerly *Chryseobacterium* and *Flavobacterium*) *meningoseptica*. *Plesiomonas shigelloides* infection has become recognized as an opportunistic pathogen; a case of bacteremia and epididymo-orchitis was reported in a patient with HIV and chronic hepatitis C. *Nocardia* infection is a rare cause of epididymo-orchitis and usually involves other organs at the same time. Cytomegalovirus was isolated from the urine and semen of a patient with HIV infection who had epididymitis that was refractory to antibiotics. HIV infection may also increase the risk of genitourinary tuberculosis (TB) with involvement of scrotal contents, although such infections are more often seen in settings where patients are already at higher risk for TB.

Noninfectious

Although most cases of epididymo-orchitis are of an infectious etiology, several noninfectious causes have been described. Amiodarone can cause a reversible epididymitis on rare occasions. Epididymitis has been reported in patients with polyarteritis nodosa (PAN); one case report has described bilateral epididymitis that did not respond to antimicrobial therapy as the presenting symptom of PAN. Epididymitis is a rare manifestation of Behçet's disease and may be associated with more severe disease. Other systemic vasculitides, including Henoch–Schönlein purpura, have been associated as well. Sarcoidosis can affect the genitourinary system in 5% of patients. The etiology of some cases of acute epididymitis remains "idiopathic," but advances in microbiology and molecular diagnostic techniques may elucidate specific infectious causes in the future.

CLINICAL FEATURES AND DIFFERENTIAL DIAGNOSIS

Exquisite unilateral testicular tenderness, scrotal edema, and swelling occur early and are often the dominant features of epididymo-orchitis. Fever, rigors, and leukocytosis may be present. In a retrospective study of 121 patients with acute epididymitis, dysuria was present in 33% of patients, urethral discharge was present in only 5%, and positive urine cultures were found in less than 25% of patients. Urethritis or pyuria, in the absence of bacteriuria, is usually associated with sexually transmitted acute epididymitis. Bacteriuria and irritative voiding symptoms – such as dysuria, frequency, and urgency – tend to be associated with urinary obstruction and/or structural urogenital disease in older men.

The differential diagnosis of an acutely painful, swollen scrotum includes acute epididymo-orchitis, torsion of the spermatic cord, torsion of testicular appendages, testicular tumor, incarcerated hernia, acute hydrocele, or trauma. Although these entities have overlapping signs and symptoms, identifying testicular torsion is important because it necessitates immediate surgical intervention. Testicular torsion cannot be excluded based on physical examination

alone, but the absence of a cremasteric reflex in a patient with acute, unilateral scrotal tenderness suggests the diagnosis. Elevation of the scrotum usually relieves the pain of acute epididymitis but not torsion.

DIAGNOSTIC WORKUP

Evaluation of suspected epididymo-orchitis is initially based on clinical suspicion of disease from patient complaints of pain and/or swelling within the scrotum. Although referred scrotal pain from other pelvic processes can occur, the first challenge is ruling out testicular torsion. The distinction between torsion and inflammation or infection needs to be made quickly, particularly in prepubescent boys, because untreated torsion can jeopardize the testis. Expert urologic consultation may be urgently required. There are two useful noninvasive tests for blood flow to the testes. Radionuclide scanning is sensitive but not routinely available; markedly increased perfusion of technetium is associated with infection, whereas perfusion is never increased with testicular torsion. Color Doppler ultrasound showing an enlarged, thickened epididymis with normal to increased testicular blood flow is 70% sensitive and 88% specific in patients with epididymitis. In torsion, the ultrasound reveals a normal-appearing testicle with decreased blood flow and is 82% sensitive and 100% specific. C-reactive protein (CRP) may be helpful in distinguishing torsion vs. infection, as patients with epididymitis have elevated CRP (96% sensitive and 94% specific). Surgical exploration should not be delayed if diagnosis remains unclear.

If torsion is not considered likely, the best initial diagnostic study is urine collection for urinalysis and culture. A first-void specimen should be collected if a sexually transmitted infection is thought to be the etiology, whereas a midstream specimen is recommended if the cause is more likely due to an enteric pathogen. If urethral secretions are present, Gram stain is highly sensitive and specific for diagnosing urethritis (>5 leukocytes/oil-immersion field) and can establish gonococcal infection by demonstrating leukocytes containing intracellular gram-negative diplococci. Nucleic acid amplification tests of urine specimens are highly sensitive for *N. gonorrhoeae* and *C. trachomatis* and have largely supplanted urethral cultures to diagnose these infections.

In patients who do not respond to empiric therapy, particularly in those who have unique risk factors based on host immune status, travel history, or geographic location, a more exhaustive workup should be performed in conjunction with urologic consultation. This may include further imaging, additional cultures (e.g., acid-fast bacillus [AFB] and fungal cultures), and direct sampling of the epididymis in some cases.

TREATMENT

Treatment includes antimicrobial therapy in combination with analgesics, bed rest, and scrotal elevation. Empirical therapy should be initiated before laboratory results are available. For acute epididymitis likely caused by *N. gonorrhoeae* or *C. trachomatis* infection, the Centers for Disease Control and Prevention (CDC) current recommendations should be sought as resistance patterns are changing rapidly. In the 2012 update to the guidelines for the treatment of sexually transmitted diseases, the CDC recommends dual therapy with ceftriaxone 250 mg IM in a single dose plus either azithromycin 1 g as a single dose or doxycycline 100 mg orally twice a day for 7 days. Azithromycin is preferred over doxycycline due to ease of administration and higher rates of resistance to tetracyclines. Oral cefixime alone is no longer recommended due to increasing rates of resistance and concern for use contributing to the development of resistance to ceftriaxone. If cefixime is to be used, a 400 mg single dose should be given in conjunction with either oral azithromycin or doxycycline with a test of cure in 1 week. For patients with cephalosporin and/or tetracycline allergies, azithromycin 2 g as a single dose can be used with test of cure in 1 week. Sex partners of patients with epididymitis caused by *N. gonorrhoeae* or *C. trachomatis*, who had contact within 60 days of symptoms, should be referred for evaluation and treatment. Although it is prudent to counsel patients that sexual intercourse should be avoided until they and their sex partners have completed therapy and are without symptoms, the optimal duration of this period of abstinence has never been studied.

When non-sexually transmitted disease (STD) infection is suspected, treatment for epididymitis mirrors that for urinary tract infection (UTI) in men. Because there are no controlled trials of epididymitis treatment, it is not known which antibiotics are most effective. Fluoroquinolones have good oral bioavailability, spectrum of activity, and penetration of genitourinary tissues and have been widely used for prostatitis and UTI in men; by extension, they have been proposed as

drugs of first choice for epididymitis. The CDC recommends levofloxacin, 500 mg orally once daily for 10 days, but antibiotic choice and duration should be tailored to the specific pathogen if one is cultured. Other agents active against uropathogens (e.g., trimethoprim–sulfamethoxazole, amoxicillin) can be tried in the event of fluoroquinolone failure or intolerance.

Patients should respond clinically in the first few days of treatment, and failure to improve may indicate abscess, tumor, vasculitis, or fungal, mycobacterial, or an uncommon and resistant bacterial pathogen. As an example, investigators (Kashiwagi *et al*.) described three cases of acute epididymitis-orchitis due to *Pseudomonas aeruginosa* infection treated with several weeks of antibiotic therapy, and at the time of orchiectomy, an abscess was discovered. Thus, persistence of symptoms should prompt a more exhaustive workup.

CONCLUSION

Diseases of the epididymis and testis are uncommon compared to other andrologic and urinary problems of boys and men. However, their management can be challenging because tests for a specific etiologic diagnosis are often invasive and hard to perform in the office or even the emergency room. Once the diagnosis of testicular torsion has been ruled out, the management of epididymal disease can begin with a limited set of diagnostic tests and an empiric trial of antibiotics. For patients with more complex or chronic disease, comanagement with a urologist can allow for access to better clinical and diagnostic tools. Uncommon problems such as noninfectious diseases related to connective tissue disease or vasculitis can be challenging in patients who do not already have such a diagnosis. Unusual or exotic infections such as brucellosis or regional fungal infection should be considered in patients with the appropriate travel history. The only drug that has been strongly associated with epididymitis is amiodarone. Pure orchitis is sometimes viral and should be considered in any male with mumps (particularly if mumps virus is known to be in circulation or if there is an outbreak of febrile disease with parotitis). If patients do not respond to initial therapy, further workup should be pursued.

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62. Genital ulcer adenopathy syndrome

Allan Ronald

The control and prevention of genital ulcer disease (GUD) is an important public health priority. Ulcerative lesions may produce significant local genital pain, some pathogens are transmitted from mothers to their infants, and genital lesions increase the risk of human immunodeficiency virus (HIV) acquisition and transmission during sexual intercourse. Table 62.1 lists the infectious and noninfectious etiologies that may produce genital ulcerations with or without adenopathy. The most commonly transmitted GUD diagnosis and etiologies are syphilis (*Treponema pallidum*), herpes simplex (HSV-1 and-2), chancroid (*Haemophilus ducreyi*), lymphogranuloma venereum (LGV), L1, L2, and L3 serovars of *Chlamydia trachomatis*; and granuloma inguinale or donovanosis (*Calymmatobacterium granulomatis*). Trauma, erosive balanitis, and fixed drug eruptions are the most common nontransmissible causes of GUD. Neoplasia, fungi, and mycobacteria, if suspected, should be excluded by biopsy. Because of the limitations of diagnostic tests, a specific etiology is obtained in only 50% to 80% of patients.

Major geographic variation exists in the etiology and prevalence of GUD (Table 62.2). In Europe and North America, fewer than 10% of patients who present to sexually transmitted disease (STD) clinics have a genital ulcer compared with 20% to 40% of patients presenting to similar clinics in Africa and Asia. Herpes simplex virus (HSV) is the most common cause of genital ulcerations in Europe and North America, whereas chancroid has been the common cause elsewhere. However, herpetic ulcers are now more common, particularly in patients coinfected with HIV, whereas chancroid has largely disappeared. LGV is endemic in some areas of the tropics and has reappeared as an epidemic among men in developed countries who have sex with men, many of whom are HIV positive. Donovanosis was endemic in New Guinea, India, and Southern Africa but has become rare.

Table 62.1 Etiologies of genital ulcer disease

Infectious
Bacterial
Haemophilus ducreyi (chancroid)
Treponema pallidum (syphilis)
Chlamydia trachomatis (lymphogranuloma venereum)
Calymmatobacterium granulomatis (donovanosis)
Balanitis (often polymicrobial but *Candida albicans* is often present)
Viral
Herpes simplex
Varicella zoster[a]
Epstein–Barr virus
Cytomegalovirus[a]
Parasitic
Sarcoptes scabiei[a]
Phthirus pubis[a]
Entamoeba histolytica[a]
Trichomonas vaginalis[a]
Noninfectious
Trauma
Fixed drug eruptions
Pyoderma gangrenosum[a]
Behçet's disease[a]
Reiter's syndrome[a]
Wegener's granulomatosis[a]
Neoplasms[a]
Unknown

[a] Unusual.

Table 62.2 Geographic variation in the prevalence of genital ulcer diseases

	Southeast Asia/India	Africa	North America/ Europe
Chancroid	+/–	+/–	+/–
Syphilis	+++	+++	++
Genital herpes	++++	++++	++++
Lymphogranuloma venereum	+	+	+
Donovanosis	+/–	+/–	+/–

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Table 62.3 Clinical characteristics of genital ulcer adenopathy syndromes

	Syphilis	Herpes simplex virus	Chancroid	Lymphogranuloma venereum	Donovanosis
Incubation period	9–90 d	2–7 d	1–14 d	7–21 d	8–80 d
Primary lesion	Papule	Vesicle	Papule or pustule	Papule, pustule, or vesicle	Papule
Number of lesions	Usually solitary	Multiple	Multiple	Usually solitary	Variable
Classical ulcer characteristics					
Size (mm)	5–15	1–10	2–20	2–10	Variable
Margins	Well demarcated Elevated Round or oval	Erythematous	Ragged, irregular Undetermined	Elevated Round or oval	Variable Elevated, irregular
Depth	Superficial or deep	Superficial	Excavated	Superficial or deep	Elevated
Base	Red, smooth, nonpurulent	Red, smooth, serous discharge	Purulent exudate	Variable	"Beefy" red, rough
Induration	++	–	–	–	++
Pain	–	++	++	±	–
Lymphadenopathy	++[B]	++[B]	++[U]	++[U]	–[P]
Characteristics of lymphadenopathy					
Consistency	Firm	Firm	Fluctuant	Fluctuant	–
Tenderness	–	++	++	++	–

[B] Bilateral;[U] unilateral;[P] pseudolymphadenopathy.

Syphilis persists as a global pandemic that has recently reappeared with large outbreaks among men who have sex with men. Males who are circumcised have a markedly reduced probability of acquiring chancroid and to a lesser extent of acquiring herpes or syphilis following heterosexual intercourse.

CLINICAL PRESENTATIONS

Clinical features of GUD are listed in Table 62.3. The incubation period is usually less than 1 week for genital herpes and chancroid, 1 to 3 weeks for LGV, and 2 to 6 weeks for syphilis and donovanosis. Depending on the etiology, the initial lesion can be a papule, pustule, or vesicle which erodes to form an ulcer. In men the ulcers are often located on the coronal sulcus but may also be found on the glans, prepuce, and shaft of the penis or less often on the scrotum or surrounding skin. Herpes and chancroid have a predilection for involving the frenulum. In women, the ulcers may occur on the labia, in the vagina, on the cervix, on the fourchette, or on the perianal area. Perianal and intrarectal ulcers are common among men who have sex with men.

Genital herpes

HSV-1 is transmitted primarily by oral contact and in the developing world, the initial infection occurs in infancy and genital HSV-1 infections are uncommon. However, in the developed world most adolescents have not acquired HSV-1, and this virus is frequently transmitted sexually particularly with oral–genital sex. In all societies, HSV-2 is almost always transmitted by sex. Genital herpes due to both viruses presents as multiple, small vesicles that rapidly become superficial ulcers with erythematous margins. Urethral, gynecologic or cutaneous symptoms may predominate depending on the site of vesicles. Systemic symptoms of fever, myalgias, and headache can occur with an initial infection. A prodrome of paresthesias 12 to 48 hours before the appearance of vesicles is often reported with recurrences. Painful lymphadenopathy can be present. Following the initial infection, both HSV-1 and HSV-2 remain latent in the sensory ganglion but recur unpredictably. Recurrences are usually less severe. However, they tend to be severe and persistent in HIV-infected individuals and large, painful, often single, ulcers are common, particularly in the perianal area.

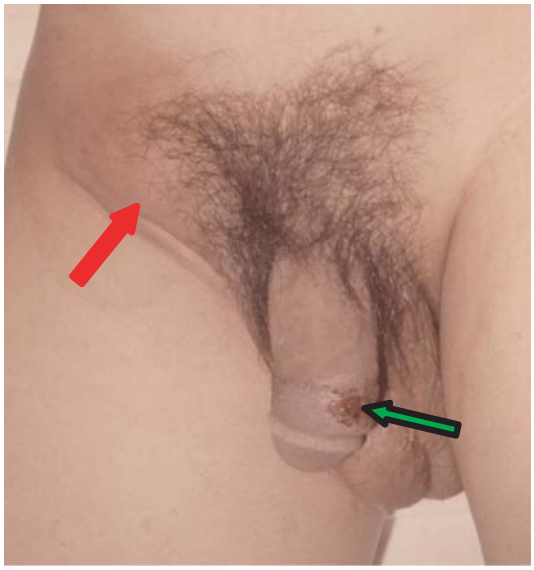

Figure 62.1 Chancroid; note penile lesion (*green arrow*) and inguinal adenopathy (*red arrow*). (Public Health Image Library; content provider CDC/Susan Lindsley.)

Syphilis

The ulcer of primary syphilis is classically solitary, painless or minimally tender with elevated, well-demarcated margins and an indurated nonpurulent base. Multiple ulcers are common in women. Lymphadenopathy, if present, is usually bilateral with firm, nontender nodes. Secondary syphilis can have many cutaneous features, including condyloma and superficial ulcers.

Chancroid

Chancroid typically produces painful, excavated ulcers with irregular, undetermined margins and a purulent base (Figure 62.1). The ulcers can be superficial and may resemble herpetic ulcers. Approximately 50% of the patients will develop painful inguinal lymphadenopathy, which can be unilateral. Lymph nodes may become fluctuant (buboes) and rupture. Untreated ulcers may persist for months and heal with scarring.

Lymphogranuloma venereum

The ulcer of LGV is transient, usually superficial and painless. It precedes the development of inguinal lymphadenopathy by 7 to 30 days and fewer than a third of the patients recall having had an ulcer. The lymph nodes are tender and may become fluctuant with eventual rupture and formation of draining sinuses. A "groove" sign may be present if nodes above and below Poupart's ligament are involved. Women and homosexual men may have involvement of perianal and perirectal tissues and present with proctitis. Complications of untreated infection include genital elephantiasis, rectal strictures, and perianal fistulas. Other manifestations include meningoencephalitis, hepatitis, erythema nodosum, and erythema multiforme.

Donovanosis

Patients present with a slowly progressive painless ulceration of the genital area characterized by heaped-up granulomatous tissue. Local extension, healing, and fibrosis may occur simultaneously. Lymphadenopathy is unusual, but "pseudobuboes" caused by subcutaneous extension of the granulomatous process into the inguinal area are common. Systemic spread with involvement of liver, thorax, and bones has been reported but is rare.

LABORATORY DIAGNOSIS OF GUD

Clinical diagnosis of GUD is imprecise because of overlap between the clinical syndromes, the presence of mixed infections, and atypical presentations. Because of these limitations, the diagnosis must be confirmed whenever possible using the relevant laboratory tests (Table 62.4). Specimens should be collected for *H. ducreyi*, *C. trachomatis*, and herpes simplex cultures and, if available, DNA identification with polymerase chain reaction (PCR). If possible, a dark-field examination should be performed in all patients presenting with GUD unless classical vesical lesions in clusters provide definite evidence of herpes genitalis. The ulcer base is washed with saline, dried with a cotton gauze, and squeezed between the thumb and forefinger until an exudate appears. This can be collected directly onto a coverslip for dark-field microscopy. Vesicles and pustules should be aspirated with a fine-gauge needle or de-roofed and swabbed for viral culture. Fluctuant lymph nodes should be aspirated for *H. ducreyi* and *C. trachomatis* culture. Both *Treponema pallidum* particle agglutination (TPPA) and non-treponemal rapid plasma reagin (RPR), serologic tests should be obtained in all patients with GUD to exclude syphilis. LGV diagnosis is confirmed by PCR or by rising antibody titers or a single titer of 1:64 by complement fixation or 1:512 by microimmunofluorescence.

Table 62.4 Recommended tests for diagnosing genital ulcer diseases

	Recommended tests	Other tests
Chancroid	Culture	Gram stain/PCR
Syphilis	Dark-field examination Direct fluorescent antibody test Serology (e.g., RPR/VDRL, FTA-ABS, MHA-TP)	PCR
Genital herpes	Viral culture	Antigen detection (ELISA), PCR, Serology
Lymphogranuloma venereum	PCR	*Chlamydia* culture Serology (complement fixation, microimmunofluorescence)
Donovanosis	Giemsa or Wright stains of tissue smears Histopathology	

Abbreviations: PCR = polymerase chain reaction; RPR = rapid plasma reagin; VDRL = Venereal Disease Research Laboratories; FTA-ABS = fluorescent treponemal antibody absorption; MHA-TP = microhemagglutination test for *Treponema pallidum*; ELISA = enzyme-linked immunosorbent assay.

APPROACH TO THE PATIENT WITH GUD

An algorithm for investigating a patient with genital ulceration is given in Figure 62.2. The history is crucial. Information should be collected about sexual risks, demographics, medication, and travel. Risk factors such as sex work or recent prostitute contact are associated with syphilis and chancroid. Travel may suggest the diagnosis of an otherwise uncommon diagnosis such as donovanosis. Self-medication with topical or systemic antibiotics may lead to a false-negative dark-field examination.

TREATMENT

The drug regimens currently recommended for treating GUD are given in Table 62.5. Treatment traditionally has been initiated only once a laboratory diagnosis has been established; however, the delay inherent in obtaining laboratory results makes it necessary to initiate empiric syndromic therapy at the time of the initial visit. Syndromic therapy should usually be effective for syphilis. Fluctuant buboes should be incised or aspirated. All patients with GUD should be tested for HIV infection.

Patients should be reassessed at 7 days to assess response to therapy. Most patients will show improvement; failure of the lesions to respond should prompt a search for an alternative diagnosis. The RPR as well as a treponemal test should be repeated in all patients following a negative test on initial evaluation. Serology can be negative in 30% of patients when they first present with primary syphilis. Specific treatment recommendations for the common causes of GUD are given in the following sections.

Syphilis

A single intramuscular (IM) injection of benzathine penicillin G, 2.4 million U, is the treatment of choice for both HIV-infected and -uninfected patients with primary or secondary syphilis. Doxycycline or tetracycline for 14 days can be used in patients with a documented penicillin allergy. Azithromycin resistance is now widespread and the macrolides are no longer recommended. All patients should be followed with a quantitative RPR or VDRL at 3, 6, 12, and 24 months after treatment. Treatment failure is diagnosed if clinical signs persist or recur, a sustained 4-fold rise in titer occurs, or an initially high titer (>1/8) fails to decline by at least 4-fold at 6 months. Patients who fail treatment as determined by these criteria should undergo a lumbar puncture. If the cerebrospinal fluid (CSF) is normal, they should be treated with benzathine penicillin G, 2.4 million U IM weekly for 3 weeks. Patients with CSF abnormalities should be treated for neurosyphilis. Because tetracyclines are contraindicated in pregnancy, pregnant patients with a proven penicillin allergy must be desensitized and treated with penicillin. All persons who had sexual contact during the preceding 90 days should be treated and followed with serology.

Chancroid

Trimethoprim–sulfamethoxazole (TMP–SMX) is no longer recommended for the treatment of chancroid because *H. ducreyi* are generally resistant. Erythromycin, 250 mg three times daily for 7 days, is effective in both HIV-infected and -uninfected patients. A single dose of azithromycin, 2 g or ciprofloxacin, 500 mg, is also effective, with cure

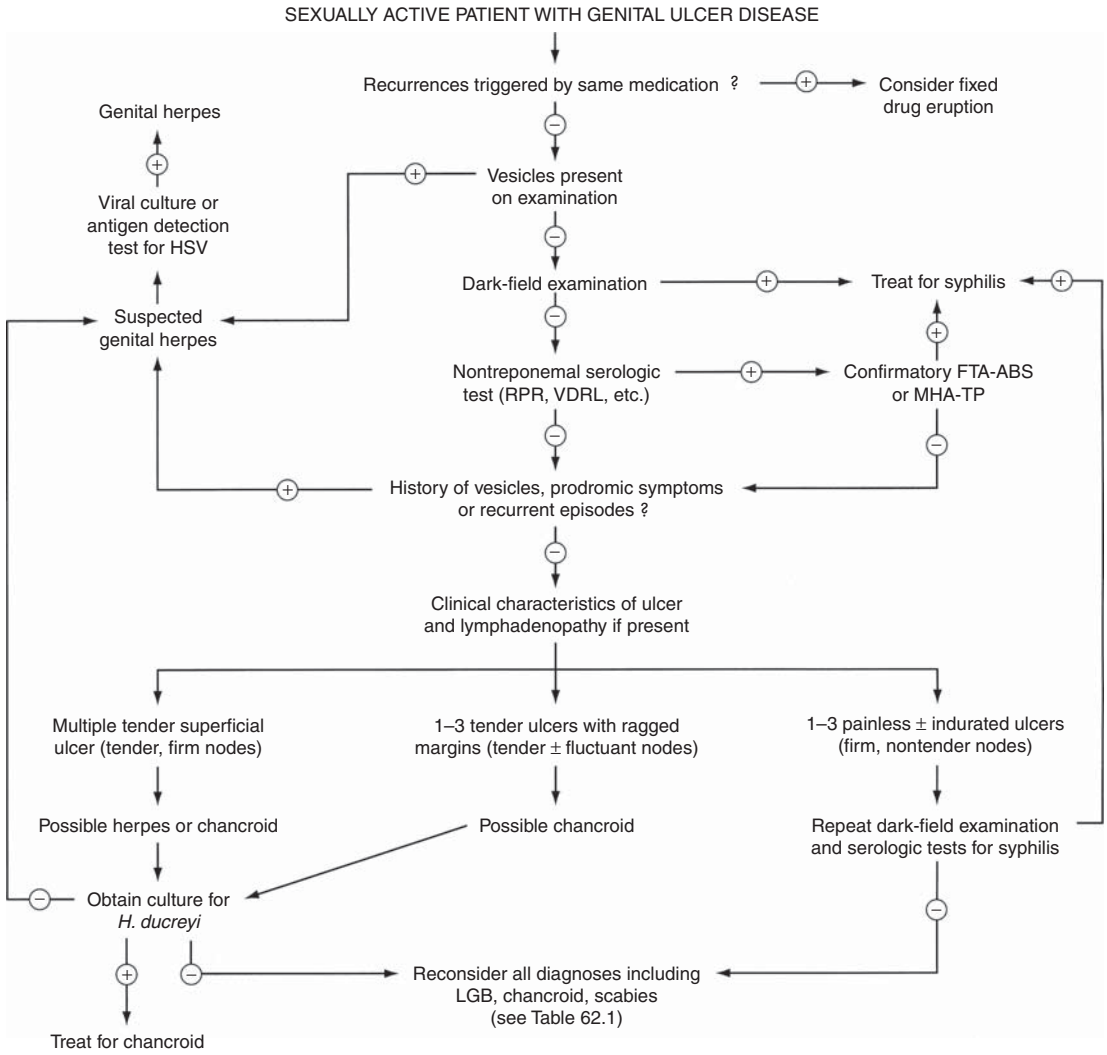

Figure 62.2 Diagnostic algorithm for patients with genital ulcer disease.

rates of over 95%. All chancroid patients with initially negative serologies for HIV and syphilis should have these tests repeated at 3 months. All persons who had sexual contact with the patient in the preceding 3 weeks should be treated regardless of evidence of infection. Erythromycin can be prescribed in pregnant patients.

Lymphogranuloma venereum

Doxycycline for 21 days is the treatment of choice for LGV, but treatment failures may occur, especially in the presence of proctitis, and repeated longer courses should be prescribed. Pregnant patients should be treated with erythromycin. All sexual contacts within the last 30 days should be investigated for rectal, urethral, or cervical chlamydial infection and treated regardless of laboratory confirmation.

Donovanosis

Doxycycline remains the treatment of choice for donovanosis, although treatment failures occur. When therapy fails, patients can be treated with TMP–SMX or ciprofloxacin.

Genital herpes

Acyclovir, valacyclovir, or famciclovir should be used to treat the initial clinical episode of genital herpes, and for severe cases, intravenous acyclovir therapy may be required. Prophylaxis is indicated

Table 62.5 Treatment regimens for infectious causes of the genital ulcer adenopathy syndrome

Disease	Recommended regimen	Alternative regimens	Comments
Primary syphilis	Benzathine penicillin G (2.4 million U IM)	Doxycycline (100 mg PO BID × 14 days) or Tetracycline (500 mg PO QID × 14 days)	The Jarisch–Herxheimer (J-H) reaction (acute onset of fever accompanied by headache, myalgia, malaise, nausea, and tachycardia) may occur 2–24 h after initiating therapy for syphilis. Although the J-H reaction may produce fetal distress or premature labor in a pregnant woman, this is not an indication to delay therapy
Chancroid	Erythromycin (250 mg PO QID × 7 days) Erythromycin (500 mg PO QID × 7 days)	Azithromycin (1 g PO × 1 dose) or Ciprofloxacin (500 mg PO × 1 dose) or Amoxicillin-clavulanic acid (500/125 mg PO TID × 7 days)	Single-dose regimens are contraindicated in HIV-seropositive patients because of unexpectedly high failure rates
Lymphogranuloma venereum	Doxycycline (100 mg PO BID × 21 days)	Erythromycin (500 mg PO QID × 21 days) or Sulfisoxazole (500 mg PO QID × 21 days)	Contacts may require treatment
Donovanosis	Doxycycline (100 mg PO BID)	TMP–SMX (160/800 mg PO BID) Ciprofloxacin (500 mg PO BID) Tetracycline (500 mg PO QID)	Treat until all lesions are healed (may take up to 4 wk)
Genital herpes (primary)	Acyclovir (200 mg PO 5 × daily × 10 days) Famciclovir (250 mg PO TID × 5–10 days) Valacyclovir (1 g PO BID × 5–10 days)		Recurrences require treatment only if severe

Abbreviations: HIV = human immunodeficiency virus; IM = intramuscularly; PO = orally; BID = twice a day; QID = four times a day; TID = three times a day; TMP–SMX = trimethoprim–sulfamethoxazole.

for patients with concomitant HIV infection or frequent recurrences. Acyclovir, 400 mg twice daily, famciclovir, 250 mg twice daily, or valacyclovir, 1 g once daily, each prevents 90% or more of recurrences. See Chapter 187, Herpes simplex viruses 1 and 2, for more details of treatment.

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63. Prostatitis

Jonathan M. Zenilman

Prostatitis and pelvic pain syndromes in men are a common clinical problem and can be due to infectious or noninfectious etiologies. It is estimated that nearly 9% of the male population suffer from prostatitis and pelvic pain symptoms, and that there are >2 million annual physician visits for prostatitis. Over half of patients presenting with prostatic symptoms get treated with antibiotics at some time.

In acute prostatitis, the acute inflammatory response often involves most if not all of the gland, whereas chronic prostatitis is often focal. Noninfectious pathology may be cofactors. For example, prostatic concretions may be a nidus for infection, and focal prostatic necrosis (benign prostatic hyperplasia) may cause prostatic inflammation, even without infection.

The majority of bacterial prostatitis cases occur due to reflux of infected urine into the prostatic ducts and canaliculi, and these cases are seen most commonly in older men, usually associated with other structural or functional abnormalities of the genitourinary tract. Bacterial prostatitis is more common in patients with previous prostate disease, diabetes mellitus, and a history of urethral instrumentation (such as catheterization).

Since urethritis is the initial symptom of gonococcal and chlamydial infection, patients seek care early, and with the widespread availability of effective treatments, the infections are eradicated. Nevertheless, sexually transmitted diseases (STDs), especially chlamydia, have been increasingly implicated in a small proportion of cases, usually men <35 years old. STD-associated chronic prostatitis is rare. Prostatitis due to hematogenously disseminated organisms is unusual and is seen either in immunocompromised hosts or malignancy, and can be caused by *Mycobacterium tuberculosis, Cryptococcus neoformans, Coccidioides immitis, Histoplasma capsulatum, Aspergillus* spp. *a*nd *Candida*.

PROSTATITIS: CLINICAL SYNDROMES

Except for acute prostatitis the accurate clinical diagnosis of prostatitis is difficult. Clinical symptoms are typically nonspecific, and the differential diagnosis often includes a host of noninfectious urologic problems. Many patients seek urologic or infectious disease consultation for prostatitis evaluation after previous diagnoses of lower urinary tract infection or STD syndromes; therefore they have often been treated with antibiotics previously. Because of the gland's location, definitive histopathologic diagnosis by biopsy is rarely an option, unless malignancy is strongly suspected.

In 1995, an NIH Consensus Conference differentiated four types of prostatitis. The Mears–Stamey prostatitis localization protocol (see below) can be especially helpful in differentiating these types, especially types 2–4.

Type 1

Acute prostatitis is usually caused by an ascending urinary tract bacterial infection and is characterized by an abrupt, febrile illness with symptoms referable to the lower genitourinary tract. Chills, leukocytosis, urinary frequency, and occasional bladder outlet obstruction are present. A rectal examination typically shows an enlarged, boggy, exquisitely tender prostate.

Type 2

Chronic bacterial prostatitis is diagnosed on the basis of prostatic or pelvic pain symptoms, including lower genitourinary tract symptoms such as perineal, penile, scrotal and lower back pain, urinary urgency, feeling of incomplete voiding, frequency, nocturia, and dysuria. Diagnosis is based on culture of a pathogen in the expressed prostatic

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secretions (EPS) or post-prostatic massage voided bladder specimen (see below).

In both acute and chronic prostatitis caused by ascending urinary tract infection, the most common organisms present are *Escherichia coli* (50% to 70%), followed by *Klebsiella, Proteus*, and *Enterococcus*. In patients with recent hospitalization or recent genitourinary instrumentation, nosocomial organisms such as *Pseudomonas, Serratia*, and gram-negatives with resistant determinants such as extended-spectrum β-lactamases, or carbapenemases need to be considered.

Type 3

Chronic prostatitis/pelvic pain syndrome is defined as the presence of symptoms of chronic prostatitis, similar to those found in type 2, but where no bacterial etiology is found after careful investigation, including culture of expressed prostatic secretions and post-prostatic massage urine. Systemic symptoms are unusual, and rectal examination of the prostate is typically unremarkable. In practice, most men come for evaluation after being treated initially with antibiotics for community-acquired urinary tract infection. Type 3 prostatitis is subdivided into two categories – those patients with symptoms who have evidence of inflammation (white cells found in expressed prostatic secretions), and those without physical evidence of prostatic inflammation (formerly termed *prostadynia*). The etiology of chronic prostatitis is not known in most cases. Inflammatory cytokines and prostaglandins have been implicated, but even if this is the case, the ultimate causal pathway and inciting event is not known.

Although prostatitis/pelvic pain syndrome is common the important differential diagnosis includes ruling out prostatic hyperplasia due either to benign prostatic hypertrophy or tumor, and urethral stricture due to previous undertreated urethritis. Carcinoma of the bladder should be considered, especially in patients with hematuria. Urine cytology is useful in ruling out this diagnosis. Neuromuscular urologic disorders may also be involved, and should be considered in consultation with the urologist if laboratory investigations fail to reveal an etiology for the symptoms.

Type 4

Asymptomatic prostatitis is defined as physical evidence of prostatic inflammation in the prostatic secretions, but absent symptoms. This is typically diagnosed as an incidental finding in persons being evaluated for other, noninflammatory prostate or lower genitourinary tract disorders, such as benign prostatic hypertrophy.

LABORATORY EVALUATION

The laboratory evaluation for prostatitis is difficult and often by conjecture, since direct tissue culture is not performed. Prostatic-specific antigen is not useful. A clean-catch urinalysis and urine culture should be performed. In patients with acute prostatitis, the urine culture is often positive. In patients with type 2 disease who also have recurrent urinary tract infections diagnosed by culture, it is reasonable to impute that bacterial chronic prostatitis is present.

Structural and functional measures should be evaluated in the workup for chronic disease and include measurement of the post-void residual, as well as CT to evaluate for obstruction or calculi. Rarely, recurring urinary tract infections and chronic prostatitis may be the initial manifestation of a malignancy.

The "classic" diagnostic modality is evaluating expressed prostatic secretions for inflammatory cells and bacterial pathogens using Stamey and Meares' technique.

Procedure

The patient should have a full bladder and should not have taken antibiotics for 48 hours. The penis is washed with sterile water and (if appropriate) the foreskin is retracted. The patient is asked to void. The first 10 cc are collected (VB_1) and a midstream sample is collected (VB_2). After voiding 200 cc, the patient is instructed to kneel. After prostatic massage, the EPS are collected. The patient is then asked to empty his bladder, and the first 10 cc of this final void (VB_3) are collected. A Gram stain is prepared from the EPS, and leukorrhea is defined as presence of 12 WBC/high-power field. The midstream urine and prostatic secretions are sent to the laboratory for culture, including request for low colony count cultures.

A two-step simplified version uses the initial midstream urine and the post-massage prostatic secretions.

Evaluation of results

The staging of prostatitis is achieved by using the data from the expressed prostatic secretions and

Table 63.1 Differential diagnosis of prostatitis

	Midstream urine		EPS	
	WBC	Culture	WBC	Culture
I. Acute bacterial				
Prostatitis	++	+	++	+
II. Chronic bacterial				
Prostatitis	+	+	+	+
III. Chronic non bacterial prostatitis				
Inflammatory	−	−	+	−
Noninflammatory	−	−	−	−

the midstream urine (VB_2) and is summarized in Table 63.1. Acute bacterial prostatitis has a large number of organisms and PMN; the diagnosis is seldom subtle. Chronic prostatitis is diagnosed by presence of polymorphonuclear neutrophils (PMNs) in the expressed prostatic secretions. Culture results from the EPS differentiate bacterial (type 2) and noninfectious bacterial causes (type 3).

TREATMENT OF BACTERIAL PROSTATITIS (TYPES 1 AND 2)

For types 1 and 2 (acute and chronic bacterial prostatitis), determining bacterial etiology is desirable. If the patient has taken antibiotics prior to evaluation, false-negative cultures will occur. Except in cases of acute prostatitis, the clinician may want to consider discontinuing antibiotics, waiting for 48 to 72 hours, and then obtaining the prostatic fluid and urine cultures.

The organisms typically isolated are those associated with lower urinary tract infection (Table 63.2). Enteric gram-negative rods are most common, followed by *Enterococcus*, *Staphylococcus saprophyticus, Proteus*, and *Klebsiella*. Streptococci and anaerobes are rarely involved. If the patient has been recently instrumented or catheterized in a hospital setting, *Pseudomonas, Serratia*, *Enterococcus*, and resistant enterics would be the major concerns. Furthermore, these organisms are found frequently as commensals in normal hosts and their role as pathogens is controversial.

In sexually active patients, especially those with multiple partners, *Chlamydia* and *Trichomonas* are rarely found. These organisms are difficult to culture. Fungal and mycobacterial causes can usually be diagnosed only by prostatic biopsy.

Table 63.2 Organisms implicated in bacterial prostatitis

Gram-negative
Escherichia coli
Proteus mirabilis
Klebsiella
Healthcare associated
Pseudomonas aeruginosa
Serratia
E. coli (ESBL positive)
Klebsiella (ESBL or KPC positive)
Gram-positive
Enterococcus
Staphylococcus saprophyticus

Abbreviations: ESBL = extended-spectrum β-lactamase; KPC = *Klebsiella pneumonia* carbapenemase.

Issues in treatment

Evaluating treatment efficacy of prostatitis is complicated by:

1. The difficulties in making an accurate clinical diagnosis, especially in the substantial fraction of patients with prior antibiotic therapy for lower urinary tract infection.
2. The lack of a standardized definition of cure. Most studies of treatment, even those which evaluate prostatic secretions for bacteriology, do not repeat the procedure at post-therapy evaluation.
3. The optimal duration of therapy is not definitively known, although most authorities treat acute prostatitis for 2 to 4 weeks, and chronic prostatitis for 4 to 6 weeks
4. There are few longitudinal, randomized controlled trials which have evaluated prostatitis treatment efficacy.

TREATMENT FOR ACUTE PROSTATITIS

If patients with acute prostatitis require hospitalization, they should be treated with intravenous antimicrobials until they defervesce and stabilize. Antimicrobial choice is dependent on whether they have had recent hospitalization or genitourinary instrumentation.

Patients with community-acquired disease may be treated with either a quinolone (ciprofloxacin IV 400 mg twice daily, levofloxacin 500 mg once daily), or ceftriaxone 1 g daily, or ertapenem, 1 g daily. Patients where sexually transmitted organisms are a consideration should be treated with

ceftriaxone, with the addition of azithromycin, 1 g as a single dose. Treatment duration is usually 2 to 4 weeks.

Patients with nosocomial infection should be treated with intravenous regimens effective against *Pseudomonas*, such as piperacillin–tazobactam or cefipime. If an ESBL-resistant organism is suspected an infectious diseases specialist should be consulted, and meropenem would be the regimen of choice.

In all cases, antimicrobial therapy should be adjusted after culture results become available.

Special consideration – post prostate biopsy: Infectious complications of transrectal prostate biopsy include acute prostatitis as well as disseminated sepsis syndromes. These patients have a higher prevalence of ESBL-resistant organisms and should be treated empirically with meropenem until the organism is isolated.

TREATMENT FOR CHRONIC PROSTATITIS

Most authorities believe that treatment regimens for chronic bacterial prostatitis should include:

1. An antimicrobial effective against the most likely organisms.
2. An antimicrobial that is well absorbed into prostate tissue and has an acid dissociation coefficient (pK_a) favorable to trap the drug in prostate tissue (compared to the acidic urinary tract environment).
3. Because of the long treatment course, drugs which require less frequent dosing would be preferred to facilitate compliance.

The quinolones and sulfa-trimethoprim (Table 63.3) meet these criteria. Quinolones are preferred because they are associated with fewer side effects, especially in older patients, and are more active against the gram-positive organisms. Adequate regimens include ciprofloxacin 500 mg twice daily and levofloxacin 500 mg once daily. Moxifloxacin *should not* be used since this drug is excreted primarily in the bile and does not achieve high urinary concentrations. If enterococcus is suspected amoxicillin–clavulanate (amoxicillin 875 mg/clavulanate 125 mg) three times daily should be used. The amoxicillin is active against enterococcus (which is quinolone-resistant), and the clavulanate inhibits the β-lactamase secreted by the enteric genitourinary pathogens.

Table 63.3 Therapy options for chronic prostatitis

Trimethoprim-sulfa DS (160/800 mg) BID
Ciprofloxacin 500 mg twice daily
Levofloxacin 500 mg once daily
Amoxicillin–clavulanate (875 mg/125 mg) (enterococcus)
Oral therapy duration is 4–6 weeks

Abbreviation: DS = double strength.

Recurrent disease is common – reported in as many as 40% of patients. In patients with well-documented disease which recurs, antimicrobials should be resumed for a minimum of 3 months. Recurrence after cessation of antibiotics in patients with poorly documented disease should be viewed as an opportunity to fully evaluate the syndrome.

TREATMENT OF NONBACTERIAL PROSTATITIS

Treatment of nonbacterial chronic prostatitis is notoriously difficult. These patients should be referred to a urologist for a more complete evaluation. Patients often present having had multiple evaluations and procedures; in one study, over half of patients had had cystoscopic evaluation.

In carefully controlled studies, antimicrobial therapy for treatment of putative noncultivable organisms has not been shown to be effective, and is NOT recommended.

SUMMARY

- Acute prostatitis is usually self-evident and presents with severe prostatic pain, fever; urinary and/or prostatic fluid cultures are typically positive.
- Chronic prostatitis is part of a spectrum of prostatitis/pelvic pain syndromes, most of which are non-infectious.
- Antimicrobial therapy duration in acute prostatitis is 2 to 4 weeks.
- In patients where chronic bacterial prostatitis is suspected, documentation with urinary cultures or of expressed prostatic secretions should be attempted.
- Chronic prostatitis therapy should be guided by antibiotic susceptibility data, when available. If not, quinolone therapy for 4 to 6 weeks is the most commonly used option.

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64. Pelvic inflammatory disease

William J. Ledger

INTRODUCTION

The current emphasis upon evidence-based medicine has poorly served our approach to pelvic inflammatory disease (PID). On paper, the goal of determining the best therapeutic strategy by prospective randomized double-blind studies is laudable, but it makes the assumption that patients with similar risk factors can be grouped into large study groups for such endeavors. It is increasingly apparent that this has not been the case.

PID is a classification that attempts to encompass too wide a range of clinical syndromes. It includes seriously ill women with a tubo-ovarian abscess, who require hospitalization, intravenous antibiotics, and sometimes operative intervention for a cure. In contrast, most women with PID either are asymptomatic or have such mild symptoms that they do not seek medical care. To address these concerns, the International Infectious Disease Society for Obstetrics-Gynecology (I-IDSOG-USA) suggested the term "upper genital tract disease" (UGTI) be used with the designation of the etiologic agent. In addition, the UGTI can be placed in stages, depending upon the clinical severity of the infection.

Epidemiology studies have added to the confusion about risk factors for PID. For the past two decades, study after study has shown bacterial vaginosis (BV) and douching as risk factors for the development of PID, but in separate prospective studies, on BV and douching, no increased risk was seen.

In addition, epidemiologic studies that suffer from inaccurate reporting of condom use and imperfect diagnosis of sexually transmitted disease (STD) infection have been used to bolster the faith-based emphasis upon abstinence over condoms to prevent infection.

MICROBIOLOGY

The diversity of the clinical picture of PID is matched by the variety of microbiologic findings. There are infections in which a single pathogen dominates, such as *Neisseria gonorrheae*, *Chlamydia trachomatis*, and the group A *Streptococcus*. In contrast, most infections are polymicrobial with aerobes, *Mycoplasma hominis*, *Ureaplasma urealyticum*, or anaerobes involved. Gram-negative anaerobes are particularly important in those women who develop a tubo-ovarian abscess.

CLINICAL DIAGNOSIS

The clinical diagnosis of PID remains a work in progress. More sensitive and more specific invasive techniques to diagnose PID, including laparoscopy, endometrial biopsy, and needle culdocentesis, have been confined to research studies and are not used routinely by clinicians. There is a dependence upon clinical findings, which are variable. In some women, the diagnosis is obvious. This is particularly true in patients requiring care in urban emergency departments. When *N. gonorrheae* is one of the pathogens, the patient usually has severe lower abdominal discomfort, excruciating pain on pelvic examination, and an elevated temperature. This is what a clinician expects with a bacterial infection. Patients seen in the early stages of a gonococcal infection, however, may present with minimal symptoms, including a new discharge, abnormal bleeding, or urinary urgency and frequency. Another group with an obvious diagnosis are those women with a pelvic abscess. These patients are usually febrile, have tender pelvic masses detected on pelvic examination and confirmed by imaging study such as a pelvic ultrasound. In contrast, women infected with *C. trachomatis* with PID have minimal or no symptoms, and are usually afebrile without an elevated white blood cell count. Many do not seek medical care. Because of this, I share the concerns of the Centers for Disease Control and Prevention (CDC) about the validity of the minimal criteria for physician diagnosis. These criteria – lower

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Table 64.1 Parenteral treatment

Recommended parenteral regimen A
Cefotetan 2 g IV every 12 hours
OR
Cefoxitin 2 g IV every 6 hours
PLUS
Doxycycline 100 mg orally or IV every 12 hours
Parenteral treatment can be discontinued 24 hours after a patient improves. Clinical oral therapy with doxycycline 100 mg twice a day to complete 14 days of therapy.
Recommended parenteral regimen B
Clindamycin 900 mg IV every 8 hours
PLUS
Gentamicin loading dose IV or IM (2 mg/kg of body weight), followed by a maintenance dose (1.5 mg/kg) every 8 hours. Single daily dosing (3–5 mg/kg) may be substituted.
Parenteral treatment can be discontinued 24 hours after a patient improves. Oral therapy should then be given to complete 14 days of therapy, either clindamycin 450 mg four times a day or doxycycline 100 mg twice a day.
Alternative parenteral regimen
Ampicillin–sulbactam 3 g IV every 6 hours
PLUS
Doxycycline 100 mg orally or IV every 12 hours

Table 64.2 Oral treatment

Recommended oral regimen
Ceftriaxone 250 mg IM in a single dose
PLUS
Doxycycline 100 mg orally twice a day for 14 days
WITH OR WITHOUT
Metronidazole 500 mg orally twice a day for 14 days
OR
Cefoxitin 2 g IM in a single dose and probenecid, 1 g orally administered concurrently in a single dose
PLUS
Doxycycline 100 mg orally twice a day for 14 days
WITH OR WITHOUT
Metronidazole 500 mg orally twice a day for 14 days
OR
Other parenteral third-generation cephalosporin (e.g., ceftizoxime or cefotaxime)
PLUS
Doxycycline 100 mg orally twice a day for 14 days
WITH OR WITHOUT
Metronidazole 500 mg orally twice a day for 14 days

abdominal tenderness, adnexal tenderness, and cervical motion tenderness – exclude more women who do not have PID, but they also reduce the number of women with PID who are identified.

There are other signs of early infection that should be called into play by clinicians. Suspect a pelvic infection in a young sexually active woman who has either a new sexual partner or a promiscuous male partner who does not use condoms. Consider this diagnosis whenever these women complain of urgency and frequency of urination, whose urination culture shows no significant growth of bacteria, irregular vaginal bleeding with no obvious cause found on pelvic examination or, most commonly, a new vaginal discharge.

Another problem is that more relaxed physician standards that increase the likelihood of a diagnosis of PID are of no value if the patients do not present for care. The current reality in the United States is that many of these women with few or no symptoms do not consider themselves sick enough to seek medical care. We need a new direction in patient care. Women need to be educated and made aware of the risks of infection if exposed to a new male partner who does not use a condom. They also should be made aware of the subtle signs of pelvic infection and to seek medical care. One possible future strategy will be to have these women test themselves with a vaginal swab that will be polymerase chain reaction (PCR) tested for the presence of *C. trachomatis*. Studies indicate that this would be a feasible strategy.

TREATMENT

There are no prospective studies available with the statistical power to dictate absolute criteria to determine hospital admission or the best choice of antibiotics to prevent long-term morbidity. One study to compare inpatient versus outpatient therapy had 78.1% of the patients with well-established infections, with symptoms for more than 3 days, before treatment was begun. Well-established infections are not as responsive to antibiotic therapy. In addition, the current clinical reality of care is that treatment regimens have to be initiated before culture or PCR studies identify the pathogens present. Because of this, initial regimens should include antibiotics effective against *N. gonorrheae, C. trachomatis*,

and gram-negative anaerobes. Changes in initial choices can be made if bacterial identification suggests that other agents should be used.

In Sexually Transmitted Diseases Treatment Guidelines, 2010, the CDC provide the following options: parenteral treatment (Table 64.1) and oral treatment (Table 64.2). Patients who fail to respond to systemic antibiotic treatment should be evaluated to see whether pelvic abscess formation has occurred. In women in whom an abscess is discovered aspiration can be done under direct laparoscopic vision or ultrasonographic-guided needle aspiration. The patients who fail to respond to this intervention are few in number, but they may need operative removal of infected tissue to achieve a cure.

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65. Urinary tract infection

Keith W. Hamilton and Judith A. O'Donnell

Urinary tract infections (UTIs) are the most common infections identified in both outpatient and inpatient settings. UTIs occur in patients of all ages, affecting females throughout life and males at each end of the age spectrum. They represent approximately 8.6 million visits in the ambulatory setting and are the most commonly diagnosed healthcare-associated infection. The term *urinary tract infection* encompasses a group of conditions that includes cystitis, pyelonephritis, and asymptomatic bacteriuria. Appropriate management of a patient with a UTI requires consideration of multiple factors, including age, sex, underlying comorbidities, pregnancy, history of prior UTIs, location of infection, and the pathogen involved.

Determination of the location of the infection as upper versus lower tract is essential to selection of optimal therapy. *Lower urinary tract infection* is infection involving the bladder, or cystitis, and is characterized by dysuria, pyuria, urinary frequency, or urinary urgency. *Upper urinary tract infection*, or pyelonephritis, is infection involving the bladder and kidney that classically presents with fever and flank pain, with or without the symptoms of lower tract infection.

Differentiating uncomplicated from complicated UTI is also critical to developing an appropriate treatment strategy. An uncomplicated UTI is an infection occurring in an otherwise healthy individual who has no functional or structural abnormalities of the kidneys, ureters, bladder, or urethra. Most adult women with cystitis fall into this category. Complicated UTIs are those infections occurring in the setting of functional or anatomic abnormalities of the upper or lower tract (such as urinary retention from anatomic obstruction or neurogenic bladder and nephrolithiasis), in the presence of an indwelling bladder catheter, or in patients with underlying conditions such as pregnancy, diabetes mellitus, or renal transplantation. Infections with unusual or multidrug-resistant bacteria are often considered complicated. UTIs in adult men are uncommon without complicating factors (such as urinary obstruction or prostatitis), and most cases should be treated as complicated infections. These complicating factors are associated with less favorable treatment responses.

Uncomplicated lower UTIs respond well to therapy of short duration of 3 to 7 days depending on the chosen agent (see Table 65.1). Complicated infections are often associated with factors that may predispose the patient to complications or recurrence, and usually require longer courses of therapy (7 to 14 days or more), but few studies have been performed to determine the optimal treatment courses for complicated UTIs.

PATHOGENESIS

The pathogenesis of most upper and lower UTIs is related to the ability of microorganisms to establish colonization in the periurethral area and to ascend into the urinary tract, causing infection. These organisms are typically derived from the gastrointestinal tract or vagina. After colonization, the ensuing events that lead to infection are not entirely understood but likely depend upon virulence factors of the organism, and host anatomy and immune response. Urinary catheters can facilitate both colonization and infection. They are commonly colonized by periurethral flora that migrate along the catheter surface. Interactions between the catheter and infecting or colonizing organisms facilitate adhesion to the catheter and production of a biofilm, which aids certain microorganisms in evading host defenses. Rarely, UTIs may occur through a hematogenous route of infection.

The majority of upper and lower UTIs are monomicrobial. *Escherichia coli* is the most common pathogen, causing 70% to 90% of all UTIs. Other members of the Enterobacteriaceae family such as *Klebsiella*, *Proteus*, and *Enterobacter*

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Table 65.1 Antibiotics for uncomplicated lower urinary tract infections

Drug	Dose and duration	Comments
First-line agents		
TMP–SMX	1 DS (160/800-mg) tablet twice daily for 3 days	First-line agents unless ≥10–20% rate of *Escherichia coli* resistance to TMP–SMX locally, history of antibiotic use, within past 3 months, or history of recent hospitalization FDA pregnancy category C; avoid in third trimester
Nitrofurantoin (monohydrate macrocrystals)	100 mg twice daily for 7 days	May be less effective than TMP–SMX Consider for patients with mild to moderate symptoms, and with ≥10–20% rate of *E. coli* resistance to TMP–SMX locally, sulfa allergy, or antibiotic use other than nitrofurantoin within past 3 months FDA pregnancy category B
Fosfomycin	3 g as single dose	May be less effective than TMP–SMX Consider for patients with mild to moderate symptoms, and with ≥10–20% rate of *E. coli* resistance to TMP–SMX locally, sulfa allergy, or antibiotic use other than fosfomycin within past 3 months FDA pregnancy category B
Second-line agents		
β-lactams (e.g., amoxicillin-clavulanate, cephalosporins)	3–7 days (dose depends on individual agent)	There are less efficacy data for these agents compared to data for first-line agents and fluoroquinolones Consider β-lactams if ≥10–20% rate of *E. coli* resistance to other agents and rates of resistance to selected β-lactams ≤ 20% Amoxicillin or ampicillin should not be used as monotherapy for empiric treatment FDA pregnancy category B
Fluoroquinolones Ciprofloxacin Levofloxacin	250 mg twice daily for 3 days 250 mg daily for 3 days	Consider fluoroquinolones if ≥10–20% rate of *E. coli* resistance to TMP–SFX locally, patient allergy to other agents, and antibiotic use other than fluoroquinolones within past 3 months FDA pregnancy category C

Note: Antibiotic dose recommendations assume normal renal function.

Abbreviations: TMP–SMX = trimethoprim–sulfamethoxazole; DS = double strength; FDA = Food and Drug Administration.

species are also common UTI pathogens. Among the gram-positive organisms, *Staphylococcus saprophyticus* and *Enterococcus* species are the most frequently identified pathogens. Other bacteria, such as *Pseudomonas*, *Serratia*, and *Candida* species can be seen more frequently in association with indwelling urinary catheters, and polymicrobial UTIs can also occur in this setting. A polymicrobial infection in the absence of a urinary catheter may suggest an enterovesical fistula or contamination during the specimen collection process. *Candida albicans* is the most common etiologic agent in fungal UTIs, but other *Candida* species are becoming increasingly common. Several sexually transmitted infections (STIs), including *Chlamydia trachomatis, Neisseria gonorrhoeae, Trichomonas vaginalis*, and genital herpes simplex virus infection, can cause urethritis, which mimics symptoms of UTI. Therefore, appropriate diagnostic evaluation for STIs should also be performed as part of a UTI workup in sexually active patients, especially if another pathogen is not isolated.

LOWER UTI: CYSTITIS

Typical symptoms of lower UTIs include dysuria, urinary frequency, urgency, and, occasionally, hematuria or suprapubic pain. The presence of fever or flank pain should raise the concern for pyelonephritis. In addition to history and physical examination findings, laboratory tests are often used in the diagnosis of cystitis.

Diagnosis

The diagnosis of cystitis can be made using a combination of clinical and laboratory criteria. Some symptoms, including dysuria, urinary frequency, and hematuria, increase the likelihood of UTI. The absence of dysuria or back pain and presence of vaginal irritation or discharge decrease the likelihood of UTI. Women with at least one symptom have at least a 35% to 50% likelihood of having cystitis. The presence of dysuria and urinary frequency combined with

the absence of vaginal discharge increases the likelihood of UTI to greater than 90%. Patients with a high pretest probability for cystitis and no complicating factors should be treated empirically without additional testing. Patients with a lower pretest probability should have diagnostic testing performed. In these patients, the diagnosis of cystitis can be evaluated using urine dipstick, microscopy, and/or culture.

In ambulatory settings, urine dipstick testing has largely replaced microscopy to diagnose UTI because it is cheaper, faster, and more convenient. Dipstick testing can detect the presence of leukocyte esterase, an enzyme released by white blood cells, and nitrites, by-products of nitrate metabolism produced by Enterobacteriaceae. A positive test for either leukocyte esterase or nitrite has a sensitivity of 75% and specificity of 82%. Because of the limited sensitivity and specificity of the dipstick test, the dipstick may be most useful for rapid rule-out of UTI among women with a moderate to low pretest likelihood of infection, such as minimally symptomatic patients or those with both bladder and vaginal symptoms. Urine microscopy has a higher sensitivity and specificity compared to the dipstick test. Hemocytometer (counting chamber) measurement of urine leukocytes in an unspun specimen provides the most accurate assessment of pyuria, which is defined as a leukocyte count $\geq$10 leukocytes/mm^3. Pyuria is present in almost all women with cystitis in the absence of neutropenia. Another method of urinalysis involves the microscopic examination of urine sediment from centrifuged samples. The accuracy of this method depends on the skill of the operator and the level of procedural standardization. The presence of bacteriuria on urine microscopy can also be used to assess the presence of UTI, but it is often difficult to interpret, given the ease of specimen contamination with periurethral flora during collection, as well as the overgrowth of bacteria that may result from the improper handling of specimens. Therefore, bacteriuria alone in the absence of pyuria should not be used to make the diagnosis of UTI.

Urine culture is not necessary in most otherwise healthy women with cystitis because the causative organisms and their susceptibility patterns are predictable. However, urine cultures should be obtained in patients with refractory symptoms, recurrent UTIs, suspected pyelonephritis, or complicated UTI. Urine cultures should also be obtained in patients with history of, or risk factors for, antibiotic-resistant pathogens, including in those patients with recent antibiotic use, recent hospitalization, or residence in a long-term care facility. Although suprapubic aspiration or straight catheterization has the best chance of minimizing contamination, midstream, or "clean-catch," urine collection remains the most practical method of obtaining urine samples. Quantitative urine cultures are the gold standard for microbiologic diagnosis of UTIs. Growth, identification, and susceptibility testing of the pathogen can offer the most effective means for establishing infection and determining appropriate antimicrobial therapy. Traditionally, bacteriuria with $\geq 10^5$ colony-forming units (CFU) of bacteria per milliliter of urine has been considered diagnostic. This threshold was extrapolated from studies of pyelonephritis and asymptomatic bacteriuria in women. However, based on more recent studies, lower colony counts (10^2 to 10^4 CFU/mL) in association with signs and symptoms of cystitis have also been accepted as diagnostic. The quantitative threshold for UTIs in men remains unclear, but many authorities recommend a lower threshold of 10^3 CFU/mL.

Therapy

Treatment of uncomplicated cystitis can be accomplished with a short course of an effective antimicrobial agent. Because therapy is typically started in the absence of a culture or before culture results become available, understanding common pathogens and local susceptibility patterns is essential. Given that *E. coli* is the predominant UTI pathogen, its susceptibility patterns typically drive empiric antibiotic choices. Table 65.1 outlines general treatment recommendations for uncomplicated cystitis.

In many areas, resistance rates for nitrofurantoin, fosfomycin, and trimethoprim–sulfamethoxazole (TMP–SMX) are less than 10%. Therefore, these drugs have become the recommended first-line empiric agents for uncomplicated cystitis. However, the rates of resistance vary considerably by geographic region and can exceed 20% in some areas. In particular, the rapidly increasing rate of resistance of *E. coli* to TMP–SMX has raised significant concern about its empiric use for UTI. In vitro and mathematical modeling studies suggest that TMP–SMX should not be used when local resistance rates exceed 20%. Individual risk factors for resistance should also be considered before using TMP–SMX for empiric therapy.

Studies have suggested that the highest risk of UTI caused by TMP–SMX-resistant *E. coli* is associated with recent TMP–SMX or other systemic antibiotic use. Other risk factors include recent hospitalization, residence in a long-term care facility, and travel outside the United States within the last 3 to 6 months.

The potential benefits of nitrofurantoin and fosfomycin use for UTI treatment include that both have a relatively narrow spectrum of activity, have little in vitro resistance, and that neither achieve high concentrations outside the urinary tract. Both nitrofurantoin and fosfomycin have been studied only for treatment of lower UTIs, and as they do not achieve high drug concentration levels in the upper urinary tract, they should not be used to treat upper UTIs. Nitrofurantoin used for 5 days has similar clinical cure rates as TMP–SMX used for 3 days. Fosfomycin can be administered as a single dose for uncomplicated cystitis, and it is a reasonable first-line therapy. A few small studies suggest clinical cure rates may be slightly inferior when fosfomycin is compared with other first-line agents. One potential disadvantage of fosfomycin is that most microbiology laboratories do not perform routine fosfomycin susceptibility testing and require a special request to do so. Fosfomycin retains in vitro activity against many multidrug-resistant organisms, including extended-spectrum β-lactamase (ESBL)-producing organisms, and can sometimes be prescribed for uncomplicated lower UTIs caused by these organisms, thus avoiding intravenous therapy. As multidrug-resistant organisms become more prevalent in the community, fosfomycin will likely have a more prominent role in empiric therapy.

The fluoroquinolones have often been used as first-line empiric therapy for cystitis. Currently fluoroquinolone resistance rates in *E. coli* are highly variable depending upon geography. In some areas, resistance rates to fluoroquinolones can exceed 20%. Even when resistance rates are less than 10%, fluoroquinolone use can select for development of multidrug-resistant organisms. Therefore, fluoroquinolones should be reserved as alternative therapy and prescribed for patients who do not tolerate or are not eligible to receive recommended first-line agents. Moxifloxacin and gemifloxacin achieve poor levels in the urine and are not approved for treatment of UTI. Levofloxacin or ciprofloxacin are the fluoroquinolones recommended for treatment of genitourinary tract infections.

Selected β-lactam agents may also be appropriate therapeutic options for uncomplicated cystitis, as resistance rates for these agents are less than 10% in many geographic regions. As compared to TMP–SMX and the fluoroquinolones, there are far fewer clinical outcome data with these agents. Historically, β-lactam agents have been noted to be less effective than TMP–SMX, and to potentially cause more disruption of the vaginal flora, leading to vaginal yeast infection. However, in the current climate of increasing resistance to TMP–SMX and fluoroquinolones, the β-lactam agents have once again become a reasonable therapeutic option in some settings. In most regions of the United States, rates of resistance of *E. coli* to amoxicillin exceed 20%, making amoxicillin a poor choice for empiric therapy. The β-lactams that may be considered as UTI treatment based on local susceptibility patterns include amoxicillin-clavulanate, second-generation cephalosporins (cefaclor), third-generation cephalosporins (cefdinir and cefpodoxime), and, in some instances, first-generation cephalosporins (cephalexin and cefadroxil). Broad-spectrum β-lactam agents should be prescribed with caution, as their use has also been associated with development of drug resistance.

Patients with cystitis who may not be appropriate candidates for more traditional empiric treatment recommendations include those at higher risk for acquisition of multidrug-resistant pathogens. Patients with recent antibiotic exposure, infection with multidrug-resistant bacteria, hospitalization, or residence in a long-term care facility all carry a higher risk of resistance to first-line agents. Urine should be submitted for culture and susceptibility in such patients, and if empiric therapy is desired prior to culture results, it should be based on prior culture results and recent antibiotic use.

Complicated UTI

A UTI is considered complicated if any of the criteria discussed in the introduction to this chapter are present. Symptoms of complicated UTI can be similar to those associated with uncomplicated cystitis, including dysuria, hematuria, urinary frequency, and suprapubic pain. However, symptoms can be atypical, especially in those patients with functional or structural abnormalities or with a urinary catheter. The management of candiduria and UTIs occurring in catheterized patients is discussed in detail in Chapter 108, Infections associated with urinary catheters. Urine culture and sensitivity should be performed for all patients with complicated

UTI. Treatment duration for complicated UTIs, including UTIs in men, is usually 7 to 14 days, due to the potential for higher rates of treatment failure and relapse in complicated infections treated for short courses.

The issues regarding antibiotic choice in light of increasing rates of resistance are similar to those discussed previously for uncomplicated UTIs; however, consideration should be given to the potentially higher risk of resistant pathogens in many populations with complicated UTIs. Therefore, TMP–SMX, nitrofurantoin, and fosfomycin are generally not recommended for the empiric treatment of complicated infections. Nitrofurantoin and fosfomycin, which both poorly penetrate into tissue of the upper urinary tract, should be avoided in situations where there is diagnostic uncertainty of upper versus lower UTI.

Because of the increased rates of resistance, likelihood of upper tract infection, and the limitations of first-line agents in complicated UTI, empiric therapy should be initiated with a broad-spectrum antibiotic such as a fluoroquinolone. Parenteral therapy may be necessary, especially in hospitalized patients or those who cannot tolerate oral medications. In these cases, reasonable choices include third- or fourth-generation cephalosporins or the fluoroquinolones. Choice of empiric therapy should be based on local susceptibility patterns and prior culture data. Therapy should be modified as needed or narrowed where possible once the culture and susceptibility results are available.

UPPER UTI: PYELONEPHRITIS

Pyelonephritis is defined as an infection of the urinary tract that ascends to involve the renal pelvis. The organisms that cause pyelonephritis are similar to those that cause cystitis. Characteristic symptoms and signs of pyelonephritis include fever, nausea, vomiting, flank pain, and costovertebral angle tenderness. Symptoms of cystitis may or may not be present. However, pyelonephritis may also mimic appendicitis, cholecystitis, and pelvic inflammatory disease. Therefore, a careful history and physical exam are essential, and a pelvic examination or dedicated imaging studies should be considered in patients who present with atypical symptoms.

As is true with other types of UTI, pyuria is almost always present. Urine dipstick tests for leukocyte esterase and nitrites can be used to screen for the presence or absence of infection but they cannot differentiate upper from lower tract diseases. Furthermore, they are generally not sensitive enough to rule out pyelonephritis; therefore, urinalysis should be performed. Urine culture and sensitivity should be performed in all cases of suspected pyelonephritis and therapy adjusted based on susceptibility results. The accepted diagnostic threshold for significant bacteriuria in pyelonephritis is $\geq 10^5$ CFU/mL, although colony counts as low as 10^3 CFU/mL of urine may be seen. Blood cultures should be performed in patients with fever or severe disease. Pregnancy should be ruled out in all women of childbearing age because pregnancy is a predisposing condition for pyelonephritis, and many antibiotics including fluoroquinolones, are contraindicated during pregnancy.

Many patients with uncomplicated pyelonephritis may be treated as outpatients with oral antibiotics. Indications for hospitalization include severe nausea or vomiting, signs of sepsis or severe disease (e.g., high fevers, tachycardia, and hypotension), diagnostic uncertainty, or concerns regarding ability to adhere to treatment plans or follow-up. If the patient is deemed an appropriate candidate for outpatient oral therapy, fluoroquinolones are generally recommended as the first-line agents given the variable and rising rates of resistance to TMP–SMX (Table 65.2). TMP–SMX should be used in pyelonephritis only if culture and sensitivity results are available and if the infecting organism is known to be susceptible. There are less data for the use of oral β-lactams for the treatment of pyelonephritis, and these agents may be inferior to fluoroquinolones. If an alternative agent other than a fluoroquinolone is used for outpatient treatment or if fluoroquinolone resistance exceeds 10%, a single dose of a long-acting parenteral agent, such as ceftriaxone or an aminoglycoside, should be administered pending culture and susceptibility. If a urine Gram stain reveals gram-positive cocci (suggesting a possible enterococcal infection), amoxicillin should be added to the regimen.

Antibiotics should be narrowed or adjusted according to culture and susceptibility results. For treatment of mild cases of pyelonephritis in the outpatient setting, the duration of therapy should be 5 to 7 days if a fluoroquinolone is used. If an alternative agent is used, a 10- to 14-day duration of therapy is generally recommended. Patients usually improve within the first 48 to 72 hours of therapy, and it is important for appropriate follow-up within this period to review clinical response and culture results. In the absence of improvement, the patient should be admitted to

Table 65.2 Antibiotics for uncomplicated pyelonephritis

Drug	Dose and duration	Comments
Outpatient therapy[a]		
Fluoroquinolones Ciprofloxacin Levofloxacin	 500 mg twice daily for 7 days 750 mg daily for 5 days	Fluoroquinolones are first-line agents for treatment of pyelonephritis in outpatient setting except when contraindicated Must follow-up in 48–72 h to assess response FDA pregnancy category C
TMP–SMX	1 DS (160/800-mg) tablet twice daily for 14 days	Use TMP–SMX only if causative organism is shown to be susceptible If C/S not available, add single dose of parenteral agent (ceftriaxone or aminoglycoside) pending susceptibility data FDA pregnancy category C; avoid in third trimester
Other agents	14 days (dose depends on individual agent)	There are less data for these agents in empiric treatment of pyelonephritis If an agent other than a fluoroquinolone is used for empiric therapy in absence of C/S, add single dose of parenteral agent (ceftriaxone or aminoglycoside) pending susceptibility data Amoxicillin and ampicillin should not be used for empiric treatment of pyelonephritis Nitrofurantoin and fosfomycin should not be used for treatment of pyelonephritis even if isolate is susceptible to these agents
Inpatient therapy[b,c]		
Fluoroquinolones Ciprofloxacin Levofloxacin	 400 mg IV twice daily 250–500 mg IV daily	FDA pregnancy category C
β-lactams Ceftriaxone Cefotaxime Cefepime	 1 g IV daily 1 g IV q8h 1 g IV q8h	FDA pregnancy category B
Aztreonam	1 g q8h	FDA pregnancy category B
Aminoglycosides Gentamicin Tobramycin	 5 mg/kg IV daily 5 mg/kg IV daily	FDA pregnancy category D

[a] If enterococcus suspected add amoxicillin to regimen.

[b] If enterococcus suspected add ampicillin to regimen.

[c] Empiric use of broader-spectrum agents may be necessary in severe disease or if risk factors for antibiotic-resistant bacteria are present. Streamline therapy based on culture and sensitivity data. Patient can be switched to oral agents once patient responds and if oral option available.

Note: Antibiotic dose recommendations assume normal renal function.

Abbreviations: TMP–SMX = trimethoprim–sulfamethoxazole; DS = double strength; C/S = culture and sensitivity; FDA = Food and Drug Administration.

the hospital for alternative treatment regimens and further diagnostic evaluation.

Patients requiring hospitalization for management of pyelonephritis should be treated initially with parenteral agents (Table 65.2). Local susceptibilities should drive empiric treatment decisions. Reasonable choices include fluoroquinolones, extended-spectrum cephalosporins (third and fourth generation), extended-spectrum penicillins (ampicillin–sulbactam, piperacillin–tazobactam, and ticarcillin–clavulanate), or aminoglycosides. If gram-positive cocci are observed on Gram stain, the addition of ampicillin or use of ampicillin–sulbactam is recommended. Consultation with an infectious diseases expert should be considered in cases of treatment failure or in patients with risk for, or history of, multidrug-resistant pathogens.

Antibiotic coverage should be narrowed if possible when culture and sensitivity results are available. A 14-day course of therapy is generally recommended for hospitalized patients. If the patient has not improved within the first 72 hours of therapy, dedicated imaging such as renal ultrasound or computed tomography (CT) is suggested to evaluate for perinephric abscess, nephrolithiasis, obstruction, or other complication. (See Chapter 67, Focal renal infections and papillary necrosis.)

ASYMPTOMATIC BACTERIURIA

Asymptomatic bacteriuria is defined as the presence of significant bacteriuria ($\geq 10^5$ CFU/mL) in the absence of signs or symptoms of UTI.

The diagnosis of asymptomatic bacteriuria in women is made when *two* separate clean-catch, voided urine specimens demonstrate the same organism. Only *one* sample is required to make the diagnosis in males. In men and women with chronic catheterization, one sample with bacteriuria $\geq 10^2$ CFU/mL is considered diagnostic. Asymptomatic bacteriuria is common in certain populations. Reported prevalence rates range from 1.0% to 5.0% among healthy premenopausal women, 1.9% to 9.5% among pregnant women, and up to 16% of elderly ambulatory women. The prevalence of asymptomatic bacteriuria is even greater among persons in long-term care facilities and in patients with spinal cord injuries. The rate of asymptomatic bacteriuria approaches 100% in patients with chronic urinary catheterization.

Treatment of asymptomatic bacteriuria in most patient populations has no clinical benefit. The only patients who should be screened and treated for asymptomatic bacteriuria are pregnant women and patients undergoing a urologic procedure with a reasonable risk of mucosal bleeding. Pregnant women with asymptomatic bacteriuria have an increased risk of pyelonephritis and are more likely to have premature delivery and low-birth-weight infants. Patients with asymptomatic bacteriuria undergoing urologic procedures with mucosal bleeding such as transurethral prostate resection have a higher rate of bacteremia and sepsis. Pregnant women ideally should be screened between weeks 12 and 16 of gestation, but may be screened later if the first prenatal visit occurs after 16 weeks.

Bacteriuria in pregnancy should be treated for 3 to 7 days. Choice of antibiotic should depend on susceptibility results of the urine culture. Fluoroquinolones are contraindicated in pregnancy. Reasonable choices for treatment in this setting include an oral cephalosporin, TMP–SMX, trimethoprim alone, or nitrofurantoin. TMP–SMX should be avoided in the final weeks of the third trimester. Pregnant women should be screened periodically for recurrent bacteriuria following treatment, but the proper screening interval is not known; many obstetricians screen monthly.

Patients undergoing urologic procedures should be screened for asymptomatic bacteriuria prior to the procedure, and treatment should be tailored based on the susceptibility results if the urine culture is positive. Antibiotics should be discontinued at the completion of the procedure, unless an indwelling catheter is left in place.

RECURRENT CYSTITIS

Recurrent cystitis is defined as two episodes of cystitis over 6 months or three or more infections in a year. Recurrent cystitis can be categorized into two types: relapse and reinfection, although the distinction between the two can be difficult. A recurrent infection is considered a relapse if it occurs within 2 weeks of finishing treatment for the previous infection and the pathogen is the same strain. Reinfection is defined as recurrent infection with a different strain of bacteria or, if the infection is with the same strain, it occurs greater than 2 weeks after finishing the last treatment course. Relapsing infections can result from inadequate length of therapy, nephrolithiasis, urinary tract obstruction, structural abnormality, perinephric abscess, and chronic bacterial prostatitis. If relapse occurs despite appropriate treatment, further investigation for these syndromes should be undertaken.

Reinfection, which represents a majority of cases of recurrent UTIs, is often multifactorial. Some associated risk factors for women with reinfection include new sex partners, spermicide use, urinary retention, and structural abnormality. Treatment strategies are aimed at modifying these risk factors.

When appropriate, behavioral modification should be the first strategy in management of women with recurrent UTI. Although postcoital voiding in women has not been studied in controlled trials, it is often recommended based on biologic plausibility and anecdotal evidence. Given the minimal costs and side effects, it is reasonable to suggest postcoital voiding to women with postcoital UTIs. Cranberry juice has long been suggested as a preventative measure for UTIs, and a natural compound present in cranberry juice has been shown to inhibit the binding of uropathogens to uroepithelial cells. No strong evidence exists on the clinical efficacy of cranberry juice and cranberry products to prevent recurrent cystitis; however, many patients and healthcare providers have anecdotal success with this preventative treatment. In women who use spermicides, alternative methods of contraception can be considered as a modification strategy to prevent recurrent UTI.

Loss of estrogen with menopause leads to elevated vaginal pH, loss of lactobacilli in the vagina, and uropathogen-dominant vaginal flora. In postmenopausal women with recurrent UTIs, estrogen replacement therapy has been attempted, and limited clinical data suggest that

Table 65.3 Summary of treatment recommendations for recurrent urinary tract infections

Prophylaxis	Antimicrobial agent	Dose	Comments
Postcoital (single dose)	TMP–SMX	40 mg/200 mg (12 single-strength tablet)	Eliminates vaginal reservoir without disturbing other flora FDA pregnancy category C; may be used in pregnancy up until end of third trimester
	Nitrofurantoin (macrocrystals)	50–100 mg	FDA pregnancy category B
	Cephalexin	250 mg	Disrupts vaginal flora FDA pregnancy category B
	Ciprofloxacin	125 mg	FDA pregnancy category C; avoid in pregnancy
Continuous[a]	TMP–SMX	40 mg/200 mg (12 single-strength tablet)	Give daily or 3 times a week Eliminates vaginal reservoir without disturbing other flora Safe for years of use FDA pregnancy category C
	TMP	100 mg	See above
	Nitrofurantoin (macrocrystals)	50–100 mg	FDA pregnancy category B
	Cephalexin	125–250 mg	Disrupts vaginal flora FDA pregnancy category B
	Cefaclor	250 mg	Disrupts vaginal flora FDA pregnancy category B
	Ciprofloxacin	125 mg	FDA pregnancy category C

[a] All doses are given daily unless otherwise specified.

Note: Antibiotic dose recommendations assume normal renal function.

Abbreviations: TMP–SMX = trimethoprim–sulfamethoxazole; FDA = Food and Drug Administration.

topical estrogens can help prevent recurrent UTI when compared with placebo. Topical vaginal estrogen therapy offers a reasonable management strategy in postmenopausal women when behavioral interventions fail.

In patients where reinfection affects quality of life despite more conservative interventions, various antibiotic strategies can be highly effective. These strategies include patient-initiated self-treatment, postcoital prophylaxis, and continuous prophylaxis. Patient-initiated self-treatment may be used with short-course regimens in patients with two or fewer episodes per year. Only patients who will reliably contact their physicians if their symptoms do not improve in 48 hours should be considered for this strategy. Alternatively, postcoital prophylaxis can be offered to patients who can temporally associate their UTI recurrences with sexual activity.

In the remainder of women with three or more UTIs per year, continuous low-dose antimicrobial prophylaxis can be considered. Continuous prophylaxis has been shown to be highly effective, although the benefits must be weighed against the expense and the risks of adverse drug reactions and development of antimicrobial resistance. Continuous prophylaxis may be given for 6 to 12 months and a variety of agents may be used. In general, when prophylaxis is discontinued, women with recurrent UTI usually revert back to their baseline pattern of recurrent infection. If this occurs, prophylaxis can be reinitiated if the uropathogens remain susceptible. Recommended regimens for postcoital prophylaxis and continuous prophylaxis are listed in Table 65.3.

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66. Candiduria

Jack D. Sobel

Since the early 1980s, the prevalence of candiduria in hospitals has increased by 200% to 300% such that in a community hospital, 5% of urine cultures may yield *Candida*, and in tertiary care centers, *Candida* accounts for almost 10% of urinary isolates, including a quarter of Foley catheter-associated infections. Most positive *Candida* urine cultures are isolated or transient findings of little significance and represent colonization of catheters rather than true infection. Although less than 10% of candidemias are the consequence of candiduria, *Candida* urinary tract infections (UTIs) have emerged as important nosocomial infections.

Candida albicans is the most common species isolated from the urine, whereas non-*albicans Candida* species account for almost half the *Candida* urine isolates. *Candida glabrata* is responsible for 25% to 35% of infections.

PREDISPOSING FACTORS

Candiduria is rare in the absence of predisposing factors. Most infections are associated with use of Foley catheters, internal stents, percutaneous nephrostomy tubes, and age extremes of life. Diabetic patients, especially when their diabetes is poorly controlled, are particularly at risk primarily because of increased instrumentation, urinary stasis, and obstruction secondary to autonomic neuropathy. Concomitant bacteriuria is common and bacterial adherence to bladder epithelium may play a key role in the pathogenesis of *Candida* infection. Antimicrobials similarly play a critical role in that candiduria almost always emerges during or immediately after antibiotic therapy. Antibiotics, especially broad-spectrum agents, act by suppressing protective indigenous bacterial flora in the gastrointestinal (GI) tract and lower genital tract, facilitating *Candida* colonization of these sites with ready access to the urinary tract. Nosocomial candiduria is more common in intensive care unit (ICU)-based catheterized women with concomitant contributory vaginal *Candida* colonization. The pool of critically ill, immunosuppressed medical, and surgical patients has increased, and this increase, together with improved technology, provides an expanded population at risk of developing *Candida* infection.

Most lower UTIs are caused by retrograde infection from an indwelling catheter or genital or perineal colonization. Biofilm formation contributes to *Candida* persistence in the presence of catheters and stents. The upper urinary tract is uncommonly involved during ascending retrograde infection and then only in the presence of urinary obstruction, reflux, or diabetes. Renal candidiasis is usually the consequence of secondary hematogenous seeding of the renal parenchyma; *Candida* species have a unique tropism for the kidney and result in anterograde candiduria.

CLINICAL ASPECTS

Most adult patients with candiduria are asymptomatic, especially those with indwelling bladder catheters. Only 4% to 14% of patients with candiduria have symptoms of urinary infection. Clinical manifestations depend on the site of infection. *Candida* cystitis may present with frequency, dysuria, urgency, hematuria, and pyuria. Ascending infection resulting in *Candida* pyelonephritis is characterized by fever, leukocytosis, and rigors and is indistinguishable from bacterial pyelonephritis. Excretory urography may reveal ureteropelvic fungus balls or papillary necrosis. Renal candidiasis is difficult to diagnose when secondary to hematogenous spread and presents with fever and other signs of sepsis. By the time renal candidiasis is considered, blood cultures are usually no longer positive; however, unexplained deteriorating renal function is often evident.

In contrast to adult patients, candiduria in low-birth-weight infants, especially extreme low weight

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(<1000 g), is synonymous with disseminated *Candida* infection and is associated with high mortality. This patient population is not further considered in this review.

Because isolation of *Candida* from a urine specimen may represent contamination, colonization, or superficial or deep infection of the lower or upper urinary tract, diagnosis is difficult and management depends on the site of infection. Contamination of the sample is particularly common in women with vulvovaginal colonization and may be excluded by repeating urine culture with special attention to proper collection techniques. Differentiating infection from colonization may be extremely difficult if not impossible in some patients, especially if they are catheterized. Accordingly, I often rely on accompanying clinical features to determine the significance of candiduria; unfortunately these are often nonspecific in critically ill patients, and fever and leukocytosis may have several other sources.

Quantitative urine colony counts have some value in separating infection from colonization but only in the absence of a Foley catheter. The latter negates any diagnostic value of quantitative cultures. In noncatheterized patients, counts greater than 10^4 colony-forming units (CFU)/mL are usually associated with infection. It is rare for patients with invasive disease of the kidney, pelvis, or bladder to have 10^3 CFU/mL or less. No definitive cutoffs for defining candiduria have been substantiated. Most patients with urinary tract *Candida* infection have pyuria, but the value of this finding is similarly diminished in the presence of a catheter or concomitant bacteriuria and in neutropenic subjects. Serologic tests of *Candida* tissue invasion are not available. Treatment is preceded by attempts to localize the source or anatomic level of infection. Unfortunately, no reliable tests to differentiate renal candidiasis from the more frequent lower tract infections exist. The extremely rare finding of *Candida* microorganisms and pseudohyphae enmeshed in renal tubular casts is useful when present. Ultrasonography and computed tomography (CT) scans have a useful but limited role in localization. A 5-day bladder irrigation with amphotericin B may be of value in localizing the source of candiduria in catheterized subjects in that post-irrigation persistent candiduria originates from above the bladder, thus identifying patients with need for further studies. Unfortunately, the lengthy nature of this diagnostic test excludes its utility in most febrile, critically ill subjects.

PROGNOSIS

Prognosis depends on the anatomic site of *Candida* infection and the presence of urinary drainage tubes, obstruction, and concomitant renal failure. A high mortality rate of 20% is found in candiduria patients, which is more a reflection of the multiple serious illnesses found in these patients than the consequence of candiduria per se.

MANAGEMENT

More important than the knowledge of antifungal agents for treating candiduria is understanding the indications and rational basis for initiating treatment. Regrettably, despite the availability of a variety of potent antifungal agents, data from controlled studies are scant.

ASYMPTOMATIC CANDIDURIA

No antifungal therapy is required for asymptomatic candiduria in catheterized adult patients, a common condition, because candiduria often is transient only, and even if persistent rarely results in serious morbidity. Moreover, relapse of candiduria following therapy is common if the patient remains catheterized: In catheterized patients, removal of the catheter and discontinuation of antibiotics often results in cessation of candiduria (40%). Change of catheter results in elimination of candiduria in only approximately 20% of patients.

In contrast, persistent candiduria in noncatheterized patients should be investigated because the likelihood of obstruction and stasis is high. Persistent asymptomatic candiduria in catheterized, low-birth-weight infants, as well as in afebrile neutropenic patients, requires antifungal therapy and investigation to exclude the possibility of renal or systemic involvement. Patients with asymptomatic candiduria in whom urologic instrumentation or surgery is planned should have candiduria eliminated or suppressed before and during the procedure to prevent precipitating invasive candidiasis and candidemia. Successful elimination can be achieved by amphotericin B irrigation using a concentration of 50 μg/dL of sterile water for 7 days or with systemic therapy using amphotericin B, flucytosine, or fluconazole. Fluconazole, 200 to 400 mg/day, oral therapy should continue for at least 14 days to maximize cure rates. The management of asymptomatic candiduria in the renal transplant patient is perplexing. Many

recipients are diabetic, are receiving perioperative antibiotics and immunosuppressive agents, and have Foley catheters and temporary ureterocystic stents. The risk of ascending infection is high given the above and frequent reflux. Fortunately, occurrence of symptomatic renal infection and candidemia is rare. A large study by Safdar et al. found that treatment and eradication of candiduria did not enhance graft on patient survival.

CANDIDA CYSTITIS

Symptomatic cystitis requires treatment with either amphotericin B bladder irrigation (50 μg/dL) or systemic therapy, once again using intravenous (IV) amphotericin B, flucytosine, or oral fluconazole. Oral azole agents ketoconazole, itraconazole, and voriconazole are poorly excreted in the urine, and there is limited and suboptimal clinical experience only. In contrast, fluconazole is water soluble, well absorbed orally with more than 80% excreted unchanged in the urine, achieving high urine concentrations, and is highly effective. The optimal dose and duration of fluconazole therapy has yet to be determined, but usually 200 to 400 mg/day is prescribed for 7 to 14 days. Similarly, the duration of therapeutic bladder irrigation with amphotericin B is arbitrary, lasting 5 to 7 days. Amphotericin B bladder irrigation is extremely labor intensive and has largely fallen out of favor, even in symptomatic patients, being replaced by oral fluconazole except in the presence of azole-resistant *Candida* strains. Flucytosine is also excreted unchanged in high concentrations in the urine and is highly active against most *Candida* species, including *C. glabrata*; nevertheless, because resistance develops rapidly to flucytosine when used alone, this agent is rarely used especially because its use is precluded in renal insufficiency.

Single-dose IV amphotericin B, 0.3 mg/kg, has also been shown to be highly efficacious in the treatment of lower urinary tract candidiasis, achieving therapeutic urine concentrations for considerable time after the single administration. More prolonged systemic IV amphotericin B (7 to 10 days) and at conventional dosage of 0.5 to 0.7 mg/kg/day is preferable for resistant fungal species.

ASCENDING PYELONEPHRITIS AND *CANDIDA* UROSEPSIS

Invasive upper UTI requires systemic antifungal therapy as well as immediate investigation and visualization of the urinary drainage system to exclude obstruction, papillary necrosis, and fungus ball formation. Previously favored therapy consisted of IV amphotericin B, 0.5 to 0.7 mg/kg/day, for a variable duration depending on severity of infection, presence of candidemia, and response to therapy, in general 1 to 2 g total dose. However, systemic therapy with fluconazole, 5 to 10 mg/kg/day (IV or oral) for at least 2 weeks offers an effective and less toxic alternative regimen. Moreover, although the echinocandin class of antifungals (caspofungin, micafungin, and anidulafungin) achieves low urinary concentrations, they are effective for kidney parenchymal infections and particularly useful for *Candida* species resistant to azoles. Infection refractory to medical management should be treated surgically with drainage, or in cases of a nonviable kidney, nephrectomy may be indicated. An obstructed kidney with hydronephrosis requires a percutaneous nephrostomy. In some cases, nephrostomy drainage must be combined with local amphotericin B irrigation (50 μg/dL) or fluconazole, particularly with end-stage renal disease and low urinary levels of antifungal agents.

RENAL AND DISSEMINATED CANDIDIASIS

Management of renal candidiasis secondary to hematogenous spread is that of systemic candidiasis, including IV amphotericin B, 0.6 to 1.0 mg/kg/day, or IV fluconazole, 5 to 10 mg/kg/day. IV voriconazole, 4 mg/kg twice a day, or any of the echinocandins could be used in preference to amphotericin B. Dosage modifications of fluconazole but not the echinocandins are necessary in the presence of moderate to severe azotemia. Prognosis depends on correction of underlying factors, that is, resolution of neutropenia, removal of responsible intravascular catheters, and susceptibility of the *Candida* species, but most importantly the nature and prognosis of the underlying disease per se. Systemic candidiasis involving metastatic sites of infection requires prolonged therapy for approximately 4 to 6 weeks.

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67. Focal renal infections and papillary necrosis

David B. Banach and Louise M. Dembry

Focal infections of the kidney can be divided into intrarenal and perirenal pathology (Table 67.1). The classification of intrarenal abscess encompasses renal cortical abscess and renal corticomedullary abscess; the latter includes acute focal bacterial nephritis, acute multifocal bacterial nephritis, and xanthogranulomatous pyelonephritis. Perirenal abscesses are found in the perinephric fascia external to the capsule of the kidney, generally occurring from extension of an intrarenal abscess. Papillary necrosis is a clinicopathologic syndrome that develops during the course of a variety of syndromes, including pyelonephritis, affecting the renal medullary vasculature, leading to ischemic necrosis of the renal medulla.

Table 67.1 Focal renal infections

Intrarenal abscesses
Renal cortical abscesses
Renal corticomedullary abscesses
Acute focal bacterial nephritis
Acute multifocal bacterial nephritis
Xanthogranulomatous pyelonephritis
Perinephric abscesses

RENAL CORTICAL ABSCESS

A renal cortical abscess results from hematogenous spread of bacteria from a primary focus of infection outside the kidney, often the skin. The most common causative agent is *Staphylococcus aureus* (90%). Predisposing conditions include entities associated with an increased risk for staphylococcal bacteremia, such as hemodialysis, diabetes mellitus, and injection drug use. The primary focus of infection may not be apparent in up to one-third of cases. Ascending infection is an infrequent cause of renal cortical abscess formation. Ten percent of renal cortical abscesses rupture through the renal capsule, forming a perinephric abscess.

Patients present with chills, fever, and back or abdominal pain, with few or no localizing signs (Table 67.2). Most patients do not have urinary symptoms as the process does not generally communicate with the excretory passages. Physical examination may reveal costovertebral angle tenderness and involuntary guarding in the upper lumbar and abdominal musculature. A flank mass or bulge in the lumbar region with loss of lumbar lordosis may be present.

Laboratory data vary, though leukocytosis is common. Radiologic techniques can establish the diagnosis. Ultrasonography is useful diagnostically and may guide percutaneous drainage of the abscess and follow response to therapy. Computed tomography (CT) is the most precise noninvasive diagnostic technique and may guide percutaneous aspiration. Magnetic resonance imaging (MRI) with gadolinium may help diagnose renal abscess and define its extent, with accuracy comparable to CT but without exposure to radiation and ionizing contrast.

Renal cortical abscesses often respond to antibiotics alone without surgical intervention. If the diagnosis is suspected and bacteriologic evaluation of the urine or aspirated abscess fluid reveals large, gram-positive cocci or no bacteria, antistaphylococcal therapy should be started promptly (Table 67.3). The choice of empiric therapy depends on the susceptibility patterns of *S. aureus* in the community. If methicillin-susceptible *S. aureus* (MSSA) is suspected a semisynthetic penicillin (oxacillin or nafcillin) is appropriate empiric therapy. For penicillin-allergic patients, a first-generation cephalosporin, such as cefazolin, may be used. Vancomycin should be used for patients with a severe immediate β-lactam allergy. If the prevalence of methicillin-resistant *S. aureus* (MRSA) is high, empiric therapy with vancomycin should be initiated. In the absence of occult bacteremia, parenteral antibiotics are administered for 10 days

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Table 67.2 Clinical and laboratory findings of renal and perirenal abscesses

	Renal cortical abscess	Renal corticomedullary abscess	Perinephric abscess
Epidemiology	Males 3× > females, 2nd–4th decades, hematogenous seeding of kidneys	Males = females (females > males in xanthogranulomatous pyelonephritis), incidence increases with age, associated with underlying abnormality of the urinary tract	Males = females, 25% of patients are diabetic, rupture of intrarenal suppurative focus into perinephric space
Clinical presentation	Chills, fever, localized back or abdominal pain	Chills, fever, flank or abdominal pain, nausea and vomiting (65%)	Insidious onset over 2–3 weeks: fever (early), flank pain (late)
Urinary symptoms	None[a]	Dysuria/other urinary tract symptoms variably present	Dysuria 40%
Physical exam	Flank mass	Flank mass in 60%, hepatomegaly in 30%	Flank or abdominal mass in ≤50%, 60% have abdominal tenderness
Organisms	*S. aureus*	Enteric aerobic gram-negative rods (*Escherichia coli*, *Klebsiella* species, *Proteus mirabilis)*	Enteric aerobic gram-negative rods and *S. aureus*; occasionally *Pseudomonas* species, gram-positive bacteria, obligate anaerobic bacteria, fungi, mycobacteria; 25% polymicrobial
Urinalysis	Normal[a]	Abnormal in 70%	Abnormal in 70%
Urine cultures	Negative[a]	Generally positive	Positive in 60%
Blood cultures	Often negative	Often positive	Positive in 40%

[a] If there is no communication between the abscess and the collecting system.

to 2 weeks, followed by oral antistaphylococcal therapy for at least 2 to 4 more weeks. Fever generally resolves after 5 to 6 days of antimicrobial therapy. If there is no response to therapy in 48 hours, percutaneous aspiration should be considered, and, if unsuccessful, open drainage should be undertaken. The prognosis is good if the diagnosis is made promptly and effective therapy is instituted immediately.

RENAL CORTICOMEDULLARY ABSCESS

Renal corticomedullary abscesses occur most commonly as a complication of bacteriuria and ascending infection accompanied by an underlying urinary tract abnormality. The most common abnormalities include obstructive processes, genitourinary abnormalities associated with diabetes mellitus or primary hyperparathyroidism, and vesicoureteral reflux. Enteric aerobic gram-negative bacilli, including *Escherichia coli, Klebsiella*, and *Proteus* species, are common causative organisms. Acute focal bacterial nephritis, a severe form of acute bacterial interstitial nephritis involving a single renal lobe, represents focal inflammation of the kidney without frank abscess formation and may be an early phase of acute multifocal bacterial nephritis. Xanthogranulomatous pyelonephritis is an uncommon but severe chronic infection of the renal parenchyma. It may be related to a combination of renal obstruction and chronic urinary tract infection. Predisposing factors include renal calculi, urinary obstruction, lymphatic obstruction, partially treated chronic urosepsis, renal ischemia, and secondary metabolic alterations in lipid metabolism, abnormal host immune response, diabetes mellitus, and primary hyperparathyroidism.

Patients typically present with fever, chills, and flank or abdominal pain. Two-thirds of patients have nausea and vomiting, and dysuria may not be present. In some patients symptoms may be subtle, delaying the diagnosis. Patients may have a history of recurrent urinary tract infections, renal calculi, or prior genitourinary instrumentation. On exam, 60% of patients have a flank mass and 30% have hepatomegaly. The urinalysis is often abnormal with bacteriuria, pyuria, proteinuria, and hematuria. Patients with acute focal or multifocal bacterial nephritis are frequently bacteremic. Many patients (75%) are anemic, and up to 50% of patients with xanthogranulomatous pyelonephritis have hyperuricemia.

The nonspecific clinical presentation is associated with a variety of renal processes, including renal cortical abscess, perinephric abscess, renal cysts, and tumors. Radiographic techniques are necessary to differentiate these various

Table 67.3 Therapy of renal and perirenal abscesses

	Empiric therapy[a]	Duration[a]	Drainage	Surgery
Renal cortical abscess	Antistaphylococcal penicillin: oxacillin or nafcillin (1–2 g IV every 4–6 h) Penicillin allergy: First-generation cephalosporin: cefazolin (2 g IV every 8 h) or vancomycin (15 mg/kg IV every 12 h) if severe immediate β-lactam allergy or if MRSA is suspected	Intravenous antibiotics for 10 days to 2 weeks followed by 2–4 weeks oral antistaphylococcal antibiotic depending on antibiotic susceptibility testing	If no response to treatment after 48 h → percutaneous drainage followed by open drainage if no response	
Renal corticomedullary abscess				
Acute focal bacterial nephritis	Extended-spectrum penicillin (piperacillin–tazobactam 3.375 g IV every 6 h), extended-spectrum cephalosporin (ceftriaxone 1 g IV every 24 h, cefotaxime 1 g every 8 h), fluoroquinolone (ciprofloxacin 200–400 mg IV every 12 h), ampicillin (1 g IV every 4–6 h) with gentamicin or cefazolin (1 g every 8 h) with gentamicin	Intravenous for 24–48 h after resolution of symptoms and fever followed by 2 weeks oral antibiotics based on results of susceptibility testing (cefpodoxime 200 mg every 12 h or ciprofloxacin 500 mg every 12 h)	Generally not necessary	
Acute multifocal bacterial nephritis	Same as acute focal bacterial nephritis	Same as acute focal bacterial nephritis	If slow response to antibiotics or large abscess, presence of obstructive uropathy, urosepsis, or advanced age	
Xanthogranulomatous pyelonephritis	Same as acute focal bacterial nephritis	Same as acute focal bacterial nephritis		Surgical excision usually necessary for cure (partial nephrectomy or total nephrectomy)
Perinephric abscess	Antistaphylococcal agent with an aminoglycoside or an ESBL agent. Vancomycin should be included if suspect MRSA. If isolate *Pseudomonas aeruginosa*, an antipseudomonal β-lactam (piperacillin–tazobactam 4.5 g IV every 6 h, cefepime 2 g IV every 12 h, ceftazidime 2 g IV every 8 h) should be added to the aminoglycoside. Alternatively, add ciprofloxacin 200–400 mg IV every 12 h and discontinue the aminoglycoside. For ESBL-producing organisms, use a carbapenem. For enterococcus, treatment of choice is ampicillin 2 g IV every 4–6 h (or vancomycin 15 mg/kg IV every 12 h for penicillin-allergic patients) plus gentamicin	Initial parenteral therapy until clinical improvement, change to appropriate oral therapy until radiographic studies indicate resolution of process	Requires percutaneous drainage followed by open surgical drainage if no resolution	Nephrectomy in cases that do not resolve with antibiotics and drainage

[a] Dosages based on normal renal and hepatic function.

Abbreviations: MRSA = methicillin-resistant *Staphylococcus aureus*; ESBL = extended-spectrum β-lactamase.

space-occupying lesions. Ultrasonography and CT scanning are both used for diagnosing renal corticomedullary abscesses except for xanthogranulomatous pyelonephritis, for which ultrasound is less specific than CT. MRI may be considered for patients with renal insufficiency or allergy to iodinated contrast material.

Most patients with acute focal and multifocal bacterial nephritis respond to antibiotic treatment alone within 1 week of starting therapy.

Radiologic techniques should be used to ensure resolution of the parenchymal abnormalities after clinical resolution. An intensive trial of appropriate antibiotic therapy can be attempted before considering surgical drainage for lesions localized to the renal parenchyma. A large, well-established abscess may be more difficult to treat successfully with antimicrobial agents alone. Most intrarenal abscesses less than 3 cm respond to antimicrobial therapy alone, whereas abscesses larger than 3 cm often require percutaneous or surgical drainage. Parenteral antimicrobial agents and intravenous hydration should be administered promptly when the diagnosis is considered. Empiric antimicrobial therapy is directed against the common bacterial organisms in this setting, including *E. coli, Klebsiella*, and *Proteus* species (Table 67.3). An extended-spectrum penicillin (e.g., piperacillin–tazobactam) or cephalosporin (ceftriaxone or cefotaxime), or ciprofloxacin are all appropriate choices. Antimicrobial therapy should be modified based on the results of culture and sensitivity testing. Duration of therapy should be individualized. Parenteral antimicrobial therapy should be continued for at least 24 to 48 hours after improvement of symptoms and resolution of fever. Oral antibiotic therapy, based on antimicrobial susceptibility results, is then administered for an additional 2 weeks.

Acute focal bacterial nephritis typically responds to antimicrobial therapy alone, with follow-up radiographic studies showing complete resolution of the intrarenal lesion. Only occasionally is a drainage procedure necessary. Factors associated with failure to respond to antimicrobial therapy alone include large abscesses, obstructive uropathy, advanced age, and urosepsis. Percutaneous abscess aspiration, sometimes with repeated aspirations, combined with parenteral antibiotics has been successful. If obstructive uropathy is present, prompt drainage by percutaneous nephrostomy until the patient is stable and afebrile is appropriate at which time the lesion should then be corrected. Nephrectomy is reserved for patients with diffusely damaged renal parenchyma or patients requiring urgent intervention for survival in the setting of sepsis.

Patients with xanthogranulomatous pyelonephritis generally require surgical excision of the xanthogranulomatous process for cure, although there have been case reports of successful treatment without surgical intervention. Once the tissue is removed, the xanthogranulomatous process ceases and does not recur; however, bacteriuria may recur and require treatment. After excision, the prognosis in those without other urinary pathologic conditions is excellent.

PERINEPHRIC ABSCESS

The common etiologic agents of intrarenal abscesses, *E. coli, Proteus* species, and *S. aureus*, are also the common organisms associated with perinephric abscesses. Other gram-negative bacilli associated with this entity are *Klebsiella*, *Enterobacter*, *Pseudomonas*, *Serratia*, and *Citrobacter* species. Occasionally enterococci are implicated and anaerobic bacteria may account for culture-negative abscesses. Fungi, particularly *Candida* species, are also important, as is *Mycobacterium tuberculosis*. Perinephric abscesses may be polymicrobial in up to 25% of cases.

A perinephric abscess is a collection of suppurative material in the perinephric space between the renal capsule and Gerota's fascia. Most perirenal abscesses result from the rupture of an intrarenal abscess into the perinephric space, chronic or recurrent pyelonephritis, particularly in the presence of obstruction, and xanthogranulomatous pyelonephritis. Predisposing conditions for perinephric abscesses are similar to those for intrarenal abscesses. Most patients have underlying urinary tract abnormalities. Patients with polycystic kidney disease, neurogenic bladders, or chronic or recurrent urinary tract infections, with or without calculi, may also be at increased risk. Up to 25% of patients are diabetic.

The symptoms of perinephric abscess develop insidiously over a period of 2 to 3 weeks (Table 67.2). Fever is present in most patients. Unilateral flank pain is common (70% to 80%), whereas chills and dysuria are less common (40%). Costovertebral angle tenderness is often present on exam, and 60% of patients may have abdominal tenderness. Half the patients have flank or abdominal mass.

The diagnosis should be strongly considered in any patient with a febrile illness and unilateral flank pain that does not respond to therapy for acute pyelonephritis. CT is the radiographic study of choice as it identifies the abscess and defines its extent beyond the renal capsule and the surrounding anatomy, including extension into the psoas muscle. MRI is an acceptable imaging modality when avoidance of exposure to radiation and iodinated contrast is desired. Ultrasound may identify the abscess structure and extent, though sensitivity is less than CT imaging.

Early recognition, prompt drainage, and antimicrobial therapy have all contributed to

decrease the mortality associated with this entity. However, antimicrobial therapy alone is usually inadequate and percutaneous drainage should be considered. Surgical drainage is considered when an abscess is multilocular, and percutaneous drainage fails or is contraindicated. Most cavities spontaneously resolve after drainage and antimicrobial therapy. Acute nephrectomy is occasionally indicated. Empiric antimicrobial therapy should be directed against the most common gram-negative pathogens and *S. aureus* (Table 67.3). An aminoglycoside and an antistaphylococcal β-lactam (oxacillin, nafcillin, or cefazolin) are appropriate initial antibiotics. If MRSA is suspected, vancomycin should be used instead of an antistaphylococcal β-lactam. An extended-spectrum β-lactam (ESBL) may be used in place of an aminoglycoside for gram-negative coverage. When *Pseudomonas aeruginosa* is cultured, an antipseudomonal β-lactam (piperacillin–tazobactam, cefepime, or ceftazidime) should be included with or without an aminoglycoside. Alternatively, the aminoglycoside may be discontinued and ciprofloxacin given. If an ESBL-producing gram-negative is suspected a carbapenem should replace a β-lactam. If enterococcus is isolated, ampicillin plus gentamicin is the treatment of choice. Therapy should be modified based on culture and antimicrobial susceptibility testing results. Perinephric abscesses caused by mycobacteria and fungi are treated with appropriate antimicrobial agents based on the organism and antimicrobial susceptibility testing.

Perinephric abscesses may cause ureteral compression leading to hydronephrosis. Even after drainage, ureteral stenosis from periureteritis may evolve during the healing process, a late complication of this disease.

RENAL PAPILLARY NECROSIS

Renal papillary necrosis is an uncommon severe complication of pyelonephritis (2% to 5% of patients) that occurs most often with underlying structural renal abnormalities or host immunocompromise (over half of patients are diabetic) (Table 67.4). When papillary necrosis is caused by infection, both kidneys are frequently affected with one or more pyramids involved. As the lesion progresses, a portion of the necrotic papilla may break off, producing a calyceal deformity that results in a recognizable radiologic filling defect. The sloughed portion may be voided and can be recovered from the urine.

Table 67.4 Conditions associated with development of papillary necrosis

Diabetes mellitus
Pyelonephritis
Obstruction
Analgesic abuse
Sickle cell disease
Renal transplantation

Patients present with worsening symptoms of pre-existing pyelonephritis. They may have lumbar pain, hematuria, and fever. The diagnosis should be considered in diabetic patients with active pyelonephritis who experience a rapid clinical deterioration and/or worsening renal function. Multiphasic helical CT is helpful in identifying early papillary necrosis.

Therapy is directed toward control of infection generally caused by common uropathogens including *E. coli*, *Proteus*, and *Klebsiella* species (Table 67.3, renal corticomedullary abscess treatment). If the patient does not respond promptly to appropriate antimicrobial therapy and infection is not controlled, nephrectomy may be needed.

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PART IX

Clinical syndromes: musculoskeletal system

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68. Infection of native and prosthetic joints

Shahbaz Hasan and James W. Smith

NATIVE JOINT INFECTIONS

Infections of native joints generally occur in patients with predisposing factors such as trauma, underlying arthritis, immunosuppressive therapy, diabetes mellitus, malignancies, intravenous drug abuse, and other infections (e.g., endocarditis, skin infections, and urinary tract infections). Hematogenous spread of the organism through the highly vascular synovial space leads to an influx of polymorphonuclear leukocytes (PMLs) into the synovium and then to a release of enzymes that destroy the articular surface.

Diagnosis

Patients present with pain and limited motion of the joint. Fever may be mild, with only a few patients having a temperature higher than 39°C (102.2°F). Joint tenderness can be minimal to severe, but most patients have swelling as a result of joint effusions in response to the infection. Involvement of multiple joints is seen in 10% to 20% of cases, especially in viral arthritis and rheumatoid arthritis. Laboratory findings suggestive of septic arthritis include an elevated erythrocyte sedimentation rate and synovial fluid cell counts exceeding 50 000/mL, with more than 75% PMLs. In no individual case do any of these findings distinguish infected from inflammatory arthritis, such as rheumatoid or crystalline arthropathy, so the diagnosis is based on cultures of synovial fluid. On occasion, blood cultures may be positive. In patients with a chronic monoarticular process caused by mycobacterial or fungal organisms, synovial tissue cultures provide a better yield than synovial fluid cultures. Serum antibody tests provide the diagnosis of Lyme or viral arthritis. Polymerase chain reaction (PCR) assay of the joint fluid may yield the diagnosis in partially treated patients or in patients' infections caused by fastidious organisms such as *Mycoplasma*, *Chlamydia*, or *Borrelia burgdorferi* (Lyme disease). Plain radiographs are seldom of use diagnostically. Computed tomography (CT) and magnetic resonance imaging (MRI) provide more detail of the surrounding soft tissue and may reveal adjacent osteomyelitis. Radionuclear scans may be needed to visualize the sacroiliac joint; however, they are unable to distinguish septic arthritis from other inflammatory arthritis.

Staphylococcus aureus is the most common organism isolated in native bacterial arthritis. However, a variety of other gram-positive and gram-negative organisms have been reported as agents in monoarticular bacterial arthritis. *Neisseria gonorrhoeae* is the main cause of bacterial arthritis in sexually active individuals with no underlying joint disease. It presents with a syndrome of fever, skin lesions, and polyarticular involvement, often with associated tenosynovitis. Any of a number of mycobacterial and fungal organisms can cause a chronic, slowly progressive infection of a single joint with tenosynovitis. Viral agents commonly associated with arthritis include rubella and parvovirus B19 (erythema infectiosum or fifth disease) in women and mumps in men. Hepatitis B infection may manifest as a prodromal syndrome consisting of arthritis and urticaria that disappear with the onset of jaundice.

Therapy

Empiric antimicrobial therapy for suspected bacterial arthritis is started after obtaining appropriate fluid specimens for analysis and culture. The choice of antibiotics depends on the patient's age, risk factors, and results of the synovial fluid Gram stain (Figure 68.1). The antibiotics are modified after obtaining the culture results. The usual course of antibiotics is 2 weeks. Infections from staphylococci and gram-negative bacilli require 3 weeks of treatment. Mycobacterial and fungal infections are treated for up to a year. Initial therapy by causative organism is given in Table 68.1.

Infected joint effusions require repeated needle aspirations of recurrent joint effusions during the

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Table 68.1 Therapy for bacterial arthritis of native joints

Microorganism/infection	Treatment	Duration
Staphylococcus aureus	Penicillinase-resistant penicillins,[a] first-generation cephalosporin,[b] or cefuroxime, 1.5 g q8h	3–4 wk
Methicillin-resistant *S. aureus* or patient allergic to penicillin	Vancomycin, 1 g q12h daptomycin 4–6 mg/kg/d, or linezolid 600 mg q12h	3–4 wk
Streptococci	Penicillin G, 4 million units q6h, or first-generation cephalosporin[b] or clindamycin, 300 mg q8h	2 wk
Gram-negative bacilli	Antipseudomonal cephalosporins,[c] carbapenem,[d] quinolone[e]	3–4 wk
Disseminated gonococcal infection	Ceftriaxone, 1 g q24h until response, then cefixime, 400 mg PO BID	7–10 d
Septic gonococcal arthritis	Ceftriaxone, 1 g q24h	3 wk
Lyme arthritis	Doxycycline, 100 mg PO BID, or ceftriaxone, 2 g q24h IV	4 wk, 2 wk
Mycobacterium tuberculosis	Isoniazid, 300 mg/d, plus rifampin, 600 mg/d, with ethambutol, 15 mg/kg/d, and pyrazinamide, 1500 mg/day for the first 2 mo	1 y
Fungal arthritis	Amphotericin B, 0.5–0.7 mg/kg/d for a total of 2 g, then itraconazole, 200–400 mg/d PO, or fluconazole, 200–400 mg/d PO	1 y

[a] Nafcillin, 2 g q6h IV.
[b] Cefazolin, 1 g q8h IV, or cephalothin, 1–2 g q6h IV.
[c] Ceftazidime, 2 g q8h IV, or cefepime, 1 g q12h IV.
[d] Imipenem–cilastatin, 500 mg q6h IV, or meropenem, 500 mg q8h IV.
[e] Ciprofloxacin, 400 mg q12h IV, or levofloxacin, 500 mg q24h IV.
Abbreviations: PO = orally; BID = twice a day; IV = intravenously.

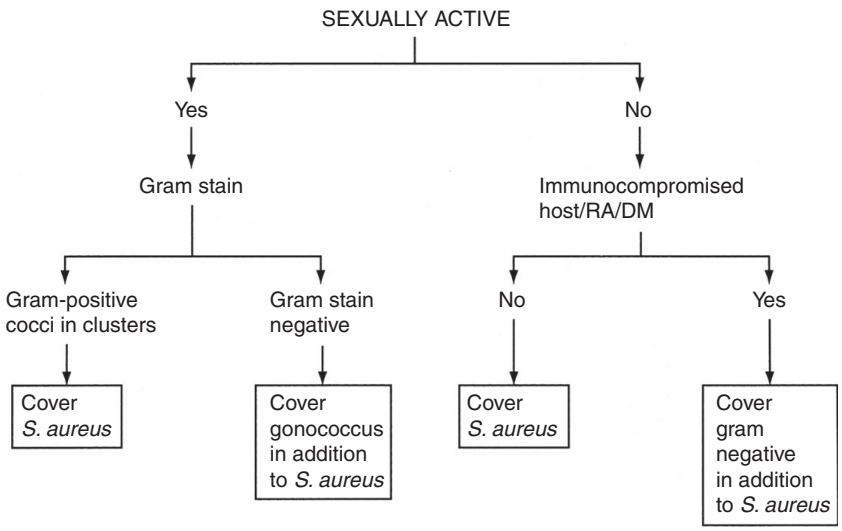

Figure 68.1 Empiric antibiotic coverage for nontraumatic, acute monoarticular arthritis. RA = rheumatoid arthritis; DM = diabetes mellitus.

first 5 to 7 days of antimicrobial therapy. Most patients respond to needle aspiration. If the volume of fluid and number and percentage of PMLs decrease with each aspiration, no drainage is required. However, if the effusion persists for more than 7 days or the cell count does not decrease, surgical drainage is indicated. Surgical drainage is also indicated when effective decompression with needle aspiration is unlikely (hip joint) or when the joint is not accessible for aspiration (sternoclavicular and sacroiliac joints); if the joint space has become loculated as a result of formation of adhesions; or if thick, purulent material resisting aspiration is encountered. Arthroscopic drainage is an alternative to open drainage for the knee, shoulder, and ankle joints.

Prognosis

Bacterial arthritis is associated with a mortality of 10% to 15%. Up to 25% to 50% of surviving patients are left with residual loss of joint function. Poor outcomes are commonly seen in the elderly and those with severe underlying joint disease, hip infections, or infections caused by mycobacterial or fungal agents.

PROSTHETIC JOINT INFECTIONS

Prosthetic joint surgery has been used with increasing frequency over the past 4 decades. About 1 000 000 arthroplasties are performed in the United States each year. Although most procedures involve the hip and knee joints, arthroplasties of the elbow, shoulder, and wrist are also being performed. Primary indications for surgery generally include rheumatoid arthritis, degenerative joint disease, fractures, and septic arthritis.

Ten-year implant survival rates of 70% to 90% are being achieved at most centers. Most failures result from aseptic loosening of the prosthesis, with infectious complications accounting for fewer than 1% of implant failures. These prosthesis infections necessitate extensive surgical procedures and prolonged use of antibiotics, all of which result in increased cost, morbidity, and rarely, mortality. Risk factors for the development of prosthesis infection include rheumatoid arthritis, previous surgeries at the joint, postoperative wound infection, hematoma, and unhealed or draining wounds at hospital discharge. Other risk factors include sinus tracts to the surgical site, obesity, age, use of immunosuppressive therapies, diabetes mellitus, and distant site infections, especially urinary tract and skin infections. Varying frequency of infection is noted with different joints: Incidence of infections for hip arthroplasties is less than 1%; for knees 1% to 2%; and for elbows 4% to 9%.

Direct inoculation of the joint at the time of surgery and intraoperative airborne contamination probably account for most infections. Evidence of the importance of this is demonstrated by the preponderance of infections caused by skin commensals (Table 68.2) and by reduction in frequency of infection that accompanies the use of prophylactic antibiotics. Hematogenous seeding of the implants is implicated in infections occurring more than 2 years postoperatively.

Table 68.2 Microbiology of prosthetic joint infections

Organism	Percentage
Staphylococcus aureus	25
Coagulase-negative staphylococci	25
Streptococci	5–10
Enterococci	3–5
Gram-negative bacilli	8–10
Anaerobes	5–10
Mixed	10–15
Others (fungi, mycobacteria, actinomyces, brucella)	1–2

Diagnosis

The diagnosis of acute prosthetic joint infection is suspected in those who develop pain and fever within 6 months of the procedure. These findings are similar to those of acute septic arthritis in a native joint. However, most infections tend to be indolent and manifest with local pain and mechanical loosening of the prosthesis. Clinical features, laboratory tests, and imaging techniques may be insufficient to differentiate between aseptic and septic complications (Table 68.3). Hence, the diagnosis of an infection often has to be confirmed on the basis of the intraoperative appearance of the tissues and the presence or absence of acute inflammatory reaction on the intraoperative histopathology specimens. Given the heterogeneity of organisms (see Table 68.2), the joint fluid and tissues must be submitted for aerobic and anaerobic bacterial, fungal, and mycobacterial cultures. Microbiologic culture yield is improved if sampling of tissues is performed with the patient being off antimicrobials for 1 to 2 weeks.

Therapy

The object of successful management of prosthetic joint infections is 2-fold: eradication of infection and maintenance of functional integrity of the joint. Two-stage reimplantations offer the best possible chance for eradication of infection. However, not all patients may be suitable candidates for this extreme surgical undertaking either because of poor bone stock, inability to withstand prolonged immobilization, or inability to eradicate the infectious agent. Such cases may call for other salvage techniques that usually sacrifice joint function for microbiologic cure (Table 68.4).

Table 68.3 Diagnostic features of prosthetic joint infections

	Suggestive findings	Comments
History	Rest pain; lack of postoperative pain-free interval; difficult wound healing; fever	These findings are not specific; they may also be found in aseptic loosening of the prosthesis. Infected prosthesis may be asymptomatic
Physical findings	Swelling; tenderness; limitation of motion; fever; sinus tract	As above
Laboratory tests	Leukocytosis; elevated ESR or CRP	Elevations in these parameters noted in most acute infections but may be normal in chronic, indolent infections
Radiology	Periostitis; endosteal scalloping; focal or diffuse osteolysis	Radiologic findings may be normal. Cannot distinguish mechanical loosening from septic arthritis
Nuclear imaging	Enhanced uptake in the region of the prosthesis	Subjective and reader dependent. Sequential bone and tagged white cell scans provide greater sensitivity and specificity than if done alone. Provides no information about organisms
Joint aspiration	Positive cultures	Sensitivity 60%–80%; specificity 85%–95%; dry taps 10%–15%. More useful in symptomatic cases; provides specific information about organisms and sensitivities; detection of previously undetected infections. Yield improved if patient is off antibiotics for 2 weeks

Abbreviations: ESR = erythrocyte sedimentation rate; CRP = C-reactive protein.

Table 68.4 Treatment options for prosthetic joint infections

Technique	Method	Comments
Reimplantation (exchange arthroplasty)	Removal of prosthesis and cement, immediate reimplantation (one stage) or delayed reimplantation (two stages)	Technique of choice. Excellent functional results and good microbiologic cure. Patient must be physically able to undergo major surgery and prolonged immobilization. Adequate bone stock necessary for reimplantation
Resection arthroplasty	Removal of prosthesis and cement, extensive debridement of adjacent bone	Used if reimplantation not possible because of major bone loss, recurrent infections, poorly responsive organisms (e.g., fungi) and patient mobility not essential/necessary for reimplantation Provides good microbiologic cure at the expense of joint function
Arthrodesis	Removal of prosthesis and cement and fusion of joint	If mobility is needed but patient cannot undergo reimplantation May require prolonged immobilization
Amputation		Radical treatment may be necessary following multiple revision attempts, intractable pain, or life-threatening infection
Implant salvage	Chronic antibiotic suppression, alone or with local debridement and retention of prosthesis	Indicated if patient is unable or refuses to undergo major surgery. May be successful provided duration of symptoms $\leq$ 3 wk, no sinus drainage, no radiologic evidence of loosening, and the microorganism is highly susceptible to antibiotics

Antibiotic selection is based on the susceptibility pattern of the organisms isolated. The antibiotics of choice for the isolated organisms are similar to those used in native joint infections (see Table 68.1). Unlike native joint infections, the most common organisms isolated in prosthetic joint infections are coagulase-negative staphylococci (see Table 68.2). Therefore this organism should not be considered a contaminant but should be treated. If the prosthesis is removed, parenteral antibiotics are administered for 6 to 8 weeks; however, if management includes retention of the prosthesis, a prolonged course of oral antibiotics (6 months to 1 year) should be given after the completion of the course of parenteral antibiotics. With regard to staphylococci, 2 to 6 weeks of parenteral antibiotics in combination with rifampin is followed by a further 6 weeks of oral agents. Oral agents may include quinolones, if susceptible, such as ciprofloxacin, 750 mg twice daily, or levofloxacin, 500 mg once daily, combined with rifampin, 600 mg once

daily. Other alternatives include minocycline or doxycycline, 100 mg twice daily.

Prevention

Perioperative antibiotic coverage includes agents directed against the most common causative agents, that is, gram-positive cocci. A first-generation cephalosporin will achieve this. The antimicrobial agents are administered within 30 to 60 minutes of surgery and are continued for up to 24 hours postoperatively. For patients known to be colonized with methicillin-resistant *S. aureus* (MRSA), an additional dose of vancomycin should be administered. Antibiotic-impregnated beads and cement have also been used extensively because they have the advantage of delivering high local levels of antibiotics with minimal systemic toxicity. Laminar air-flow devices and body exhaust suits have been recommended to prevent intraoperative contamination; however, it is unclear whether these considerably expensive techniques are cost-effective.

There is no convincing evidence of benefit of routine prophylaxis with antibiotics for patients with prosthetic joints undergoing uncomplicated dental, urinary, or gastrointestinal procedures. The risk of infection is similar to that of endocarditis developing in the general population. In a joint advisory statement, however, the American Dental Association and the American Academy of Orthopedic Surgeons have suggested prophylaxis regimens similar to those set out by the American Heart Association for endocarditis in certain high-risk patients undergoing high-risk dental procedures.

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69. Bursitis

Richard H. Parker

Inflammation of bursal sacs, or bursitis, is a common condition. Bursa are fluid-filled sacs that act as cushions between tendons and either bone or skin. There are more than 150 bursae in the human body. Most cases of bursitis involve either the olecranon or the prepatellar bursa, and the majority are related to trauma. At most 20% to 30% are infected either primarily or secondary. A much smaller percent are the result of inflammation associated with rheumatologic disorders. Possibly the most common scenario for septic arthritis is a needlestick for corticosteroid injection into a bursa as therapy for nonseptic bursitis. Septic bursitis can also occur as a complication of bacteremia without a history of trauma to the involved area. Septic bursitis is less common in the pediatrics patient but does occur and is usually associated with acute trauma such as sports-related injuries.

Septic and nonseptic bursitis of superficial bursae such as at the olecranon and prepatellar sites may present as both red and tender areas (Figure 69.1). Clinical features, including fever or infection at another site, may help differentiate infected from noninfected. Bursitis of deeper bursae, such as trochanteric bursitis is usually not infectious but tuberculous bursitis of the greater trochanter and other deeper sites has occurred. Microorganisms from the skin cause most infectious bursitis. *Staphylococcus aureus* may cause about 90% of infected bursa. However, any microorganism (hemolytic streptococci, gram-negative bacilli, or fungi) if introduced can infect these spaces. As with other infectious diseases, the immunocompromised host may be infected with unusual opportunistic microorganisms.

Diagnosis of septic bursitis requires aspiration of fluid for microscopy, culture, cell counts, and glucose (Table 69.1).

THERAPY

Therapy is started following a decision as to whether the inflammation is infectious or noninfectious (Figure 69.2). Noninfectious bursitis is treated with immobilization, heat, and anti-inflammatory agents and referred to

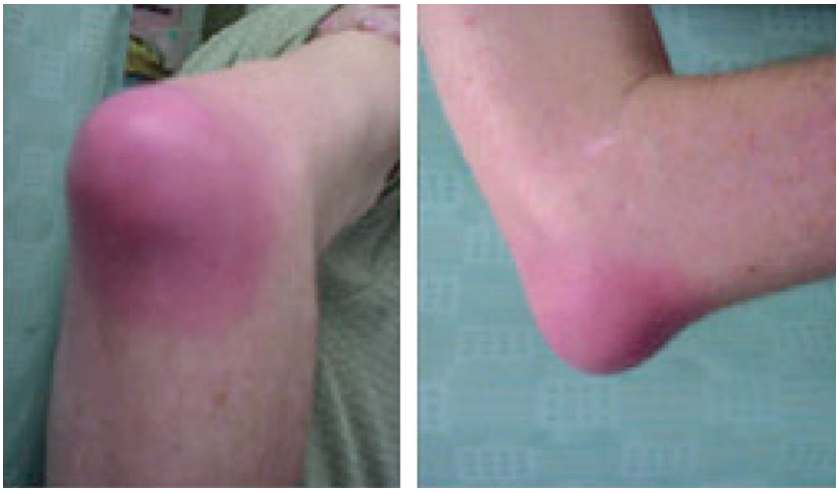

Figure 69.1 Red, swollen olecranon bursa. (From *Resident and Staff Physician*, March 2006.)

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Table 69.1 Findings in bursal fluid related to causes of bursitis

Finding	Normal	Trauma	Sepsis	Rheumatoid inflammation	Microcrystalline inflammation
Color	Clear yellow	Bloody xanthochromic	Yellow, cloudy	Yellow, cloudy	Yellow, cloudy
WBC	0–200	$\leq$ 5000	1000–200 000	1000–20 000	1000–20 000
RBC	0	Many	Few	Few	Few
Glucose	Normal[a]	Normal[a]	Decreased	Decreased (slight)	Variable
Gram stain, culture	Negative	Negative	Positive	Negative	Negative

Abbreviations: WBC = white blood cell; RBC = red blood cell.
[a] Fluid glucose/blood glucose = 0.6–1.

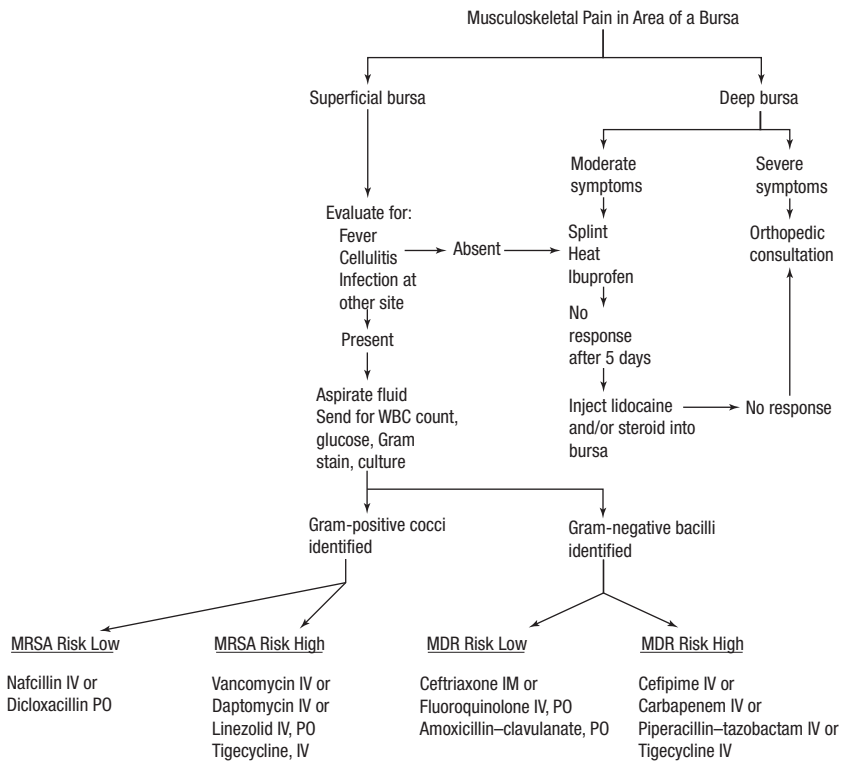

Figure 69.2 Algorithm for the management of musculoskeletal pain in the area of a bursa. MRSA = methicillin-resistant *Staphylococcus aureus*; MDR = multidrug resistance.

orthopedics depending on the severity or response to therapy. Septic bursitis might require hospitalization for surgical drainage and intravenous antimicrobial therapy. However, most patients are not septic, toxic, or immunocompromised and may be considered compliant and therapy can be initiated with oral antimicrobial agents and the patient is followed closely as an outpatient. Home intravenous infusion therapy is an option but should be restricted to therapy of methicillin-resistant *S. aureus* (MRSA) or other pathogens that require use of drugs that can be given only intravenously or when patients cannot tolerate oral medications.

Initial therapy must use a good antistaphylococcal agent and may be oral therapy for nonseptic patients. In one report of 82 cases, a cloxacillin-based regimen resulted in cure of all but one patient. All patients received intravenous therapy until afebrile, including gentamicin in 35 patients. In areas where MRSA is common, intravenous vancomycin, daptomycin, or linezolid should be initiated. Linezolid has excellent bioavailability with equal efficacy for MRSA either IV or orally. Clindamycin may be

useful in community-acquired MRSA provided inducible clindamycin resistance has been ruled out by appropriate studies. Therapy to cover an infection caused by gram-negative bacilli and/or anaerobes should be started if the septic bursitis occurs in the lower extremity or in an immunocompromised patient. Oral antimicrobial agents, if not started initially, can be used within 48 to 72 hours. Well-tolerated, once-a-day therapy is considered preferable for compliance. Total duration of therapy is usually 3 to 4 weeks. The recurrence of fluid after initial aspiration requires reaspiration and consideration for surgical drainage or bursectomy.

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70. Acute and chronic osteomyelitis

Ilona Kronig, Pierre Vaudaux, Domizio Suvà, Daniel Lew, and Ilker Uçkay

INTRODUCTION, EPIDEMIOLOGY, AND CLINICAL MANIFESTATIONS

Osteomyelitis is a common term for bone infection, although noninfectious inflammation of bones and adherent structures exist. Strictly speaking, osteomyelitis implicates affection of bone and marrow. The term osteitis would be often more appropriate because no one knows how much infection is inside the marrow in a given episode. As for any infection, physicians like to create big groups of disease headed as acute (AO) and chronic osteomyelitis (CO), although this distinction does not much determine daily clinical practice. For physicians, a commonly accepted definition of AO is a recent bone infection with systemic inflammatory response, while CO requires minimal symptom duration of 6 weeks to 3 months. Another classification system is the presence of a sinus tract, sequestra, or involucra, which are anatomicopathologic hallmarks of chronic infection. Finally, surgeons have their classification schemes, based on practical aspects of the surgical approach, of which the Cierny-Mader classification is one of the most frequent. The terms acute or chronic are not used in this classification. Generally, surgeons understand a CO as infection requiring surgery, with already established sequestra and bone deformities.

AO is a hematogenous infection that occurs mostly in prepubertal children and in the elderly and is usually located in the metaphyseal area of long bones (children) or in the spine (elderly). It is the result of a local proliferation of bacteria within bone after a septicemic storm. Alternatively, AO can originate locally following trauma or orthopedic surgery (surgical site infection). In contrast, CO has two origins. It may result from either a neglected sequel of AO, or from the continuous spreading of chronic ulcers in paraplegics, bedridden patients, or diabetic patients with foot problems. Epidemiology of osteomyelitis is heterogeneous with variability among involved bones, pathogens, and settings. For example, resource-poor countries may reveal a higher proportion of tuberculous osteomyelitis or CO due to post-traumatic origin compared to resource-rich countries, as well as a higher prevalence of foot osteomyelitis among elderly patients.

PATHOGENESIS IN DETAIL

Every chronic infection begins with an acute phase. Bacteria adhere to bone matrix and orthopedic implants via receptors to fibronectin and other structural proteins, then hide intracellularly by developing a biofilm. Patchy ischemic bone necrosis occurs when the inflammation occludes the vascular tunnels. Segments of bone devoid of blood supply can become separated and are called sequestrate. This creates an ideal culture medium for bacteria and at 48 hours, abscesses are formed. Meanwhile, osteoblastic activity occurs, in some cases exuberantly, causing periosteal apposition and new bone formation, named involucrae. When sequestrate or involucrae become fibrotic, sclerosis may result. Bone sclerosis usually indicates infection present for more than 1 month.

MICROBIOLOGIC AND PATHOLOGIC CRITERIA

Infection is almost exclusively of bacterial origin, much less due to fungi (in intravenous drug abusers or in skull osteomyelitis in immunesuppressed individuals) or parasites (e.g., echinococcosis). For all categories of osteomyelitis except for the jaw, *Staphylococcus aureus* is the prominent pathogen, contributing up to two-thirds or three-quarters of the study population, followed by streptococci and gram-negative pathogens such as *Pseudomonas aeruginosa*. As for any infection, virtually any bacteria can cause osteomyelitis. Skin commensals such as coagulase-negative staphylococci, propionibacteria, corynebacteria, or *Bacillus* spp. are mostly

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encountered in implant-related infections, but almost never alone in AO or CO without implants. Polymicrobial infection is frequent in trauma and long-lasting ulcerations, but not in hematogenous infections.

DIAGNOSIS

Clinical signs (sinus tract with or without discharge) and radiographs (sequestra, involucra, fistulas) are suggestive for diagnosis of CO, but no noninvasive test can definitively establish or exclude infectious osteomyelitis. That is why it is extremely important to get adequate sampling of infected bone for bacteriologic or molecular identification by polymerase chain reactions (PCR). Swabs, even if taken from a deep area, should be avoided. The ultimate proof of infection requires growth of the same pathogen in several, at least two, (intraoperative) bone samples. In case of pretreatment with antimicrobial agents or suspicion of slow-growing pathogens such as in tuberculosis, brucellosis, or nocardiosis, the incubation time might be prolonged beyond the usual 5-day period and other, nonstandard laboratory tests, performed. Histology may help to confirm the clinical suspicion.

TREATMENT

The mainstays of management include adequate debridement, obliteration of dead space, wound protection, and targeted antimicrobial therapy.

Surgical therapy

Debridement *sensu latu* summarizes different surgical approaches: sequestrestomy, necrosectomy, intramedullary reaming, and removal of orthopedic material (when possible or indicated), except those essential for stability. Debridement must often be repeated for the removal of all nonviable tissue (second look). Surgeons know how extensively they were able to perform this debridement. There are no exact possibilities to estimate the completeness of such a debridement. A variety of techniques has been used such as cancellous bone grafting and implantation of acrylic beads impregnated with antibacterial agents. In case of vascular insufficiency, restoration of a good blood flow is performed by vascular bypass or endovascular stenting. If the stability of the bone is compromised, a two-stage procedure might be required. The first stage consists in extensive debridement, dead space management (eventually with antibiotic-containing beads or cement), bone stabilization with external fixation, and coverage with dressings. After 3 weeks of antibiotic treatment comes the second stage: new debridement, removal of the beads or cement, filling in of the dead space with bone graft, bone stabilization with internal fixation (plate and/or intramedullary nail), and soft-tissue coverage. Local administration of antibiotics, e.g., by gentamicin beads, has long been advocated because of the benefit of a local diffusion limited in time and space. However, at present, the use of local antibiotic delivery in combination with systemic antibiotic prescription has not yet shown any supplementary beneficial effect in terms of remission rates. The major disadvantage of local beads is the presumed need for a subsequent surgical removal. Small dead space is left unchanged if the soft-tissue coverage is good. Large dead spaces are filled to reduce the likelihood of continued infection and stability loss. If a cavity cannot be filled by surrounding soft tissue, a local muscle flap or free tissue transfer obliterates the space. Autologous bone grafts usually enhance stability after 6 to 8 weeks. As a last resort, the Ilizarov fixation device is used in patients with chronic extensive and difficult to treat CO. The Ilizarov technique may bridge bone defects as long as 15 cm by continuous traction that can be started 10 days after implantation of the device.

Antimicrobial therapy

In contrast to surgical science with many related publications, the optimal antibiotic treatment post-debridement for implant-free, nondiabetic long bone osteomyelitis among adults is not well defined. Most studies primarily focused on the choice of antibiotic agents, rather than their duration, dosing, or route of administration. Usually, single-agent chemotherapy is adequate for the treatment of osteomyelitis (Table 70.1). In the past decades, according to experimental models, antibiotics were parenterally administrated on a mostly empirical basis for 4 to 6 weeks, followed by an oral course of antimicrobials for several weeks or months. Without doubt, bone penetration of antibiotic agents is optimized by parenteral administration, with a serum bioavailability per definition of 100%. On the other hand, parenteral medication should be limited to save unnecessary costs, prevent catheter-related complications, and to increase patient and nursing comfort. The estimated proportion of complications attributed to a prolonged IV

Table 70.1 Antibiotic treatment of osteomyelitis[a]. Local recommendations at Geneva University Hospitals

Parenteral treatment	(Duration 0–2 weeks) Antibiotics	Alternatives
Staphylococcus aureus		
Methicillin resistant	Vancomycin 2 × 15 mg/kg	Teicoplanin (400 mg q24h, first day q12h) Daptomycin 6–10 mg/kg/d Linezolid 2 × 600 mg/d
Methicillin susceptible	Flucloxacillin 2 g q6h	Cephalosporins of I or II generation
Streptococci	Penicillin G (3 Mio U q4–6h)	Cephalosporins of I or II generation
Gram-negatives	Ceftriaxone	Ceftazidime, cefepime
Anaerobes	Amoxicillin-clavulanate	Metronidazole, carbapenems, clindamycin
Oral treatment	**(Duration 6–12 weeks)**	
Gram-positives	Clindamycin 3 × 600 mg	Levofloxacin 2 × 500 mg Trimethoprim–sulfamethoxazole 2 cp forte (2 × 960 mg) Linezolid 2 × 600 mg Fusidic acid 3 × 500 mg (not as monotherapy)
Gram-negatives	Ciprofloxacin 2 × 750 mg	Trimethoprim–sulfamethoxazole 2 × 960 mg Levofloxacin 2 × 500 mg
Anaerobes	Metronidazole 3 × 500mg	Clindamycin 3 × 600 mg

[a] Adapted from: Uçkay I, Buchs NC, Seghrouchni K, *et al*. Bacterial osteomyelitis: etiopathogenesis and management. In: Signore A, ed. *Management of Osteomyelitis*, 1st edn. Chapter 2. Rome, Italy: University of Rome; 2013:15–26.

course ranges around 15%. Recent studies allowed new approaches to antimicrobial therapy based on experimental models and clinical validations. Thus, there is a growing consensus for a switch to the oral route after 2 weeks of IV treatment. Several antimicrobial agents have already proven clinical efficacy upon oral intake: quinolones, linezolid, clindamycin, trimethoprim–sulfamethoxazole (TMP–SMX), and fusidic acid combined with rifampin. These drugs have oral bioavailabilities of 90%.

Total duration of antibiotic therapy

In general practice, the duration of antibiotic administration is standard for most pathogens with few exceptions: pathogens for which the literature provides long-lasting antibiotic treatments (tuberculosis, other mycobacteria such as in buruli ulcer, fungi, Q fever, nocardiosis, or brucellosis). There are no clinical studies or documented records indicating the superiority of the 4- to 6-week course over shorter durations. In the retrospective study of Rod-Fleury *et al*., the duration of total post-debridement antibiotic treatment or its initial parenteral part only played no role on the remission incidences. One week of IV therapy had the same success as 2 to 3 weeks or more. Four weeks of total antibiotic treatment led to the same outcome as 4 to 6 weeks or more than 12 weeks. Less than 6 weeks was equal to more than 6 weeks. Haidar *et al*. listed small individual reports in animals and humans that obtained remission of osteomyelitis with antibiotic durations ranging from 1 to 4 weeks.

Intravenous agents

The most frequently used antibiotic agents, the β-lactam antibiotics, ubiquitously show low oral bioavailability and a low intra-osseous penetration. Since the bone penetration of vancomycin is only about 15% to 30% of the serum concentration, minimal trough serum levels of 20 to 25 mg/L are believed to treat bone infections best. In continuous perfusion, the changes in serum concentrations are much lower than in intermittent application. However, continuous perfusion does not guarantee a better outcome in terms of remission. Daptomycin depolarizes bacterial membranes and yields a rapid, dose-dependent bactericidal effect. It is only available in parenteral form and administered once a day at a dose of 6 to 8 mg/kg. This makes it suitable for an outpatient treatment. Aminoglycosides are less active in synovial fluid or in bone.

Oral agents

Linezolid can be administered orally at a dose of 600 mg BID, due to its high bioavailability of 100%. Besides an expensive price, it is

associated with reversible bone marrow suppression, e.g., thrombopenia. Optic neuropathy and non-reversible peripheral neuropathy have been reported in 2% to 4% of patients with prolonged administration. A severe serotonin syndrome in co-medication with certain antidepressive drugs, such as monoamine oxidase inhibitors, has been described. TMP–SMX is an inexpensive folate antagonist. However, one reason for failure in severe osteoarticular infections might be the amount of thymidine released from damaged host tissues and bacteria. Thymidine may antagonize the antistaphylococcal effects of TMP–SMX. Hence, TMP–SMX failure may well depend on the amount of tissue damage and bacteria burden. Oral fusidic acid 500 mg tid has demonstrated efficacy in CO. Most experts do not recommend fusidic acid in monotherapy because of development of resistance. The antibiotic can be combined with rifampin. For anaerobic, streptococcal, and staphylococcal clindamycin-sensitive osteomyelitis, bacterial protein synthesis inhibition by clindamycin 600 to 900 mg TID is an option, as is metronidazole for anaerobic disease and quinolones for gram-negative infection. *Pseudomonas aeruginosa* and other nonfermenting gram-negative rods may rapidly develop resistance during quinolone monotherapy. Therefore, a combination with another parenteral drug for prolonged IV treatment in pseudomonal osteomyelitis would be wise, but antibiotic treatment adjusted to this situation has not been studied so far.

In acute flare-ups of CO that cannot be operated on due to various reasons (polymorbid patient, extended lesions compromising mechanical stability or gait), antibiotic therapy can aim for palliation. In these circumstances, a targeted antimicrobial therapy can be prescribed for 10 to 20 days, in order to calm down the situation, and not to cure. Hyperbaric oxygen therapy consumes very substantial resources. It provides oxygen to promote collagen production, angiogenesis, osteogenesis, and healing in the ischemic or infected wound. Several authors have suggested that adjunctive hyperbaric oxygen therapy might be useful in the treatment of human CO, even if the results are not consistent. The adjunctive role of hyperbaric oxygen in osteomyelitis is difficult to assess because of the multiple confounding variables of patient, surgery, organism, bone, and antibiotic therapy. Today, although recognized for reimbursement by some healthcare systems, the evidence base for hyperbaric oxygen therapy for diabetic foot care still remains weak.

Special features

VERTEBRAL OSTEOMYELITIS (IN CONJUNCTION WITH SPONDYLODISCITIS)

Apart from nosocomial infection after spine surgery, hematogenous spread is generally the most common origin of vertebral osteomyelitis and/or spondylodiscitis. The incidence is estimated at 0.2–to 2 annual cases per 100 000 patients involving mostly patients in the mid-ages with a male to female ratio of 2:1 for which the reason remains unclear. Usually, the management of a vertebral osteomyelitis is essentially conservative, but may require early drainage surgery and stabilization of the spine. The indications of surgery are failure of medical treatment, abscess formation, impending instability, or neurologic signs of spinal cord compression. The needle biopsy through CT guidance is currently the process of choice to obtain microbiologic and histologic samples. In the absence of clinical sepsis, a second biopsy should be repeated when the first one is negative (by withholding antibiotic therapy). If the culture is still negative, most physicians propose an empirical therapy or request a surgical biopsy for diagnosis. No randomized controlled studies have evaluated antibiotic regimens for vertebral osteomyelitis. Practically, the choice of antibiotic agents is not different from any other osseous infections, except that an initial parenteral treatment of at least 3 to 4 weeks is usually suggested by experts. Prolonged antibiotic treatment beyond 4 or 6 weeks is only recommended for patients with abscesses that have not been drained.

DIABETIC FOOT OSTEOMYELITIS

A diabetic foot problem is practically always a good example for multidisciplinary diagnosis and therapy. Suspicion of osteomyelitis is confirmed by microbiology or radiologic destruction in the case of toe osteomyelitis. Bone biopsy (with histology if sufficient material) is valuable for establishing the diagnosis and for defining the pathogenic organism(s). Concomitant treatment includes proper wound cleansing, debridement of callus and necrotic tissue, and offloading of pathologic pressure. There are no data to support the superiority of any particular route of delivery of systemic antibiotics or the optimal therapy duration. Therapy aimed solely at aerobic gram-positive cocci may be sufficient for mild to moderate infections in patients who have not recently received antibiotic therapy. Broad-spectrum empirical therapy is required in severe infections. Bioavailable oral antibiotics are

sufficient in most mild and moderate osteomyelitis. In severe diabetic foot infections, antibiotics are given initially IV to achieve maximal tissue concentrations in an area already compromised by arteriopathy, although no evidence for a superiority of IV medication exists. The results of conservative therapy with prolonged courses of oral antibiotics challenge conventional advice that excision of infected bone is essential. Conservative success rates are cited as 75% and as 77% over a median period of follow-up of 2 years. However, conservative treatment might not reverse the high incidence of a second episode of osteomyelitis in a long-term follow-up, since the cause has not been removed by conservative treatment in most cases. A corrective surgery or an amputation for toe and mid-foot osteomyelitis is often indicated, providing the level of amputation does not compromise walking and does not require prostheses.

SACRAL OSTEOMYELITIS

This disease is chronic and related to decubitus in patients with multiple comorbidities and/or neurologic disorders. It is particularly difficult to treat, since there is no remission if the reason for CO cannot be reversed. In these chronic decubitus patients, the infected sacral bone often cannot be excised and the patient cannot be improved neurologically. Prevention is of outmost importance. A thorough daily nursing care and debridement is the key to success. In ameliorated cases, plastic surgeons may graft on the naked bone. The ideal duration of antibiotic administration is unknown. The aim is not to eradicate bone infection, but to control it. More data are needed in this field of osteomyelitis.

JAW OSTEOMYELITIS

Chronic mandibular osteomyelitis occurs after dental procedures, trauma, or in very poor settings of noma disease. There has not been much research in the past. The causative pathogens are often polymicrobial and stem from the oral flora. *Actinomyces* spp. are particular pathogens that may mimic neoplasm. Treatment consists of maxilla-facial surgery, often repeated, and of long-lasting oral antibiotic therapy for which the choice of amoxicillin–clavulanate covers the majority of the oral flora.

Clinical follow-up during therapy

Osteomyelitis patients must be regularly followed up throughout the treatment, for early detection of complications, adverse events, and control of wounds. A substantial quality improvement of care would be the use of diagnostic imaging to judge how long therapy remains necessary; for example by repeated positron emission tomography (PET) scans (which has to be investigated yet). Indeed, the duration of antibiotic administration for CO is usually decided from the start and kept thereafter; independently of the individual case and markers. C-reactive protein (CRP) is widely used in the follow-up of patients with localized bone and implant infections, but trauma or surgery may result in its transient elevation. Indeed, many CO cases have a normal CRP level even before treatment.

PARTICULARITIES OF PEDIATRIC OSTEOMYELITIS

As a general principle, pediatric AO and CO cases are similar to those of adults. However, epidemiologically speaking, there are more primary AO than among adults, affecting 8 per 100 000 children, predominantly boys. The long bones are most frequently infected. CO of the adult may originate several years after bone contamination from an infant AO source, e.g. after bone trauma in childhood. Primary AO is mainly due to *S. aureus* (70% to 90% of cases), and rarely due to other pathogens, with one exception: *Kingella kingae* is a pathogen mostly encountered in osteoarticular infections among infants around 3 to 6 years of age. Specific PCR for *K. kingae* detection is available. *Haemophilus influenzae*, another infant pathogen, is much rarer, and declined considerably after the implementation of vaccination programs all around the world.

In terms of therapy, most infant AO cases are hematogenous without sequestrae. These cases can usually be treated without surgical debridements purely conservatively, while the duration is shorter than for adult disease. Indeed, review suggests that early transition from intravenous to oral therapy, after 3 to 4 days in patients responding well, followed by oral therapy to a total of 3 weeks may be as effective as longer courses for uncomplicated AO. This recommendation does not apply to neonates. The choice of the antibiotic agents is similar to that for adults, with a few exceptions that should be avoided (according to the manufacturer) among infants: quinolones and tetracyclines.

OUTCOME OF TREATMENT

Many experts advocate that if the bone is infected, it may remain infected throughout the life and even beyond, unless amputation is performed. Recurrences of osteomyelitis after several years, if not decades, have been reported and there is no internationally accepted minimal follow-up duration. Some authors suggest that "arrest" or "remission" is a more appropriate term than "cure" for defining outcome in CO. According to current literature, remission is "defined" as the resolution of all signs and symptoms of active infection after a minimal follow-up period of 1 to 2 years. Generally, remission rates for CO among adults oscillate between 40% and 90% with a peak of success around 80%, almost independently of the surgical technique, the duration of intravenous or total antibiotic therapy, or the causative pathogen.

FUTURE

The future will probably provide a firm place in the antibiotic armamentarium for some of today's investigational agents such as dalbavancin, telavancin, and other compounds under development. It should not be forgotten that most, if not all, new molecules might be equivalent to established antibiotics in terms of remission rates in vivo. Additional prospective trials need to be performed before innovative approaches are proposed. As an example, bacteriophage therapy is a challenging approach and may prove to be superior to established combined antibiotic therapies. Finally, it is very difficult to evaluate osteomyelitis in small clinical studies or single centers. Sample size and international definitions need to be improved. Hopefully, future data will be collected from prospective and multicenter human cohort studies.

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71. Polyarthritis and fever

Kathryn H. Dao and John J. Cush

Polyarticular joint pain with fever poses a unique diagnostic challenge given the magnitude of complaint, urgency to identify the underlying cause, and the uncertainty of outcome. Knowledge of the most prevalent causes of polyarthritis associated with fever can facilitate an accurate diagnosis and appropriate therapy. Polyarthritis is defined as inflammatory pain with swelling affecting four or more joints. The distribution, chronology of joint inflammation, and host factors (e.g., demographics, comorbidities, geography) help refine the diagnostic possibilities. The presence of fever is notable as most polyarticular conditions do not manifest substantial or sustained fever. Nevertheless, fever or pyrexia is further evidence of an inflammatory, infectious, or autoimmune disorder. This chapter will examine the diagnostic approach to polyarthritis and pyrexia.

HISTORY AND PHYSICAL EXAM

The diagnosis of any disease relies heavily on the history and physical examination. Eliciting an accurate history will identify those who are at risk for significant morbidity and mortality. The goals of the encounter are to: (1) relieve symptoms, (2) treat the underlying disease, and (3) avoid irreversible organ damage. Characteristics distinguishing arthritis include prolonged morning stiffness, warmth, erythema, tenderness to palpation, swelling, and joint effusion. Range of motion, muscle strength, and function may be limited around the inflamed joint. In an effort to reduce joint volume and pain, the patient may involuntarily hold the joint in a position of partial flexion. Hence, joint contracture may be evidence of an inflammatory process. The key elements that should be obtained from history and physical exam are as follows and simplified in Figure 71.1.

Demographics

Age, sex, and geography are important clues. Gout is more common in men. Septic arthritis is more likely in the young, elderly, and immunosuppressed. Parasites and chikungunya fever should be considered in a traveler with fever and arthritis. Giant cell arteritis (GCA) is unlikely in patients less than 50 years old.

Symptom onset

Acknowledge how and under what circumstances symptoms first manifest. Abrupt onset of symptoms, occurring in hours/days, may indicate infection or gout; whereas symptoms persisting for weeks or months suggest an autoimmune disease, chronic infection, or malignancy. Reactive arthritis (ReA) or parvovirus infection should be considered in a patient who initially presents with a viral illness then develops acute oligo- or polyarthritis.

Pattern of joint involvement

Observe the number, location, and symmetry of joint involvement. Monoarthritis is common in patients with ReA, septic arthritis, or gout. In contrast, patients who have diffuse symmetrical involvement (e.g., hands, wrists, shoulders, knees, ankles) are likely to have a chronic systemic disease such as systemic lupus erythematosus (SLE), chronic viral infections, or rheumatoid arthritis (RA). Spinal involvement may be a manifestation of tuberculous infections or a spondyloarthritis. Shoulder and hip girdle pain with high inflammatory markers should alert the clinician to polymyalgia rheumatica (PMR). The timing of joint involvement is also useful. Varying patterns of presentation have been described including: *intermittent/episodic pattern* with flares punctuated by periods of complete remission (e.g., gout, pseudogout, autoinflammatory diseases), *additive pattern* where symptoms begin with a few joints and progress to involve more joints with time (e.g., RA, SLE, hepatitis B, parvovirus), or *migratory pattern* where certain joints are affected for a time

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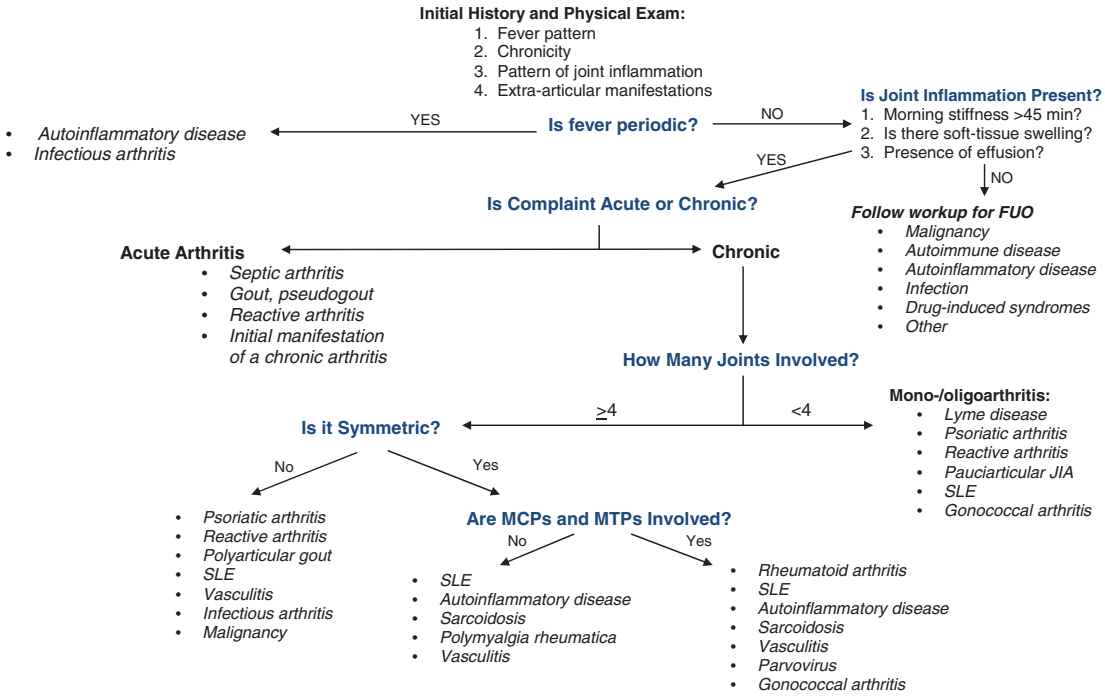

Figure 71.1 Algorithm for assessing fever and polyarthritis. FUO = fever of unknown origin; SLE = systemic lupus erythematosus; JIA = juvenile idiopathic arthritis.

then remit, only to reappear elsewhere in other joints (e.g., gonococcal arthritis, acute rheumatic fever).

Fever pattern

Fever is a nonspecific significant sign of systemic inflammation. It can also manifest in several patterns: continuous or sustained, intermittent, relapsing, or periodic (e.g., quotidian, tertian, quartan). Studies have examined the significance of fever pattern and found only a few fever curves convey any significance. Most drug reactions, vasculitides, and viral infections present with continuous fevers; the double quotidian fever curve with spikes twice a day has been associated with visceral leishmaniasis (kala-azar) and malarial infections. Patients with systemic-onset juvenile idiopathic arthritis (soJIA) or adult-onset Still's disease (AOSD) display quotidian fever that is truly circadian, occurring at the same hour each day (usually late afternoon or evening). The magnitude of fever has not been shown to correlate with the degree of disease severity; however, infections should be higher in the differential diagnoses in patients with temperatures >102°F. Despite extensive research on the topic of fever and fever patterns, it remains unclear why certain diseases are associated with a particular fever pattern.

DIFFERENTIAL DIAGNOSES FOR POLYARTHRITIS AND FEVER

Most causes of polyarthritis and fever can be classified into one of the following categories: infection, rheumatologic diseases (e.g., autoimmune, autoinflammatory, and crystalline diseases), and malignancies (Table 71.1). While literature reviews indicate infections account for the majority of fever of unknown origin (FUO), rheumatologic diseases and malignancies each account for about 20% to 25% of cases.

Infections

Bacteria, viruses, and atypical microorganisms can cause polyarthritis directly as a pathogen or indirectly through an immune-mediated response. Septic arthritis can result from hematogenous seeding of the synovial membrane due to bacteremia, direct introduction from a penetrating trauma (e.g., animal bite or joint injection), or extension from a contiguous focus of infection. Chapter 68, Infection of native and prosthetic

Table 71.1 Differential diagnoses of polyarthritis and fever

Infections
Bacterial endocarditis
Staphylococcal infections
Streptococcal infections
Escherichia coli infections
Pasteurella spp.
Gonococcal and meningococcal infections
Brucellosis
Streptobacillus moniliformis
Parvovirus B19
Viral hepatitis
Cytomegalovirus
Epstein–Barr virus
Human immunodeficiency virus
Enteroviruses
Chikungunya and other arboviruses
Rickettsial infections
Secondary syphilis
Tuberculosis
Atypical mycobacterial infections
Fungal infections
Autoimmune diseases
Systemic lupus erythematosus
Rheumatoid arthritis
Vasculitis (e.g., MPA, GCA, GPA)
Reactive arthritis
Sarcoidosis
Autoinflammatory diseases
Adult onset Still's disease (AOSD)
Systemic-onset juvenile idiopathic arthritis (SoJIA)
Muckle–Wells syndrome (MWS)
Familial Mediterranean fever (FMF)
Tumor necrosis factor receptor-associated periodic syndrome (TRAPS)
Behçet's
Crystalline diseases (gout, CPPD, calcium hydroxyapatite)
Malignancies
Lymphoma
Leukemia
Paraneoplastic syndromes
Multiple myeloma
Solid tumors +/− metastases
Miscellaneous
Serum sickness
Thyrotoxicosis
Rheumatic fever
Cryoglobulinemia
Drug-induced syndromes
Poststreptococcal arthritis
Cryoglobulinemia

Abbreviations: MPA = microscopic polyangiitis; GCA = giant cell arteritis; GPA = granulomatous polyangiitis; CPPD = calcium pyrophosphate dihydrate.

joints, details further information on evaluating the septic joint. Risk factors for developing polyarticular septic arthritis include: diabetes, chronic renal or hepatic disease, gout, and rheumatoid arthritis. Microbes cultured directly from infected joints have included: staphylococci, streptococci, enterococci, *Neisseria* spp., *Borrelia* spp., and gram-negative bacilli. Where cultures of microorganisms are unsuccessful, real-time polymerase chain reaction (rt-PCR) has proven helpful. Rt-PCR has improved sensitivity for detecting *Borrelia burgdorferi* in synovial fluid of patients with Lyme arthritis and has been used to diagnose *Tropheryma whipplei* (Whipple's disease) in elderly white males who present with weight loss, fever, arthritis, and gastrointestinal symptoms. Viruses also have been linked to polyarthritis, including: parvovirus B19, mumps, rubella, hepatitis B and C viruses, cytomegaloviruses, Epstein–Barr virus, HIV, enteroviruses, and insect-transmitted arboviruses. Severe cases of debilitating polyarthritis have been associated with the arbovirus, chikungunya virus, where human epidemics have been reported in Africa, Asia, and certain parts of Europe. A detailed travel history will guide specific testing for diseases endemic to the region.

Autoimmune and autoinflammatory diseases

Endogenous pyrogens released by an aberrant immune system drive the pathology in these diseases. SLE, sarcoidosis, and vasculitis are examples of autoimmune diseases manifesting with polyarthritis and fever, but rarely does RA present with fever. Typically, other clues are present suggesting the diagnosis. Patients with SLE may have a history of a photosensitive rash, alopecia, or serositis. In sarcoidosis, fever may accompany the triad of arthritis, erythema nodosum, and hilar adenopathy (Lofgren's syndrome). GCA, granulomatosis with polyangiitis (GPA), polyarteritis nodosa (PAN), and other vasculitides

often present with malaise and weight loss. In most autoimmune diseases, fever is low grade (e.g., <38°C) and indolent, contrasting the *autoinflammatory* diseases where fever is impressive (e.g., ≧39°C) and recurrent. High-titer autoantibodies and antigen-specific T cells are typically absent in autoinflammatory diseases. Familial Mediterranean fever (FMF), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), soJIA, and AOSD are but a few of the autoinflammatory diseases described in the last decade. Unprovoked, recurrent episodes of fever, serositis, arthritis, and cutaneous inflammation result from specific genetic mutations affecting the innate immune system. In cryopyrin-associated periodic syndromes (CAPS), which include: familial cold autoinflammatory syndrome (FCAS) and Muckle–Wells syndrome (MWS), mutations in the NLRP3 gene affect components of inflammasomes (e.g., cryopyrin) which are important in recognizing microbial products and endogenous danger signals. Interestingly, recent evidence suggests genes in the same NLR family may be implicated in gout.

Gout and crystalline diseases

Polyarticular gout and pseudogout can manifest high fevers during acute attacks. Distinguishing between septic arthritis and acute gout is difficult – both have similar presentations (high acute phase reactants, fever), and both can coexist. Up to 50% of gout patients can present with fever and have a normal serum uric acid level during the acute attack. Synovial fluid analysis can identify crystals, but empiric antibiotics may still be necessary until Gram stain/cultures are resulted. Patients presenting with crowned dens syndrome (CDS) related to calcium pyrophosphate dihydrate (CPPD) or calcium hydroxyapatite crystal deposition in the periodontoid ligaments of the atlas can exhibit high fever, severe occipital headache and neck stiffness which mimic aseptic meningitis.

Malignancy

Paraneoplastic syndromes with rheumatologic features have been described in most cancers. Lupus-like syndromes with fever, arthritis, and rash have been associated with ovarian cancer, breast cancer, and hairy cell leukemia. PMR symptoms have been described with multiple myeloma and solid tumors. Carcinomatous polyarthritis is often confused with RA, but generally has an explosive onset and asymmetric disease pattern. Rheumatic symptoms may coincide or antedate the diagnosis of malignancy. Typically, paraneoplastic manifestations do not respond to standard rheumatologic doses of steroids or disease-modifying agents but will resolve as the underlying cancer is treated.

The urgency to distinguish a rheumatic condition from malignancy is paramount in children. Seventy-five percent of childhood acute lymphoblastic leukemia (ALL) will present with fever and musculoskeletal pain before blasts appear in the peripheral smear. Several studies examined the predictive factors for malignancies vs. juvenile idiopathic arthritis (JIA) based on clinical and laboratory data in children with musculoskeletal pain. Highly predictive factors for malignancy were elevated lactate dehydrogenase (LDH), anemia, and neutropenia. An increased LDH greater than two-fold was found exclusively in children with malignancies. Musculoskeletal pain was observed at similar frequencies in children with JIA and neoplasia, though fever tended to be recurrent in those with malignancy.

Drug-induced syndromes

Certain medication adverse effects manifest as a musculoskeletal complaint with fever. Best characterized are medications that can cause drug-induced lupus such as: hydralazine, procainamide, isoniazid, propylthiouracil, sulfonamides, quinidine, TNF inhibitors, and minocycline. Symptoms may include: joint/muscle pain, fever, skin rash, pleural disease, and cytopenias which can appear weeks to months after exposure to the offending drug; remission will occur upon withdrawal of the agent.

LABORATORY TESTS AND RADIOLOGIC INVESTIGATIONS

Routine labs

While the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) provide surrogate measures of inflammation, they do not discriminate well between infection, rheumatologic diseases, or malignancy. Other laboratory measures often are used to suggest the diagnosis. Patients with soJIA or AOSD often have high ferritin and abnormal liver function tests. SLE may manifest with hypocomplementemia, lymphopenia, and

thrombocytopenia. A low haptoglobin with elevated LDH may suggest hemolysis, but high elevations in LDH should be investigated further and malignancy excluded, particularly in children or patients with concomitant weight loss, fever, and lymphadenopathy. Blood cultures are important in endocarditis and systemic infection due to bacteria and fungi.

Serologies

Autoantibodies are found in various autoimmune diseases. The presence of the rheumatoid factor (RF) and antinuclear antibody (ANA) are nonspecific and can be seen in patients with infection, malignancy, and rheumatologic disorders. Other serologic markers offer better specificity and diagnostic utility. The anti-citrullinated peptide antibodies (anti-CCP) carry the same sensitivity as RF for RA, but with better specificity (>90%). When present with the RF, the anti-CCP has a positive predictive value for RA >99%. The cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA) is also highly specific; its presence indicates GPA; similarly, double-stranded DNA and anti-Smith antibodies are specific for SLE. Antibodies against microbial antigens should be obtained when suspicion is high for infection based on contact or travel history. Relevant assays available to evaluate for infections causing fever and polyarthritis include serologies to parvovirus B19, cytomegalovirus, hepatitis B and C, streptolysin O, *Borrelia* spp., and *Brucella* spp. Further information about testing for these infections is covered in other chapters.

Synovial fluid analysis

Arthrocentesis with synovial fluid analysis is a useful adjunct to diagnosing patients and relieving symptoms. Evaluation of synovial fluid should include: cell count, crystal analysis, and Gram stain/cultures for routine and atypical (e.g., acid-fast bacilli, fungi, spirochetes, gonococci) microorganisms. Inflammatory fluid is usually yellow and turbulent; white blood cell counts (WBC) range from 5000 to 50 000 cells/mm^3, with predominance in neutrophils. In the presence of infection or gout, WBC may exceed 50 000 cells/mm^3. Synovial fluid from septic arthritis and gout generally has a higher percentage of neutrophils (>85%) compared to other inflammatory arthritides. Prompt evaluation under polarized microscopy will maximize the yield for crystal identification.

Radiography

Radiographic changes early in disease often are absent, but sometimes characteristic x-ray findings of inflammatory arthritis are found: soft-tissue swelling, joint effusion, juxtaarticular osteopenia, joint space narrowing, chondrocalcinosis, and bony erosions. Identification of these abnormalities is important as studies have shown that radiographic damage correlates with loss of productivity and increased disability.

Other imaging modalities such as magnetic resonance imaging (MRI) and ultrasound (US) have proven sensitive for detecting synovitis, abscesses, and vasculitis where clinical exam and conventional x-rays have failed. Their advantages include the ability to detect subtle inflammatory abnormalities as well as permiting more accurate placement of the needle in diagnostic arthrocentesis or tissue biopsy. Before ordering any tests, the potential benefits should be weighed against limitations of long examination times, availability of equipment, costs, and skills of the observer to interpret pathology.

Over-reliance on laboratory testing to establish a diagnosis is ill-advised; the strength of laboratory testing and imaging is greatly enhanced when they are used to confirm a reasonably strong clinical suspicion garnered from the history and examination.

CONCLUSION

Fever and joint inflammation pose a diagnostic challenge as infection, rheumatologic disease, and malignancy can present similarly. Assess the demographics, chronology, pattern of fever and joint involvement when formulating a differential diagnosis. Prompt evaluation, early referral and expedient initiation of therapy are paramount to reducing morbidity and mortality associated with polyarthritis and pyrexia.

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72. Infectious polymyositis

Elizabeth Soda and Upinder Singh

Infectious polymyositis is an entity in which there is generalized muscle damage (rhabdomyolysis) caused by an infectious agent. The syndrome of rhabdomyolysis results from muscle necrosis and is characterized by muscle pain, elevated serum creatinine phosphokinase (CPK) concentrations, and myoglobinuria possibly leading to renal dysfunction. The muscle injury in rhabdomyolysis occurs in a generalized pattern and lacks a specific focus of infection as is seen in pyomyositis. The entity of pyomyositis is discussed in Chapter 22, Deep soft-tissue infections: necrotizing fasciitis and gas gangrene.

A variety of factors can lead to rhabdomyolysis. These include crush and compression injuries, drug and alcohol ingestion, metabolic and electrolyte disturbances, hypothermia and hyperthermia, and a variety of infections. This review focuses on infectious causes. It is important to distinguish rhabdomyolysis caused by a pathogen from that caused by sepsis, hypotension, or electrolyte imbalances that accompany a severe systemic infection.

VIRAL INFECTIONS

The wide spectrum of viral infections that have been reported to cause rhabdomyolysis are listed in Table 72.1. Influenza is the most common viral etiology reported to precipitate rhabdomyolysis, followed by human immunodeficiency virus (HIV) and enteroviral infection. Whether the higher incidence with influenza results from a predilection of the virus for the muscle tissue or from the more frequent reporting due to physician awareness and ease of diagnosis is unclear. Pandemic H1N1-induced rhabdomyolysis was not clearly associated with an increased incidence or severity when compared to seasonal influenza A; however, patients with higher CPK levels fared worse with longer ICU stays.

Renal dysfunction in rhabdomyolysis secondary to influenza infection is common and not related solely to the level of CPK elevation. The precise mechanism predisposing to renal damage from influenza-induced rhabdomyolysis is unclear; however, aggressive measures should be taken to preserve renal function in these individuals.

Rhabdomyolysis adds to the spectrum of clinical presentations of HIV infection. Many musculoskeletal syndromes associated with HIV infection have been documented, ranging from myopathy to rhabdomyolysis. Muscle damage can occur in a variety of clinical scenarios in association with HIV infection, including acute seroconversion and antigenemia, end-stage disease with myopathy, and myositis resulting from

Table 72.1 Viral causes of rhabdomyolysis

Seasonal influenza virus A and B
Influenza A H5N1 (avian) and HINI (swine)
Human immunodeficiency virus
Coxsackievirus
Herpesviruses (HSV, VZV, CMV, EBV, HHV-6)
Echovirus
HTLV-1
Adenovirus
Parvovirus B19
Parainfluenza virus
RSV
Mumps
Measles virus
Hepatitis B and C
Severe acute respiratory syndrome (SARS)-associated coronavirus
Flavivirus (dengue virus; West Nile virus)
Rotavirus

Abbreviations: HSV = herpes simplex virus; VZV = varicella-zoster virus; CMV = cytomegalovirus; EBV = Epstein–Barr virus; HHV-6 = human herpesvirus 6; HTLV-1 = human T lymphotropic virus 1; RSV = respiratory syncytial virus.

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Table 72.2 Bacterial causes of rhabdomyolysis

Gram-positive bacteria	Gram-negative bacteria
Streptococcus pneumoniae	*Legionella* spp.
Staphylococcus aureus	*Francisella tularensis*
Group B streptococcus	*Salmonella* spp.
Streptococcus pyogenes	*Vibrio* spp.
Listeria spp.	*Brucella* spp.
Staphylococcus epidermidis	*Escherichia coli*
Bacillus spp.	*Herbicola lathyri*
Clostridium spp.	*Klebsiella* spp.
Viridans streptococci	*Aeromonas*
Streptococcus suis	*Haemophilus influenzae*
β-hemolytic streptococci	*Neisseria* spp.
Streptococcus gallolyticus	*Coxiella burnettii*

Table 72.3 Miscellaneous bacterial causes of rhabdomyolysis

Spirochetes	Rickettsial	Other
Leptospira spp.	*Rickettsia conorii*	*Mycoplasma pneumoniae*
Borrelia burgdorferi	*Rickettsia tsutsugamushi* *Ehrlichia equi* *Ehrlichia chaffeensis* *Anaplasma phagocytophilum*	*Mycobacterium tuberculosis* *Mycobacterium avium complex* *Mycobacterium haemophilum* *Mycobacterium bovis* *Mycobacterium leprae* Intravesical instillation of bacille Calmette–Guérin

medication side effects. Muscle biopsies of patients with HIV-induced rhabdomyolysis reveal a nonspecific inflammatory myopathy with focal necrotic areas and regenerating fibers.

The precise pathophysiology underlying virus-induced rhabdomyolysis is unknown; however, three mechanisms have been postulated: direct viral invasion, toxin generation, or an autoimmune response to the virus. Some authors have suggested that direct viral invasion of muscle fibers causes muscle necrosis. Data to support this hypothesis include the identification of viral inclusions, viral DNA, and the isolation of viruses in tissue culture from the muscles of infected patients. In addition, electron microscopy has identified viral particles, and biopsies reveal a lymphocytic infiltrate in the infected muscles. This evidence strongly suggests that direct viral invasion may have a causative role in precipitating rhabdomyolysis. However, various reports documenting normal muscle biopsies or hyaline degeneration and myonecrosis but no viral particles by immunofluorescence and electron microscopy are used to refute this theory. Biopsies of clinically affected musculature that are essentially normal raise the possibility of a circulating "toxin" or cytokine causing rhabdomyolysis. However, to date no putative toxins have been isolated.

BACTERIAL INFECTIONS

Many bacterial agents have been reported to cause rhabdomyolysis (Tables 72.2 and 72.3). The most common associations are with *Legionella* species, followed by *Streptococcus* species, *Francisella tularensis*, and *Salmonella* infections. An increasing number of bacterial agents are being associated with this entity, due to better diagnostic techniques, an increasing population of immunocompromised individuals, and increasing physician awareness. Individuals with bacterial infections resulting in rhabdomyolysis have significant morbidity (57% with renal failure in one study) and mortality (38% in one series).

Two proposed mechanisms of muscle injury by bacteria include toxin generation and direct bacterial invasion. *Legionella* is believed to release an endotoxin or exotoxin that causes rhabdomyolysis. Biopsies that are negative for the organism by immunofluorescence support this hypothesis. Organisms such as *Streptococcus* and *Salmonella* cause muscle damage by direct bacterial invasion as well as by decreasing the oxidative and glycolytic enzyme activity of skeletal muscle and activating lysosomal enzymes. A number of bacterial pathogens, including *Staphylococcus aureus, Streptococcus pyogenes, Vibrio* species, and *Bacillus* species, have been demonstrated in muscle biopsy specimens, lending credence to the hypothesis of direct bacterial invasion. Rickettsial illnesses such as Rocky Mountain spotted fever can cause muscle injury through vasculitis, as well as direct muscle invasion. A variety of cytokines, such as tumor necrosis factor-α and interleukin-1, released during systemic infections from a broad range of infections, can result in skeletal muscle proteolysis.

FUNGAL, PARASITIC, AND MYCOBACTERIAL INFECTIONS

Fungal myositis with the rare progression to rhabdomyolysis is uncommon and occurs primarily in the immunocompromised host. Alternatively, there are a variety of parasitic infections known to cause myositis that may progress to

Table 72.4 Fungal causes of rhabdomyolysis

Candida spp.
Aspergillus spp.
Mucor spp.

Table 72.6 Envenomations reported to cause rhabdomyolysis

Snakes	Other
South American rattlesnake	Hornets
Tiger snake	Wasps
Mojave rattlesnake	Bees
Russell's viper	Desert centipede
	Redback spider
	Taipan

rhabdomyolysis even in the normal host. In particular, organisms such as *Trichinella* that encyst in muscle following initial infection may result in severe myositis depending on the initial organism burden. This classically occurs in the extraocular muscles but can progress to other striated muscles and result in severe muscle weakness. *Plasmodium falciparum* has been linked to myositis with severe rhabdomyolysis resulting in renal failure with higher frequency than in the non-falciparum strains. Muscular complications of *Mycobacterium tuberculosis* and nontuberculosis mycobacterial infections are uncommon and most often are the result of contiguous spread of *M. tuberculosis* to the psoas muscles from vertebral osteomyelitis (Tables 72.3–72.5).

ENVENOMATIONS AND DRUG TOXICITY

Envenomations reported to cause rhabdomyolysis are listed in Table 72.6 Snake bites are commonly reported to cause muscle injury and include bites inflicted by the Mojave rattlesnake, Russell's viper, *Crotalus durissus terrificus* (South American rattlesnake), Australian snake, tiger snake, and seasnake. These patients present with swollen, tender muscles and high CPK levels. In contrast to viral and bacterial causes of rhabdomyolysis, envenomations generally cause a larger myotoxic insult. A large proportion of these patients also subsequently develop acute renal failure, presumably directly related to the increased renal toxicity from myoglobin. The mechanism of muscle damage in these cases appears to be a direct myotoxic activity of the various venoms.

Table 72.5 Parasitic causes of rhabdomyolysis

Plasmodium spp.
Toxoplasma gondii
Trypanosoma cruzi
Microsporidia
Trichinella spp.
Taenia solium

Table 72.7 Antimicrobials and rhabdomyolysis

Daptomycin
Raltegravir
Bactrim
Colistin
Linezolid
Fluoroquinolones
Fusidic acid
Clarithromycin Voriconazole

It is also important to remember the role of drugs, to include antimicrobials, when considering the etiology of rhabdomyolysis. Daptomycin is a commonly thought of drug with this side effect profile; however, there are a multitude of other antimicrobials that have been linked to rhabdomyolysis. Table 72.7 lists some of these agents.

RENAL FAILURE IN RHABDOMYOLYSIS

The renal dysfunction associated with rhabdomyolysis arises from a variety of interrelated factors. In muscle injury, both myoglobin and heme proteins are released, although neither is directly toxic to the glomerulus. Heme protein can result in renal tubular injury through a variety of mechanisms: (1) renal vasoconstriction, (2) direct renal tubular cell cytotoxicity, or (3) intraluminal cast formation and tubular obstruction. Therapeutic measures that increase renal blood flow and decrease tubular obstruction are useful in preventing renal injury in these patients.

THERAPY AND MANAGEMENT

The general management of rhabdomyolysis includes supportive care and treatment of the underlying predisposing condition or infection. The general approach is as follows: (1) maintenance of a high degree of suspicion for rhabdomyolysis in the appropriate clinical setting; (2)

appropriate diagnostic workup, including CPK levels, urinalysis, and urine myoglobin levels; (3) rapid institution of organism-specific drug therapy; and (4) supportive renal care. The renal function can be protected by maneuvers such as volume expansion and possibly urine alkalinization. Other metabolic disturbances resulting from muscle injury, such as hyperkalemia and metabolic acidosis, also may need specific therapy.

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73. Iliopsoas abscess

Lisa M. Kodadek and Pamela A. Lipsett

OVERVIEW

Iliopsoas abscess (IPA) is a rare condition defined by a collection of purulence in the iliopsoas compartment. IPA is classified as *primary* when a causative organism from a distant occult site spreads to the iliopsoas compartment by a hematogenous or lymphatic route, or *secondary* when a contiguous extension of an intra-abdominal infectious or inflammatory process causes the condition. Diagnosis and treatment is often delayed secondary to nonspecific features at time of presentation and outcomes from this disease are potentially poor or fatal without early and effective clinical management. Literature on this topic is limited to case reports and relatively small case series. IPA has classically been associated with *Mycobacterium tuberculosis* infection, but this etiology is increasingly rare. In current practice, *Staphylococcus aureus* is the most common organism isolated from primary IPA, with an increasing incidence of methicillin-resistant *S. aureus* (MRSA). In addition to *S. aureus*, enteric organisms are commonly isolated from secondary IPA.

ANATOMY

The iliacus muscle and psoas major muscle comprise the retroperitoneal muscle group referred to as the iliopsoas, which functions as the primary flexor of the hip. An accessory psoas minor muscle may be present in 10% to 65% of patients. The psoas major arises from T12 and the five lumbar vertebrae, passes along the posterior abdominal wall under the inguinal ligament, and inserts on the lesser trochanter of the femur. The iliacus arises from the superior portion of the iliac fossa and passes under the inguinal ligament to insert on the lesser trochanter as well as the femoral shaft. The muscles are often referred to as a single muscle, the iliopsoas, since both muscles contribute fully to the tendinous insertion at the femur. The psoas fascia invests the muscle group and runs from the lumbar vertebrae to the iliopubic eminence.

Blood supply to the psoas major is derived from the four lumbar arteries and outflow is via the lumbar veins. The medial circumflex femoral artery and the iliac branch of the iliolumbar artery supply the iliacus. The iliopsoas is susceptible to primary IPA due to this rich blood supply as well as the proximity of the retroperitoneal lymphatic system. Nerve supply to the psoas major is via the lumbar neural plexus L1–L3 and the iliacus receives innervation from L2, L3, and branches of the femoral nerve.

The anatomic location of the iliopsoas is in close proximity to the kidneys, sigmoid colon, cecum and appendix, the quadratus lumborum posteriorly, and the transverse spinous processes of the lumbar vertebrae. This proximity may allow a contiguous focus of infection, leading to cases of secondary IPA.

ETIOLOGY

Primary IPA occurs when a causative organism from a distant site spreads to the iliopsoas compartment by a hematogenous or lymphatic route. This may result from intravenous drug use, chronic disease such as renal failure or diabetes mellitus, neoplasm, human immunodeficiency virus/acquired immunodeficiency virus (HIV/AIDS) or other forms of immunosuppression. Bilateral IPA is more common in primary cases. Secondary IPA is a contiguous extension of an intra-abdominal infectious or inflammatory process. This most often results from intra-abdominal infectious or inflammatory conditions. Crohn's disease is most often implicated, but appendicitis, ulcerative colitis, diverticulitis, *Salmonella* enteritis, and colorectal cancer are other causes of IPA attributed to the gastrointestinal tract. Urinary tract infection, nephrolithiasis, urinary tract

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Table 73.1 Conditions associated with iliopsoas abscess

Condition
Primary abscess
Intravenous drug use
Human immunodeficiency virus/acquired immunodeficiency virus
Immunosuppression
Renal failure
Diabetes mellitus
Secondary abscess
Gastrointestinal disease: Crohn's disease, appendicitis, diverticulitis, colon cancer, rectal cancer
Genitourinary disease: urinary tract infection, urinary tract cancer, nephrolithiasis, genitourinary tract instrumentation
Musculoskeletal disease: vertebral osteomyelitis, septic arthritis, infectious sacroiliitis
Vascular disease: endocarditis, infected aortic aneurysm (usually following a repair), mycotic femoral pseudoaneurysm or aneurysm, infected hardware (catheter or stent)
Gynecologic disease: tubo-ovarian abscess, perforated uterus from septic abortion, intrauterine contraceptive device
Lymphatic: suppurative lymphadenitis

cancers and genitourinary tract instrumentation may also lead to IPA. Gynecologic causes may include tubo-ovarian abscess, perforated uterus from septic abortion, or an intrauterine contraceptive device. Other causes include trauma, endocarditis, infected aortic aneurysm, mycotic femoral pseudoaneurysm or aneurysm, infected vascular graft, femoral artery catheterization, vertebral osteomyelitis, and septic hip arthritis. Table 73.1 shows conditions associated with iliopsoas abscess.

Causative organisms vary between primary and secondary IPA. Most often a single organism is responsible; however, secondary cases with a gastrointestinal or urinary source may be polymicrobial. In primary IPA, the most common organism identified is *S. aureus*. In secondary IPA with a gastrointestinal or urinary source, *Escherichia coli* is most commonly implicated. *Bacteroides, M. tuberculosis, Streptococcus viridans, Enterococcus faecalis,* and *Peptostreptococcus* have also been isolated from IPA. Patients with HIV/AIDS most commonly present with a primary IPA due to *M. tuberculosis*; *S. aureus* is the second most common organism in this population. HIV patients with secondary IPA most often have a genitourinary source or lumbar spondylodiscitis. *M. tuberculosis* is generally associated with secondary IPA with a skeletal, genitourinary, or gastrointestinal source. Primary IPA from this organism may be secondary to hematologic spread from a respiratory focus.

EPIDEMIOLOGY

While IPA is certainly a rare condition, its true incidence is unknown. The earliest definitive worldwide series by Ricci *et al.* in 1986 suggested a rate of three cases annually worldwide, although underreporting certainly confounds these data. More recent studies suggest higher incidence, although most institutions still only see a few cases per year. Improved imaging modalities may have led to more accurate diagnosis and increased reported incidence. Increasing prevalence of immunocompromised patients such as transplant recipients and HIV/AIDS patients may also partially explain increased incidence.

Classically, the etiology of IPA has varied widely dependent on location. Ricci *et al.* showed that the vast majority (99.5%) of IPA cases in Asia and Africa were primary in nature while the majority (81.3%) of cases in Europe were secondary and most commonly attributed to Crohn's disease. In the United States, 61% of cases were primary, but more recent studies have shown that secondary cases are more common with the current incidence of primary cases reported between 7% and 45%. IPA may occur at any age, although the median age at presentation has been reported to range from 45 to 58.

A 2011 series reported by Alonso *et al.* evaluated admissions to the Johns Hopkins Hospital over a period of 15 years and identified 61 cases of IPA. They demonstrated an increase in the incidence of IPA from 0.5 cases per 10 000 admissions (1993–2004) to 6.5 cases per 10 000 admissions (2005–2007). Eighty percent of cases were secondary with the contiguous source most commonly identified in the skeletal system (48%) or an intra-abdominal organ (23%). Interestingly, the causative organism in this population was noted to be MRSA in 25% of all cases and 37% of those cases with a definitive microbiologic diagnosis. Risk factors included intravenous drug use in 21% of patients, neoplasm in 18%, diabetes mellitus in 15%, and HIV in 15%. Only 11% of patients had inflammatory bowel disease and 10% had suffered traumatic injury during the preceding 30 days.

A 2009 series by Navarro Lopez *et al.* evaluated admissions to 11 different hospitals in Spain over a period of 15 years and identified 124 cases of IPA. Primary IPA was diagnosed in 21.8% of patients and secondary IPA in 78.2% of patients. The most common source was the skeletal system (50.5%), gastrointestinal tract (24.7%), and urinary

Table 73.2 Clinical signs and symptoms of patients with iliopsoas abscess

Clinical sign or symptom	Percentage of patients with sign or symptoms
Fever	82%–90%
Pain	64%–100%
Abdominal	35%–100%
Flank/back	30%–35%
Hip	29%
Psoas sign	100%
Unilateral flexion deformity	29%
Mass	18%–80%
Swelling or erythema	24%
Nausea and vomiting	30%
Chills and night sweats	6%
Elevated white blood cell count	90%–100%
Positive blood cultures	70%

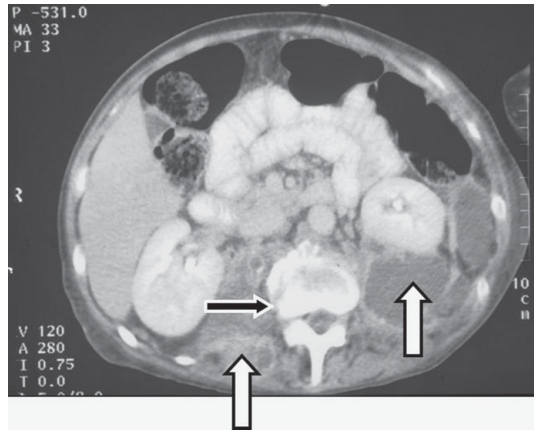

Figure 73.1 This is a CT scan with oral and intravenous contrast of a 35-year-old HIV-positive patient with evidence of bilateral iliopsoas abscesses (white arrows). The vertebral body also has signs of beginning destruction (black arrow). *Mycobacterium tuberculosis* was isolated from the abscess.

tract (17.5%). Risk factors included diabetes mellitus in 18.5% of patients, chronic liver disease in 16.1% of patients, neoplasm in 11.3% of patients and HIV in 6.3% of patients.

DIAGNOSIS

A focused history and physical exam is critical in the diagnosis of IPA. History should specifically assess for risk factors including immunosupression, history of inflammatory bowel disease, intravenous drug use, or recent infection. Symptoms including fever, night sweats, and weight loss should be queried. Full laboratory evaluation including complete blood count, comprehensive metabolic panel, C-reactive protein, and erythrocyte sedimentation rate may help confirm an inflammatory process. Many patients will demonstrate a leukocytosis and some may demonstrate elevated blood urea nitrogen and creatinine or electrolyte disturbances. Blood cultures should be obtained prior to antibiotic administration and are often positive in patients with IPA. Both blood cultures and abscess aspirate may be used to diagnose the causative organism, although direct abscess aspirate is higher yield with greater specificity.

The classic triad of IPA is back/flank pain, fever, and limp (or flexion deformity). These findings may only be seen in 10% to 30% of cases, as most patients will present with nonspecific features including fever or malaise. Symptoms may also include abdominal or flank pain and signs may include a mass in the back, flank, or groin. Patients who are debilitated or immunocompromised may have few or no signs and symptoms. Active contraction and passive extension of the iliopsoas may be painful for patients, and thus the patient tends to relax the muscle by flexion of the thigh and externally rotating the hip. A psoas sign (pain with attempted hip extension) may be seen. Table 73.2 shows signs and symptoms of IPA.

The preferred imaging modality for diagnosis is computed tomography (CT) scan with oral and intravenous contrast. CT accurately identifies disorders of the iliopsoas compartment, although this method is not always reliable to differentiate abscess from hematoma or neoplasm. Low attenuation of the lesion on CT scan is 100% sensitive for abscess but only 43% specific. CT findings that may indicate an etiology other than IPA are irregular lesion margin (67% sensitive for neoplasm) and diffuse involvement of the muscle (88% sensitive for hematoma). CT is particularly helpful for diagnosing associated pathology in cases of secondary IPA, which may require further evaluation or operative intervention. CT may also be helpful to identify bilateral iliopsoas involvement in primary cases (Figure 73.1). Definitive microbiologic diagnosis will depend upon subsequent diagnostic and therapeutic drainage or biopsy. Table 73.3 compares different CT features used to distinguish abscess from neoplasm or hematoma of the iliopsoas compartment.

Table 73.3 Comparison of different CT features in distinguishing abscesses from neoplasms and hematomas of the iliopsoas compartment

CT feature	Sensitivity (%)	Specificity (%)	Accuracy (%)
Enlargement of both psoas and iliacus muscle	29	52	41
Low attenuation of the lesion	100	43	70
Diffuse involvement of the entire muscle by lesion	19	52	36
Irregular lesion margins	52	43	48
Fat infiltration	62	48	55
Fascial disruption	57	57	57

Modified from Lenchik L, Dogvan DJ, Kier R. CT of the iliopsoas compartment: value in differentiating tumor, abscess, and hematoma. *AJR Am J Roentgenol.* 1994;162:83–86.

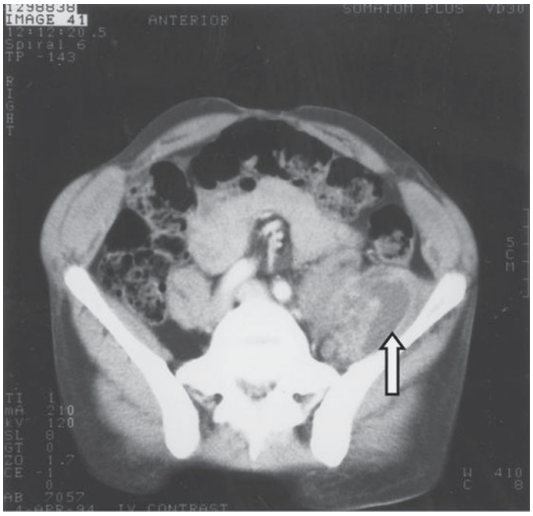

Figure 73.2 This is a CT scan with oral and intravenous contrast from the pelvis which shows involvement of the left iliopsoas compartment, in this case the iliacus (white arrow). The complex collection was drained via an operative approach and grew *Staphylococcus aureus*.

Other imaging studies to consider include magnetic resonance imaging (MRI) and ultrasound. MRI may be used to better define soft-tissue involvement and the structures of the retroperitoneum. If there is concern for epidural abscess, MRI may be preferable to CT. Unlike CT, MRI will not effectively delineate pathology of the gastrointestinal tract and thus is not the recommended first-line imaging modality. Ultrasound may be a useful screening tool in the emergency department as it is noninvasive and cost-effective. In some patients this modality may be diagnostic, or may lead to more expedient consideration of IPA in the differential. In modern practice, patients with suspicion for IPA will still proceed to CT scan.

Table 73.4 Pathogens found in iliopsoas abscesses

Iliopsoas etiology	Pathogen
Primary	*Staphylococcus aureus*, coagulase-negative staphylococci, especially methicillin-resistant
Intravenous drug abuse	
Immunocompromised	*S. aureus, Mycobacterium tuberculosis, Mycobacterium avium*
	Occasional gram negatives
Secondary	*Escherichia coli, Klebsiella, Enterococcus* spp., *Proteus* spp., *Bacteriodes* spp., *Peptostreptococcus, Clostridium, Salmonella enteritidis*
Gastrointestinal: Crohn's, fistula, cancer, pancreatic, recent operation	
Genitourinary	*E. coli, M. tuberculosis, Enterococccus* spp.
Lumbar/back	*M. tuberculosis, S. aureus, coagulase-negative* staphylococci
Trauma	Enteric and *Staphylococcus* organisms

TREATMENT

Adequate fluid resuscitation, correction of electrolyte abnormalities, and early use of broad-spectrum antibiotics to cover *S. aureus* and enteric organisms is critical for treatment of IPA. Sepsis should be recognized and treated per established guidelines. Culture sensitivities may be used to guide antibiotic therapy to address the organisms of concern.

Risk factors and known or probable etiology must be considered when choosing initial antibiotic therapy. Table 73.4 shows pathogens implicated in IPA. Antibiotics may be tailored to the specific pathogen once culture data are available. Primary IPA should include coverage for *S. aureus*, coagulase-negative *Staphylococcus*, *M. tuberculosis* and *Mycobacterium avium*. Vancomycin should be the initial choice for any critically ill patient or patients at risk for MRSA. Other options for treatment include oxacillin or clindamycin and an aminoglycoside. With cases of secondary IPA, enteric organisms should be covered including *E. coli, Klebsiella, Enterococcus, Proteus, Bacteroides, Peptostreptococcus, Clostridium,* and *Salmonella*.

Table 73.5 Treatment options for iliopsoas abscesses

Iliopsoas etiology	Treatment option
Primary Intravenous drug abuse Immunocompromised	Initial coverage should include specific coverage for *S. aureus*, but should also include gram-negative coverage until the final organism(s) are known Options: oxacillin (or nafcillin) and aminoglycoside, cephalosporins, especially cefipime, fluoroquinolones, clindamycin and aminoglycoside. Vancomycin should be considered for critically ill patients and those with high risk of methicillin resistance
Secondary Gastrointestinal, i.e., Crohn's, fistula, cancer, pancreatic, recent operation Genitourinary Lumbar/back Trauma	Initial empiric coverage for all secondary abscesses should be broad spectrum and should include gram-negative aerobes and anaerobes *Monotherapy options: moderate illness:* cefotetan (cefoxitin), ertapenem, piperacillin–tazobactam *Severe illness:* piperacillin–tazobactam, imipenem, meripenem *Combination therapy:* clindamycin and aminoglycoside, clindamycin and third-generation cephalosporin (cefotaxime, ceftriaxone), clindamycin and aztreonam, clindamycin and fluoroquinolone

Treatment options include monotherapy with cefotetan or ertapenem; critical illness may necessitate treatment with piperacillin–tazobactam, imipenem, or meropenem. For those patients allergic to penicillin, one may consider the combination of clindamycin with either an aminoglycoside, a third-generation cephalosporin, aztreonam, or a fluoroquinolone. IV antibiotics are appropriate initially. Oral antibiotics may be used once culture sensitivity data are available and once the patient has shown signs of clinical improvement. Duration of antibiotic therapy should be determined by clinical course and source control. A typical duration is 7 to 14 days. It is not necessary to continue antibiotics for the duration of time during which a drainage catheter may be in place. Table 73.5 shows treatment options for IPA.

Small abscesses may be treated with antibiotics alone, although many cases will require image-guided percutaneous drainage. Percutaneous aspiration of drainage is especially effective for patients who are critically ill and unstable for operative intervention. Interventional radiologists are particularly adept at CT-guided placement of drainage catheters and this has become the preferred management strategy for most cases of IPA. In cases with use of a percutaneous drainage catheter, it is important to ensure obliteration of the abscess cavity before removal of the drain. This may be achieved with repeat CT scan and a sinogram study (injection of contrast dye under fluoroscopy through the drain). An algorithm published by Yacoub *et al.* based on a case series of 41 patients reports a 90% success rate for resolution of IPA without surgery. This algorithm recommends CT scan for initial radiologic confirmation of iliopsoas pathology followed by determination of the dimension of the abscess. If the abscess is less than 3 cm, antibiotics alone are appropriate. For dimensions greater than 3 cm, percutaneous image-guided drainage is appropriate.

Some cases may require open surgical drainage, particularly in secondary cases with intra-abdominal pathology that requires surgical attention. Other factors that may necessitate surgical intervention include multiple loculations, recurrent abscess (as many as 15% of cases may present with recurrence), failure of percutaneous drainage catheter, or need for debridement of devitalized muscle or tissue. A lower abdominal, muscle-splitting extraperitoneal incision may be used for open drainage of primary IPA. Laparotomy may be necessary for certain cases of secondary IPA. Incision and drainage from the groin, thigh, or back is not recommended.

OUTCOME

Current mortality rate for IPA ranges from 3% to 5%. In the 1980s, mortality for primary IPA as reported by Ricci *et al.* was 2.5% and for secondary IPA was 18.9%. Sepsis was the primary cause of death and delayed or inadequate treatment was the biggest risk factor for death. The 2011 case series by Alonso *et al.* reported the in-hospital death of 2 patients out of a series of 61 cases over 15 years. Of note, neither cause of death was directly attributable to the IPA in this series. The 2009 case series by Navarro Lopez *et al.* reported an overall mortality rate of 6.6% and a mortality rate of 5% due to complications related to IPA. Specific risk factors for mortality on univariate analysis included age $>$ 65 years, bacteremia, and growth of *E. coli* from cultures. A 2008 study by Yacoub *et al.* studied 41 patients with IPA and reported a mortality rate of 3%. Ultimately, outcome is dependent on early diagnosis, appropriate antibiotic administration, and source control. With increasing incidence and more virulent pathogens implicated in development of IPA, the physician

must maintain a high index of suspicion for this rare but increasingly more common disease.

SUMMARY

- Primary IPA arises from a distant site and spreads to the iliopsoas compartment by a hematogenous or lymphatic route. Secondary IPA arises when a contiguous extension of an intra-abdominal infectious or inflammatory process causes the condition.
- *S. aureus* is the most common organism isolated from primary IPA. Enteric organisms are commonly implicated in secondary IPA.
- The classic triad of IPA is back/flank pain, fever, and a flexion deformity or limp. Most patients will only present with nonspecific features including fever or malaise.
- Risk factors for primary IPA include intravenous drug use, immunosuppression, chronic disease, and HIV. Risk factors for secondary IPA include Crohn's disease and other intra-abdominal pathology.
- CT scan is the preferred imaging modality.
- Treatment consists of antibiotics and percutaneous image-guided drainage. Surgical drainage is not required for the majority of cases, but may be necessary for complicated cases or recurrence. Secondary IPA cases may necessitate surgical intervention for associated intra-abdominal pathology.
- Early diagnosis and effective treatment with antibiotics and percutaneous image-guided drainage is critical to prevention of morbidity and mortality.

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PART X

Clinical syndromes: neurologic system

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74. Bacterial meningitis

Sarbjit S. Sandhu and Allan R. Tunkel

CLINICAL PRESENTATION

The classic clinical presentation in patients with bacterial meningitis is that of fever, headache, meningismus, and signs of cerebral dysfunction (confusion, delirium, or a declining level of consciousness). In a review of 493 cases of acute bacterial meningitis in adults, the classic triad (i.e., fever, nuchal rigidity, and change in mental status) was found in only two-thirds of patients, but all had at least one of these findings. In another review of 696 episodes of community-acquired bacterial meningitis, the triad of fever, neck stiffness, and altered mental status was present in only 44% of episodes, although almost all patients (95%) presented with at least two of the four symptoms of headache, fever, stiff neck, and altered mental status. The meningismus may be subtle, marked, or accompanied by Kernig and/or Brudzinski signs. However, in a prospective study that examined the diagnostic accuracy of meningeal signs in adults with suspected meningitis, the sensitivity of these findings was only 5% for Kernig sign, 5% for Brudzinski sign, and 30% for nuchal rigidity, indicating that they did not accurately distinguish patients with meningitis from those without meningitis, and the absence of these findings did not rule out the diagnosis of bacterial meningitis. Cranial nerve palsies and focal cerebral signs are seen in 10% to 20% of cases. In an observational study of 696 patients with community-acquired bacterial meningitis, cerebral infarction occurred in 25% of episodes, and in 36% of those specifically with pneumococcal meningitis. Seizures occur in about 30% of patients. Papilledema is observed in less than 5% of cases early in infection, and its presence should suggest an alternative diagnosis. As meningitis progresses, patients may develop signs of increased intracranial pressure (e.g., coma, hypertension, bradycardia, and palsy of cranial nerve III).

To further characterize the accuracy and precision of the clinical examination in adult patients with acute meningitis, patient data on 845 episodes of acute meningitis (confirmed by lumbar puncture or autopsy) in patients aged 16 to 95 years were reviewed. The results demonstrated that individual items of the clinical history (i.e., headache, nausea, and vomiting) had a low accuracy for the diagnosis of meningitis in adults. However, on review of the accuracy of physical examination findings, the absence of fever, neck stiffness, and altered mental status effectively eliminated the likelihood of acute meningitis; the sensitivity was 99% to 100% for the presence of one of these findings in the diagnosis of acute meningitis. Despite these findings, physicians should have a low threshold for performance of lumbar puncture in patients at high risk for bacterial meningitis.

Certain symptoms or signs may suggest an etiologic diagnosis in patients with bacterial meningitis. About half of the patients with meningococcemia, with or without meningitis, present with a prominent rash that is localized principally to the extremities. The rash typically is macular and erythematous early in the course of illness, but it quickly evolves into a petechial phase with further coalescence into a purpuric form; the rash may evolve rapidly, with new petechiae appearing during the physical examination. Patients with *Listeria monocytogenes* meningitis have an increased tendency toward focal deficits and seizures early in the course of infection; some patients may present with ataxia, cranial nerve palsies, or nystagmus as a result of rhombencephalitis. In a large review of 367 episodes of central nervous system (CNS) infection caused by *L. monocytogenes*, the most frequent findings were fever (92%) and altered sensorium (65%), with headache reported in only about 50% of patients. In addition, many patients with bacterial meningitis have predisposing illnesses; up to 40% of patients with pneumococcal meningitis have preceding ear, sinus, or lung infections.

Furthermore, some patients may not present with many of the classic symptoms or signs of

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bacterial meningitis. Elderly patients, particularly those with underlying medical conditions (e.g., diabetes mellitus, cardiopulmonary disease), may present insidiously with lethargy or obtundation, no fever, and variable signs of meningeal inflammation. In one recent 30-year study of 185 patients 65 years and older, the diagnosis of community-acquired bacterial meningitis was more difficult because of the absence of characteristic meningeal signs. Neutropenic patients may also present in a subtle manner because of the impaired ability of the patient to mount a subarachnoid space inflammatory response. In patients with head trauma, the symptoms and signs consistent with meningitis may be present as a result of the underlying injury and not meningitis. In all of these subgroups of patients, altered or changed mental status should not be ascribed to other conditions unless bacterial meningitis has been excluded by cerebrospinal fluid (CSF) examination.

DIAGNOSIS

Bacterial meningitis is diagnosed by examination of CSF obtained via lumbar puncture. In virtually all patients with bacterial meningitis, the opening pressure is elevated (>180 mm H_2O), with values greater than 600 mm H_2O suggesting the presence of cerebral edema, intracranial suppurative foci, or communicating hydrocephalus. The CSF white blood cell count is elevated (usually 1000 to 5000 cells/mm^3, with a range of ≤100 to >10 000/mm^3); patients with low CSF white blood cell counts (from 0 to 20/mm^3), despite high CSF bacterial concentrations, tend to have a poor prognosis. There is usually a neutrophilic predominance (≥80%), although approximately 10% of patients with acute bacterial meningitis will present with a lymphocytic predominance in CSF (more common in neonates with gram-negative bacillary meningitis and patients with *L. monocytogenes* meningitis). A decreased CSF glucose concentration (≤40 mg/dL) is found in about 60% of patients; a CSF-to-serum glucose ratio of less than 0.31 is observed in about 70% of patients. The CSF protein is elevated in virtually all cases (usually 100 to 500 mg/dL). Gram stain examination of CSF permits a rapid, accurate identification of the causative microorganism in about 60% to 90% of patients with bacterial meningitis; the specificity is nearly 100%, and the likelihood of detecting the organism is greater with higher CSF bacterial densities. CSF cultures are positive in 80% to 90% of patients with community-acquired bacterial meningitis; the yield of culture is decreased in patients who have received prior antimicrobial therapy. Elevated CSF lactate concentrations may help differentiate between bacterial and aseptic meningitis with a sensitivity and specificity reported as high as 97% and 96%, respectively. However, the accuracy is lowered in patients pretreated with antimicrobial therapy prior to lumbar puncture or in those with other CNS diseases such as head trauma or stroke.

In patients without a positive CSF Gram stain or culture, the diagnosis of bacterial meningitis can be difficult to establish or reject. A number of studies have examined a combination of clinical features, with or without test results, to develop models to predict the likelihood of bacterial meningitis compared to other potential agents, usually viruses. Despite positive results in a number of studies utilizing prediction models, clinical judgment should continue to be used in decisions for administration of empiric antimicrobial therapy in patients with suspected bacterial meningitis.

In patients with bacterial meningitis and a negative CSF Gram stain, several rapid diagnostic tests that can be considered for detection of specific bacterial antigens in CSF have been developed to aid in the etiologic diagnosis. Currently available latex agglutination techniques have a sensitivity ranging from 50% to 100% (although these tests are highly specific) and detect the antigens of *Haemophilus influenzae* type b, *Streptococcus pneumoniae, Neisseria meningitidis, Escherichia coli* K1, and *Streptococcus agalactiae*. However, the routine use of latex agglutination for the etiologic diagnosis of bacterial meningitis has recently been questioned and is no longer routinely recommended, because bacterial antigen testing does not appear to modify the decision to administer antimicrobial therapy and false-positive tests have been reported. Polymerase chain reaction (PCR) has been used to amplify DNA from patients with meningitis caused by several meningeal pathogens. The clinical utility of PCR for the diagnosis of bacterial meningitis was assessed in one study with a broad range of bacterial primers, yielding a sensitivity of 100%, specificity of 98.2%, positive predictive value of 98.2%, and negative predictive value of 100%. Broad-based PCR can be used to detect the most common microorganisms in only one test, can be done within 2 hours in most industrialized countries, and has adequate sensitivity and excellent specificity. Further refinements are needed,

Table 74.1 Recommended antimicrobial therapy for acute bacterial meningitis based on presumptive identification by positive Gram stain

Microorganism	Therapy
Streptococcus pneumoniae	Vancomycin plus a third-generation cephalosporin[a,b]
Neisseria meningitidis	Third-generation cephalosporin[a]
Listeria monocytogenes	Ampicillin or penicillin G[c]
Haemophilus influenzae type b	Third-generation cephalosporin[a]
Streptococcus agalactiae	Ampicillin or penicillin G[c]
Escherichia coli	Third-generation cephalosporin[a]

[a] Cefotaxime or ceftriaxone.
[b] Addition of rifampin may be considered; some experts would add rifampin if dexamethasone is also given.
[c] Addition of an aminoglycoside should be considered.

however, before this technique can be used in patients with presumed bacterial meningitis when CSF Gram stain and cultures are negative. An immunochromatographic test is also available for detection of *S. pneumoniae* in CSF; the overall sensitivity is 95% to 100%.

THERAPY

Initial approach to management

In patients with the clinical presentation of acute bacterial meningitis, the initial management includes performance of a lumbar puncture. If the CSF formula is consistent with the diagnosis of bacterial meningitis, targeted antimicrobial therapy and adjunctive dexamethasone (see below) should be initiated based on results of Gram stain (Table 74.1). However, if no etiologic agent can be identified on initial CSF analysis, empiric antimicrobial therapy and adjunctive therapy should be initiated rapidly based on the patient's age (Table 74.2). In patients with a clinical presentation of bacterial meningitis in whom there is a delay in performance of lumbar puncture or if there is suspicion of an intracranial mass lesion that is causing their neurologic presentation (i.e., those with focal neurologic deficits, abnormal level of consciousness, new-onset seizure, or papilledema on funduscopic examination or those who are immunocompromised or have a history of CNS disease), a noncontrast computed tomography (CT) scan of the head should be performed before lumbar puncture. In these patients, blood cultures must be obtained and appropriate antimicrobial and adjunctive therapy given prior to lumbar puncture, or before the patient is sent to the CT scanner, to potentially reduce the increased morbidity and mortality associated with bacterial meningitis when initiation of appropriate antimicrobial and adjunctive therapy is delayed. Although there are no prospective data on the timing of administration of antimicrobial therapy in patients with bacterial meningitis, a retrospective cohort study in patients with community-acquired bacterial meningitis demonstrated that a delay in initiation of antimicrobial therapy after patient arrival in the emergency room was associated with an adverse clinical outcome when the patient's condition advanced to a high stage of prognostic severity, supporting the assumption that treatment of bacterial meningitis before it advances to a high level of clinical severity improves clinical outcome. Although the yield of positive CSF cultures may decrease with initiation of antimicrobial therapy prior to obtaining CSF for analysis, the pretreatment blood cultures, CSF formula, and/or Gram stain will likely provide evidence for or against a diagnosis of bacterial meningitis.

Table 74.2 Common bacterial pathogens and empiric therapeutic recommendations based on age in patients with meningitis

Age	Common bacterial pathogens	Empiric antimicrobial therapy
<1 mo	*Streptococcus agalactiae, Escherichia coli, Listeria monocytogenes*	Ampicillin plus cefotaxime, or ampicillin plus an aminoglycoside
1–23 mo	*S. agalactiae, E. coli, Haemophilus influenzae, Streptococcus pneumoniae, Neisseria meningitidis*	Vancomycin plus a third-generation cephalosporin[a,b]
2–50 yr	*S. pneumoniae, N. meningitidis*	Vancomycin plus a third-generation cephalosporin[a,b,c]
>50 yr	*S. pneumoniae, N. meningitidis, L. monocytogenes*, aerobic gram-negative bacilli	Vancomycin plus ampicillin plus a third-generation cephalosporin[a,c]

[a] Cefotaxime or ceftriaxone.
[b] Add ampicillin if meningitis caused by *L. monocytogenes* is suspected.
[c] Some experts would add rifampin if dexamethasone is also given.

Adjunctive therapy

Because of the unacceptable morbidity and mortality rates in patients with bacterial meningitis, even in the antibiotic era, investigators have been studying the pathogenic and pathophysiologic mechanisms operable in bacterial meningitis in

the hopes of improving outcome from this disorder. Initial experimental studies focused on the subarachnoid space inflammatory response that occurs during bacterial meningitis to determine whether attenuation of this response would improve outcome. Through the use of experimental animal models of infection, it was determined that one corticosteroid agent, dexamethasone, was effective in reducing the CSF white blood cell response and CSF tumor necrosis factor concentrations, with a trend toward earlier improvement in CSF concentrations of glucose, protein, and lactate; these parameters improved without any apparent decrease in the rate of CSF bacterial killing.

Based on these and other studies in experimental animal models, numerous clinical trials were undertaken to determine the effects of adjunctive dexamethasone on the outcome in patients with bacterial meningitis. A meta-analysis of these clinical studies confirmed the benefit of adjunctive dexamethasone (0.15 mg/kg every 6 hours for 2 to 4 days) for *H. influenzae* type b meningitis and, if commenced with or before parenteral antimicrobial therapy, suggested benefit for pneumococcal meningitis in childhood. Evidence of clinical benefit was strongest for hearing outcomes. In adults with acute bacterial meningitis, a prospective, randomized, placebo-controlled, double-blind multicenter trial in 301 patients demonstrated that patients randomized to receive adjunctive dexamethasone were less likely to have unfavorable outcome and death; benefit was most evident among the subgroup of patients with pneumococcal meningitis. Based on the available evidence, adjunctive dexamethasone (0.15 mg/kg every 6 hours for 4 days with the first dose administered 10 to 20 minutes before, or at least concomitant with, the first dose of an antimicrobial agent) should be utilized in adults with suspected or proven pneumococcal meningitis. Adjunctive dexamethasone should not be given to adults who have already received antimicrobial therapy, because administration in this setting is unlikely to improve patient outcome. The data are inadequate to recommend adjunctive dexamethasone in adults with meningitis caused by other meningeal pathogens; continuing dexamethasone in patients with culture-proven meningococcal meningitis did not lead to improvement in rates of unfavorable outcome, although its use was not associated with harm. Some authorities would initiate dexamethasone in all adults because the etiology of meningitis is not always ascertained at initial evaluation.

Despite the positive benefits of adjunctive dexamethasone in adults with bacterial meningitis, its routine use in patients in the developing world has been controversial. In one randomized, double-blind, placebo-controlled trial from Malawi in adults, there were no significant differences in mortality, although almost 90% of the patients in this trial were infected with HIV and likely had advanced disease. In a Cochrane meta-analysis of 24 studies involving 4041 participants, adjunctive dexamethasone did not reduce overall mortality, but there was a trend to lower mortality rates in adults; corticosteroids were associated with lower rates of severe hearing loss, any hearing loss, and neurologic sequelae, but these benefits were only seen in studies from high-income countries.

In addition, the use of adjunctive dexamethasone is of concern in those with pneumococcal meningitis caused by highly penicillin- and cephalosporin-resistant strains, in which patients may require antimicrobial therapy with vancomycin. In this instance, a diminished CSF inflammatory response after dexamethasone administration might significantly reduce vancomycin penetration into CSF and delay CSF sterilization. The published trials have not examined outcome in patients with these resistant isolates who have received adjunctive dexamethasone, and it is unlikely that this question will be definitively answered in the near future, given the difficulty in enrolling adequate numbers of patients with these resistant strains into clinical trials. However, CSF vancomycin penetration was not reduced by dexamethasone in a study in which a continuous infusion of vancomycin (at a dose of 60 mg/kg/day) was utilized. For any patient receiving adjunctive dexamethasone who is not improving as expected, a repeat lumbar puncture 36 to 48 hours after initiation of antimicrobial therapy is recommended to document sterility of CSF.

Antimicrobial therapy

Once the infecting meningeal pathogen is isolated and susceptibility testing known, antimicrobial therapy can be modified for optimal treatment (Table 74.3). Recommended antimicrobial dosages for meningitis in adults with normal renal and hepatic function are shown in Table 74.4. The following sections review recommendations for use of antimicrobial therapy in patients with bacterial meningitis based on the isolated meningeal pathogen.

Table 74.3 Specific antimicrobial therapy for acute bacterial meningitis

Microorganism	Standard therapy	Duration of therapy
Streptococcus pneumoniae		10–14 d
Penicillin MIC ≤0.06 μg/mL	Penicillin G or ampicillin	
Penicillin MIC ≥0.12 μg/mL		
Cefotaxime or ceftriaxone MIC <1.0 μg/mL	Third-generation cephalosporin[a]	
Cefotaxime or ceftriaxone MIC ≥1.0 μg/mL	Vancomycin plus a third-generation cephalosporin[a, b]	
Neisseria meningitidis		7 d
Penicillin MIC <0.1 μg/mL	Penicillin G or ampicillin	
Penicillin MIC 0.1–1.0 μg/mL	Third-generation cephalosporin[a]	
Listeria monocytogenes	Ampicillin or penicillin G[c]	≥21 d
Streptococcus agalactiae	Ampicillin or penicillin G[c]	14–21 d
Haemophilus influenzae		7 d
β-lactamase – negative	Ampicillin	
β-lactamase – positive	Third-generation cephalosporin[a]	
Escherichia coli and other Enterobacteriaceae[d]	Third-generation cephalosporin[a]	21 d
Pseudomonas aeruginosa	Cefepime[c] or ceftazidime[c]	21 d
Staphylococcus aureus		10–14 d
Methicillin-sensitive	Nafcillin or oxacillin	
Methicillin-resistant	Vancomycin	
Staphylococcus epidermidis	Vancomycin[e]	10–14 d

[a] Cefotaxime or ceftriaxone.

[b] Consider addition of rifampin if the ceftriaxone MIC is >4 μg/mL.

[c] Addition of an aminoglycoside should be considered.

[d] Choice of a specific antimicrobial agent must be guided by in vitro susceptibility test results.

[e] Addition of rifampin should be considered.

Abbreviation: MIC = minimal inhibitory concentration.

STREPTOCOCCUS PNEUMONIAE

The recommended therapy of pneumococcal meningitis has been changed based on pneumococcal susceptibility patterns. Pneumococcal strains with minimal inhibitory concentrations (MICs) ≤0.06 μg/mL are considered susceptible to penicillin and those with MICs ≥0.12 μg/mL are considered resistant. Resistant strains have been reported from many countries throughout the world, including the United States, where the prevalence of penicillin-nonsusceptible *S. pneumoniae* ranges from 25% to more than 50%. Because initial CSF concentrations of penicillin are only approximately 1 μg/mL after parenteral administration of standard high dosages, penicillin cannot be recommended as empiric antimicrobial therapy when *S. pneumoniae* is considered a likely infecting pathogen in patients with purulent meningitis. Of additional concern is that pneumococcal strains resistant to the third-generation cephalosporins have been described in patients with meningitis. Several alternative agents have been examined for the treatment of meningitis caused by penicillin-resistant pneumococci. Chloramphenicol is one agent that has been studied, although clinical failures with chloramphenicol have been reported in patients with penicillin-resistant isolates. Vancomycin has also been evaluated, but as a single agent is likely to be suboptimal for therapy of pneumococcal meningitis.

Based on these data, it is recommended that, for empiric therapy of suspected pneumococcal meningitis, the combination of vancomycin and a third-generation cephalosporin (either cefotaxime or ceftriaxone) should be used pending in vitro susceptibility results. This combination was synergistic in a rabbit model of penicillin-resistant pneumococcal meningitis and was synergistic, or at least additive, in the CSF of children with meningitis. If the organism is sensitive to penicillin (MIC ≤0.06 μg/mL), penicillin is the drug of choice. For penicillin-resistant strains (MIC ≥0.12 μg/mL), in vitro susceptibility to the third-generation cephalosporins should be determined. If the MIC to cefotaxime or ceftriaxone is

Table 74.4 Recommended dosages of antimicrobial agents for meningitis in adults with normal renal and hepatic function

Antimicrobial agent	Total daily dose (IV)	Dosing interval (h)
Amikacin[a]	15 mg/kg	8
Ampicillin	12 g	4
Aztreonam	6–8 g	6–8
Cefepime	6 g	8
Cefotaxime	8–12 g	4–6
Ceftazidime	6 g	8
Ceftriaxone	4 g	12–24
Chloramphenicol[b]	4–6 g	6
Ciprofloxacin	800–1200 mg	8–12
Gentamicin[a,c]	5 mg/kg	8
Meropenem	6 g	8
Moxifloxacin[d]	400 mg	24
Nafcillin	9–12 g	4
Oxacillin	9–12 g	4
Penicillin G	24 million U	4
Rifampin	600 mg	24
Tobramycin[a]	5 mg/kg	8
Trimethoprim–sulfamethoxazole[e]	10–20 mg/kg	6–12
Vancomycin[f,g]	30–60 mg/kg	8–12

[a] Need to monitor peak and trough serum concentrations.
[b] Higher dosage recommended for pneumococcal meningitis.
[c] Intrathecal dosage is 1–8 mg; usual daily dose is 1–2 mg for infants and children, and 4–8 mg for adults. Intrathecal dosing should always be used in combination with a parenteral agent.
[d] No data on optimal dose needed in patients with bacterial meningitis.
[e] Dosage based on trimethoprim component.
[f] Maintain serum trough concentrations of 15–20 μg/mL.
[g] Intrathecal dosage is 5–20 mg; most studies have used a 10-mg or 20-mg dose.

<1.0 μg/mL, a third-generation cephalosporin is used. However, if the MIC to cefotaxime or ceftriaxone is ≥1.0 μg/mL, vancomycin plus the third-generation cephalosporin are continued for the entire treatment period. Some investigators have also recommended the addition of rifampin, although no clinical data support this recommendation; rifampin should be added only if the organism is susceptible and there is a delay in the expected clinical or bacteriologic response. In patients not responding, intrathecal or intraventricular vancomycin remains a reasonable option.

Several other antimicrobial agents appear promising for the therapy of penicillin-resistant pneumococcal meningitis. Meropenem, a carbapenem with less proconvulsant activity than imipenem, has been utilized in children and adults with bacterial meningitis, including cases caused by *S. pneumoniae*, with microbiologic and clinical outcomes similar to those following treatment with cefotaxime or ceftriaxone. However, in one study of 20 cefotaxime-resistant pneumococcal isolates, 4 were intermediate and 13 were resistant to meropenem, suggesting that meropenem may not be a useful alternative agent for treatment of pneumococcal isolates that are highly resistant to penicillin and cephalosporins. Newer fluoroquinolones (e.g., moxifloxacin) that have excellent in vitro activity against *S. pneumoniae* have also been shown to have efficacy in experimental animal models of penicillin-resistant pneumococcal meningitis, although only trovafloxacin has been shown in a clinical trial to be as efficacious as ceftriaxone, with or without vancomycin, in children with bacterial meningitis. Although trovafloxacin is no longer used because of concerns of liver toxicity, these data suggest the potential usefulness of the newer fluoroquinolones in the treatment of bacterial meningitis. Although further clinical trials are needed before these agents can be recommended as first-line therapy for patients with bacterial meningitis, a combination of a third-generation cephalosporin plus a newer-generation fluoroquinolone may emerge as the treatment of choice for pneumococcal meningitis in the future.

NEISSERIA MENINGITIDIS

The antimicrobial agent of choice for therapy of *N. meningitidis* meningitis is penicillin G or ampicillin. These recommendations may change in the future as a result of the emergence of meningococcal strains that are resistant to penicillin G, with an MIC range of 0.1 to 1.0 μg/mL. In a population-based surveillance study for invasive meningococcal disease in selected areas of the United States, 3 of 100 isolates had penicillin MICs of 0.125 μg/mL. However, the clinical significance of these isolates is unclear because patients with meningitis caused by these organisms have recovered with standard penicillin therapy. Some authorities would treat patients with meningococcal meningitis with a third-generation cephalosporin (either cefotaxime or ceftriaxone) pending susceptibility testing of the isolate. Single-dose ceftriaxone was also found to be noninferior compared with chloramphenicol when used against epidemic meningococcal meningitis in one study, suggesting that this agent should be utilized during meningococcal epidemics in the developing world.

LISTERIA MONOCYTOGENES

Despite their broad range of in vitro activity, the third-generation cephalosporins are inactive against *L. monocytogenes*. Therapy for *Listeria* meningitis should consist of ampicillin or penicillin G, with addition of an aminoglycoside considered in proven infection because of documented in vitro synergy. In the penicillin-allergic patient, trimethoprim–sulfamethoxazole, which is bactericidal against *Listeria* in vitro, should be used. Despite favorable in vitro susceptibility results, chloramphenicol and vancomycin are associated with unacceptably high failure rates.

HAEMOPHILUS INFLUENZAE

The therapy of bacterial meningitis caused by *H. influenzae* type b depends on whether the strain produces β-lactamase. For β-lactamase-negative strains, ampicillin is recommended, and for strains that produce β-lactamase, a third-generation cephalosporin (either cefotaxime or ceftriaxone) should be used. In addition, a third-generation cephalosporin should be used as empiric therapy in all patients in whom *H. influenzae* type b is a possible pathogen. Chloramphenicol is not recommended because chloramphenicol-resistant isolates have been reported throughout the world, and even in patients with chloramphenicol-sensitive isolates, a prospective study found chloramphenicol to be bacteriologically and clinically inferior to ampicillin, ceftriaxone, or cefotaxime in the therapy of childhood bacterial meningitis caused predominantly by *H. influenzae* type b. Although cefuroxime, a second-generation cephalosporin, initially appeared to be efficacious in the therapy of *H. influenzae* type b meningitis, a study comparing cefuroxime with ceftriaxone for childhood bacterial meningitis documented delayed CSF sterilization and a higher incidence of hearing impairment in the patients receiving cefuroxime. Cefepime has been compared with cefotaxime in a prospective randomized trial for treatment of meningitis in infants and children; cefepime was found to be safe and therapeutically equivalent to cefotaxime and can be considered a suitable therapeutic alternative for treatment of patients with this disease.

AEROBIC GRAM-NEGATIVE BACILLI

Outcome from meningitis caused by aerobic gram-negative bacilli has been greatly improved with the availability of the third-generation cephalosporins (cure rates of 78% to 94%). Ceftazidime, a third-generation cephalosporin with enhanced in vitro activity against *Pseudomonas aeruginosa*, led to a cure in 19 of 24 patients with *P. aeruginosa* meningitis in one study when used alone or in combination with an aminoglycoside. Similar results were observed in a study of pediatric patients in which seven patients were cured clinically and nine were cured bacteriologically when receiving ceftazidime-containing regimens. In patients with aerobic gram-negative bacillary meningitis not responding to conventional parenteral antimicrobial therapy, concomitant intraventricular or intrathecal aminoglycoside therapy should be considered, although this mode of therapy was associated with a higher mortality rate than systemic therapy alone in infants with gram-negative meningitis and ventriculitis.

Several other antimicrobial agents (e.g., imipenem, meropenem, cefepime, aztreonam, colistin) have been successfully used in isolated case reports and in small series of patients with meningitis caused by aerobic gram-negative bacilli. Imipenem has been efficacious, although a high rate of seizure activity (33% in one study) limits its usefulness in patients with bacterial meningitis. The fluoroquinolones (e.g., ciprofloxacin, pefloxacin) have also been used in some patients with bacterial meningitis, although their primary usefulness is for therapy of meningitis caused by multidrug-resistant gram-negative organisms or when the response to conventional therapy is inadequate; these agents should not be used as first-line empiric therapy in patients with meningitis of unknown etiology because of their poor in vitro activity against *S. pneumoniae* and *L. monocytogenes*. For empirical treatment of *Acinetobacter* meningitis, intravenous meropenem, with or without an aminoglycoside administered by the intrathecal or intraventricular route, has been recommended; if the organism is found to be resistant to carbapenems, colistin (usually formulated as colistimethate sodium) or polymyxin B should be substituted for meropenem and may also need to be administered by the intrathecal or intraventricular route.

STAPHYLOCOCCI AND STREPTOCOCCI

Meningitis caused by *Staphylococcus aureus* should be treated with nafcillin or oxacillin; vancomycin is used for patients who are allergic to penicillin or when the organism is methicillin resistant. For meningitis caused by coagulase-negative staphylococci (e.g., *S. epidermidis*), vancomycin is recommended; rifampin should be added if the patient fails to improve. Daptomycin, linezolid, or trimethoprim–sulfamethoxazole are considered alternative agents in patients with

staphylococcal meningitis. In patients with meningitis caused by *S. agalactiae*, ampicillin plus an aminoglycoside is recommended based on documented in vitro synergy and because of the emergence of penicillin-tolerant strains; alternatives include the third-generation cephalosporins and vancomycin.

PREVENTION

It has become clear in recent years that the spread of several types of bacterial meningitis can be prevented by chemoprophylaxis of contacts of patients with meningitis. The rationale is for eradication of nasopharyngeal colonization, thereby preventing transmission to susceptible contacts and the development of invasive disease in those already colonized. Chemoprophylaxis is recommended for contacts of a case of meningococcal meningitis. The definition of a "close contact" has not been clearly elucidated, but usually refers to persons who have had prolonged exposure of 8 hours or longer while in proximity of 3 feet or less of the index case, and include household contacts, day-care center members, and anyone directly exposed to the patient's oral secretions (e.g., through kissing, mouth-to-mouth resuscitation, endotracheal intubation, or endotracheal tube management); the index case may also need to receive prophylaxis if he or she is treated with an antimicrobial agent (e.g., penicillin or chloramphenicol) that does not reliably eradicate meningococci from the nasopharynx of colonized patients. Chemoprophylaxis should also be administered to close contacts who have received the quadrivalent meningococcal conjugate vaccine because the vaccine does not confer protection against serogroup B meningococcus. The optimal regimen to prevent invasive meningococcal disease is controversial. At present, the Centers for Disease Control and Prevention (CDC) recommend rifampin, ciprofloxacin, or ceftriaxone, which are all 90% to 95% effective at eradicating nasopharyngeal carriage. Rifampin (600 mg in adults, 10 mg/kg in children beyond the neonatal period, and 5 mg/kg in infants younger than 1 month of age) is given at 12-hour intervals for 2 days, whereas ciprofloxacin (500 mg in adults) or ceftriaxone (250 mg IM in adults) only requires one dose. However, three cases of ciprofloxacin-resistant *N. meningitidis* were reported in North Dakota and Minnesota, leading the CDC to no longer recommend ciprofloxacin for meningococcal prophylaxis in selected counties of those states; decreased susceptibility of meningococci to the fluoroquinolones has also been reported in South Africa, indicating the need for continued surveillance. Ceftriaxone is probably the safest alternative in the pregnant patient. Azithromycin (500 mg orally once) was also shown to be as efficacious as the four-dose regimen of rifampin in the eradication of meningococci from the nasopharynx. Widespread chemoprophylaxis to low-risk contacts should be discouraged because of the concern over emergence of resistant organisms and possible future limitations on this approach.

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75. Aseptic meningitis syndrome

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Aseptic meningitis syndrome is associated with symptoms, signs, and laboratory evidence of meningeal inflammation with spinal fluid findings that suggest a viral or noninfectious origin. Clinically, patients present with headache, nausea, meningismus, and photophobia, symptoms that are also common in patients with bacterial meningitis. A stiff neck, with or without a Brudzinski or Kernig sign, may be observed. Patients usually appear nontoxic but may have changes in mental status, including irritability. Other signs of possible viral infection may include pharyngitis, adenopathy, morbilliform rash, and evidence of systemic viral infection, including myalgia, fatigue, and anorexia. There are usually no signs of vascular instability, and the course is often self-limiting.

Aseptic meningitis is a syndrome of multiple etiologies, both infectious and noninfectious (Table 75.1). Infections are usually of viral origin but also may be due to mycobacteria, fungi, rickettsiae, and parasites. Group B Coxsackieviruses (mostly serotypes 2 through 5) and echoviruses (mostly serotypes 4, 6, 9, 11, 16, and 30) are responsible for more than 90% of cases of viral meningitis. Herpesvirus, arboviruses, lymphocytic choriomeningitis virus (LCM), Lyme disease, leptospirosis, and acute human immunodeficiency virus (HIV) are the etiologic agents that make up most of the remaining infectious cases. Noninfectious causes include drug reactions, collagen vascular diseases (i.e., lupus erythematosus, granulomatous arteritis), sarcoidosis, cerebral vascular lesions, epidermal cysts, meningeal carcinomatosis, serum sickness, and nonfocal lesions of the central nervous system (CNS). Specific syndromes (i.e., Mollaret's meningitis, Still's disease) may produce a similar clinical picture. The etiologic diagnosis of aseptic meningitis is often complicated by the numerous possible causes and the lack of specific diagnostic tests.

ETIOLOGY

Infectious agents

The most common causes of viral meningitis are the enteroviruses, herpesviruses, and HIV. Some viruses passively enter through the skin or respiratory, gastrointestinal, or urogenital tract and may cause initial infection at the entrance site. Some viruses spread through nerve endings by retrograde transmission via neuronal axons (i.e., poliovirus, rabies virus, herpesvirus). Enteroviruses, LCM, mumps, and arthropod-borne viruses replicate initially in muscle cells or mesodermal cells. Other viruses enter via the nose, cause infection of the submucosa, and then enter the subarachnoid space. Most viruses probably enter the CNS following viremia with primary replication at the site of entry and dissemination into the systemic circulation to either anchor and grow in the choroid plexus or pass directly through it into the CNS. Enteroviruses and HIV are carried by this route.

Enteroviruses are the most common cause of viral meningitis, occurring mostly during summer and fall but may continue to cause CNS infection also during the winter. The presentation is not distinctive, and the disease presents with abrupt onset and fever, nausea, vomiting, and photophobia. Rash and upper respiratory symptoms may be present. Another increasingly common cause of viral meningitis is represented by herpes simplex virus (HSV). Although HSV encephalitis is mostly caused by HSV-1, meningitis is generally caused by HSV-2. In patients presenting with HSV meningitis genital lesions may be present, and one-quarter of the cases presenting with primary genital herpes have meningeal involvement. However, in the case of recurrent Mollaret's meningitis, which is due to HSV-2 in 80% of cases, genital lesions are usually absent. Primary HIV can present as aseptic meningitis with headache, nausea, vomiting, fever, and stiff neck. This disease is

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Table 75.1 Causes of aseptic meningitis

Infectious	
Enterovirus	Echovirus Coxsackievirus A and B Poliovirus Enterovirus 68–71
Herpesvirus	Herpes simplex virus (HSV) 1 and 2 Varicella-zoster virus Epstein–Barr virus Cytomegalovirus HSV-6
Paramyxovirus	Mumps virus Measles virus
Togavirus	Rubella virus
Arbovirus	Eastern equine encephalitis virus Western equine encephalitis virus Venezuelan encephalitis virus
Flavivirus	Japanese encephalitis virus Murray Valley encephalitis virus St. Louis encephalitis virus West Nile virus Powassan
Bunyavirus	California encephalitis virus LaCrosse encephalitis virus Jamestown Canyon virus
Reovirus	Colorado tick fever virus
Arenavirus	Lymphocytic choriomeningitis virus
Rhabdovirus	Rabies virus
Retrovirus	Human immunodeficiency virus Human T-cell lymphotropic virus (HTLV)-I
Adenovirus	
Mycoplasma	*Mycoplasma pneumoniae*
Fungi	*Cryptococcus neoformans* *Coccidioides immitis* *Histoplasma capsulatum* *Candida* spp. *Aspergillus* *Blastocystis* *Sporothrix schenckii*
Mycobacteria	*Mycobacterium tuberculosis*
Rickettsia	*Rickettsia rickettsii* *Anaplasma*
Spirochetes	*Treponema pallidum* (syphilis) *Borrelia burgdorferi* (Lyme) *Borrelia recurrentis* (relapsing fever) *Leptospira* spp. (leptospirosis)
Parasites	*Angiostrongylus cantonensis* (eosinophilic meningitis) *Toxoplasma gondii* *Gnathostoma spinigerium*
	Taenia solium (cysticercosis) *Trichinella spiralis* *Taenia canis* (visceral larva migrants)
	Negiceria fowleri *Acanthamoeba* spp.
Bacteria	Partially treated bacterial meningitis *Listeria monocytogenes* *Brucella* *Nocardia* Acute or subacute bacterial endocarditis Parameningeal focus (brain or epidural abscess) *Chlamydia* spp. *Actinomyces* spp.
Noninfectious	
Drug reactions	Nonsteroidal anti-inflammatory agents Antineoplastic agents Antibiotics (trimethoprim–sulfamethoxazole) Immunosuppressants (orthoclone, azathioprine) Isoniazid Immunoglobulin
Malignancy	Primary medulloblastoma Metastatic leukemia Hodgkin's disease
Collagen vascular disease	Lupus erythematosus Behçet's/adult-onset Still's disease
Trauma	Subarachnoid bleed Traumatic lumbar puncture neurosurgery
Chemicals	Lead, mercury Contrast agents Disinfectants, glove powder
Neurologic disorders	Cerebral vascular lesions Epidermal cysts Brain tumors
Systemic disorders	Sarcoidosis Vasculitis
Miscellaneous	Serum sickness Mollaret's meningitis Meningeal carcinomatosis Vaccination Postinfectious viral syndromes Post-transplantation lymphoproliferative disorder Kikuchi syndrome

self-limiting and can be the only manifestation of HIV for many years. Unfortunately, if patients are not diagnosed at the time of their acute illness, they may infect a number of sexual partners before the diagnosis is established. Interestingly, early onset of aseptic meningitis has not been associated with late neurologic manifestations in HIV-1 infection, and treatment is symptomatic. Other than during the acute phase, aseptic meningitis may also be present during different stages of the disease. The diagnosis may be later complicated by the fact that cerebrospinal fluid (CSF) pleocytosis is less

Table 75.2 Diagnostic workup for aseptic meningitis syndrome

Clinical evaluation
HISTORY
Season (summer, enteroviruses, Rocky Mountain spotted fever)
Geographic area (Colorado tick fever, babesia, *Anaplasma*, Lyme disease)
Exposure to other patients (mumps, varicella)
Tick, mosquito bites (malaria, Lyme disease), tsetse fly (trypanosomiasis)
Exposure to animals (rabies, hantavirus, LCM)
Sexual history (HIV, HSV, syphilis)
IVDU (endocarditis)
Drug reactions (immunoglobulin, OKT-3, NSAIDs, antibiotics)
Physical examination
SPINAL FLUID
Opening pressure
Leukocyte count predominance
a. Neutrophils (initial echo, polio, HSV, Mollaret's, TB)
b. Lymphocytes (Coxsackie, enterovirus)
c. Eosinophils (*Angiostrongylus*, *Gnathostoma*)
d. Abnormal cells (Mollaret's, lymphoma, WNV)
Protein $\leq$ 40 mg/dL
Glucose $\leq$ 40 mg/dL or $\leq$ 50% serum
Gram stain, AFB smear, Papanicolau stain (Mollaret's meningitis)
Cryptococcal antigen, India ink
Immunoelectrophoresis
Wet mount (toxoplasmosis, amebae)
Bacterial, mycobacterial, fungal cultures
PCR for enterovirus, HSV, VZV (in immunocompromised patients), CMV, EBV
Antibodies to *Borrelia burgdorferi*, *Brucella*, *Histoplasma capsulatum* antigen and anti-histoplasma antibody testing by complement fixation, beginning with undiluted CSF, complement-fixing IgG antibodies, or immunodiffusion tests for IgM and IgG for *Coccidioides immitis* (chronic or recurrent presentation)
Serologic testing
Cryptococcal antigen
Histoplasma urinary and serum antigen (MiraVista Diagnostics)
Lyme disease ELISA, Western blot
Rocky Mountain spotted fever indirect fluorescent antibody test (state health departments)
ANA
HIV-I/HIV-2 antibody
HTLV-1
Serum and CSF VDRL
Other
PPD
Quantiferon Gold
Chest x-ray film
Computed tomography, magnetic resonance imaging
Echocardiogram

Abbreviations: LCM = lymphocytic choriomeningitis virus; HIV = human immunodeficiency virus; HSV = herpes simplex virus; IVDU = intravenous drug use; OKT-3 = orthoclone; NSAIDs = nonsteroidal anti-inflammatory drugs; TB = tuberculosis; WNV = West Nile virus; AFB = acid-fast bacilli; PCR = polymerase chain reaction; VZV = varicella-zoster virus; CMV = cytomegalovirus; EBV = Epstein–Barr virus; CSF = cerebrospinal fluid; ELISA = enzyme-linked immunosorbent assay; ANA = antinuclear antibody; HTLV-1 = human T-lymphotropic virus type 1; VDRL = Venereal Drug Research Laboratory.

common with advanced immunosuppression. Exposure to excretions of rodents can cause exposure to the LCM, a human zoonosis caused by a rodent-borne arenavirus. The infection, more common during the winter, presents often as an influenza-like syndrome.

Nonviral causes of meningitis often have a more complicated course than viral meningitis and must be recognized because they may have specific therapy. Agents such as bacteria, mycobacteria, and fungi enter the body through the respiratory tract, including the pharynx, sinuses, skin, or lung, and travel to the CNS via the bloodstream. Pneumonitis may be followed by fungemia or bacteremia. Coccidioides meningitis has to be considered in patients with indolent symptoms such as persistent fever and headache who live or traveled from the Southwestern United States and Central or South America. Meningitis is frequently not recognized in this population and may be lethal. *Treponema pallidum* and *Borrelia burgdorferi* enter the CNS after bloodstream invasion.

West Nile virus (WNV) is a bird virus and is spread within the avian reservoir by mosquitoes. The main vectors, *Culex pipiens*, *C. restuans*, and *C. tarsalis*, are abundant and ubiquitous in water in puddles and containers, sewers, storm drains, and catch basins.

It usually causes mild flu-like symptoms 3 to 14 days after infection.

However, 1 in 150 cases will develop serious manifestations, mainly meningoencephalitis, meningitis, or encephalitis. CSF invariably shows a pleocytosis, with a predominance of neutrophils in up to half the patients. Laboratory diagnosis involves testing serum or CSF for viral-specific neutralizing antibodies. Several WNV IgM ELISA kits are available in the USA.

Because the ELISA can cross-react between flaviviruses (e.g., systemic lupus erythematosus, dengue, yellow fever, WNV), it should be viewed as a screening test only. Initial serologically positive samples should be confirmed by neutralization test.

DIAGNOSTIC WORKUP

In establishing a diagnosis, clues in the history, physical examination, and CSF examination (Table 75.2) are important.

History

Many viral infections are seasonal, occurring during late summer and early fall. Examples are the enteroviruses, whereas mumps and LCM peak during winter and spring. Other viruses such as HSV-2 and HIV occur in any season. WNV and equine-associated meningoencephalitis outbreaks occur from late summer to early fall. Avian (for WNV) or equine sources (for equine encephalopathy) with spread via mosquitoes is the presumed route of infection to humans. Furthermore, a history of exposure to patients with known viral illness often suggests enteroviral infection. Similar presentation in association with genital lesions should suggest HSV-2 meningitis, although genital lesions are absent in about 15% of the cases.

Exposure to mice and rodents suggests LCM, less commonly *Leptospira* species, or hantavirus, which may cause a severe pulmonary syndrome. History of sexual contacts should be elicited because HSV, syphilis, and HIV may present with aseptic meningitis. All patients, including the elderly, should be questioned about risk factors for HIV infection, including sexual promiscuity, intravenous drug use, sexual preference, and history of transfusions with blood or blood products. Human T-cell lymphotropic virus (HTLV)-I infection may also present with the diagnosis of spastic paraparesis.

Syphilitic meningitis is an important cause of aseptic meningitis in the AIDS era. Syphilitic meningitis may coexist with the primary or secondary infection or may follow it by as much as 2 years.

Geographic location, both domicile and travel history, should be evaluated. Exposure to insects such as the tsetse fly in Africa could suggest trypanosomiasis, and mosquito bites in a traveler to India or Mauritius associated with fever and rash may suggest chikungunya (CHK). *Histoplasma capsulatum*, *Coccidioides immitis*, and *B. burgdorferi* occur mainly in certain sections of the United States. Recent contact with a pet or camping suggests *Rickettsia*, *Anaplasma*, or *Borrelia* related to a tick bite. Mosquito bites may result in WNV infection or equine meningoencephalitis virus infection. Rabies, although rare, should be considered if the patient had contact with the secretions of an infected skunk, raccoon, dog, fox, or bat. Drinking untreated water on backpacking trips may result in *Leptospira* infection, ingestion of unpasteurized milk and cheeses may cause brucellosis, and contaminated processed meats (i.e., frankfurters) may cause *Listeria monocytogenes* infection in pregnant women, elderly, and immunocompromised hosts.

Meningitis due to fungi is a consideration primarily in patients affected by HIV and in those who have organ transplantation, immunosuppressive chemotherapy, or chronic corticosteroid therapy. However, the most common pathogen, *Cryptococcus neoformans*, can occur in immunocompetent hosts.

Vasculitides found in patients of Mediterranean origin include Behçet's disease and familial Mediterranean fever. Certain drugs, including intravenous immunoglobulin, trimethoprim–sulfamethoxazole, NSAIDs, and immunosuppressants, have been associated with aseptic meningitis syndrome. Intracranial infections often present with headache and fever. Brain, epidural, or subdural abscesses may be present in patients with a history of upper respiratory tract infection (i.e., otitis media, sinusitis) or infection of the teeth or gums. Computed tomography (CT) scan or magnetic resonance imaging (MRI) may aid in this diagnosis. Aseptic meningitis syndrome has been associated with subacute bacterial endocarditis; physical stigmata, including conjunctival petechiae, cardiac murmurs, retinal lesions, and evidence of embolic phenomenon, may be found. Infection with either mycobacteria or fungi or a history of malignancy must be considered.

It is important to investigate recent antibiotic use. Partially treated bacterial meningitis should be suspected if the patient has received prior oral antimicrobial therapy and has persistently low CSF glucose or pleocytosis, with a negative Gram stain. Recurrent bouts of meningitis with a benign clinical picture and unknown etiology suggest Mollaret's meningitis.

Physical examination

A physical examination may elicit findings that may suggest a specific agent. Generally the patient is febrile and nontoxic, pulse and respiration normal, with or without evidence of meningismus. Examination of the skin may reveal a morbilliform or vesicular rash consistent with enteroviral infection, primary HIV or syphilis, or evidence of a tick bite. However, a rash can be observed also in some cases of meningococcemia. The scalp should be examined carefully, especially the area behind the ears. Petechiae on the hands and feet usually suggest rickettsial infection. Examination of the eyes for conjunctival petechiae and fundoscopic examination may

reveal lesions typical of infectious endocarditis. Other lesions usually found by fundoscopic examination are associated with cytomegalovirus (CMV) or *Toxoplasma*, especially if there is suspicion of HIV. The oral cavity may show thrush with or without cervical adenopathy. Presence of parotid or testicular swelling enlargement is consistent with mumps meningitis. The chest examination is usually normal, but a murmur in this setting suggests endocarditis; a pericardial rub suggests Coxsackievirus infection or a collagen vascular syndrome. Hepatomegaly, splenomegaly, or adenopathy may suggest a systemic disease, including disseminated viral or fungal infection. Genital ulcerative lesions may be present in vascular syndromes such as lupus erythematosus and may also be consistent with HSV-2 infection. Examination of the neck may reveal evidence of stiffness on flexion and a positive Brudzinski and/or Kernig sign. Focal or multiple cranial nerve involvement suggests lesions such as a brain, subdural, or epidural abscess; embolic phenomena may also produce these lesions. Asymmetric flaccid paralysis suggests WNV infection, as well as a macular papular rash which can occur in up to 50% of patients with WNV infection and meningitis. Physical examination may also reveal a typical malar rash or other signs of collagen vascular disease.

Laboratory data

The CSF should be examined and opening pressure recorded; in aseptic meningitis the CSF is clear with a normal or mildly increased opening pressure. The white blood cell (WBC) count is usually less than 500/mL but it can reach 1000/mL with a predominance of lymphocytes. However, CSF differential cell counts may reveal a predominance of polymorphonuclear leukocytes mostly with Echovirus, poliovirus, mumps, HSV, *Mycobacterium tuberculosis*, and Mollaret's meningitis. A shift toward a lymphocyte predominance during the first week of the disease occurs. Pleocytosis has been reported in 25% of patients with enteroviral infection. Eosinophils in the CSF suggest parasitic disease secondary to *Angiostrongylus*, *Taenia* spp., or *Schistosoma*. *Japonicum* or *Paragonimus westemani* meningeal carcinomatosis is suggested when abnormal cells are seen, and large granular cells with indistinct cytoplasm suggest Mollaret's meningitis. Fat droplets have been seen following epidermoid cyst rupture. Spinal fluid glucose should be compared with simultaneously drawn blood glucose. Normal levels of CSF glucose (40 mg/dL or >50% to 66% of the blood levels) suggest viral meningitis. However, the glucose content may be lower than normal in 18% to 33% of cases, and viruses such as herpes, mumps, LCM, and polio can cause hypoglycorrhachia (Table 75.3). A study of CSF from 334 cases of WNV infection showed that it usually presents with CSF pleocytosis, increased protein, and normal glucose. The protein levels in aseptic meningitis are usually normal or slightly elevated; levels greater than 800 mg suggest CSF block with infection or tumor, although this has also been associated with chemical meningitis. A wet prep of CSF should be examined to look

Table 75.3 Differential diagnosis of cerebrospinal fluid (CSF) glucose concentrations

Normal CSF glucose concentration	Decreased CSF glucose concentration
Enteroviruses	Partially treated bacterial meningitis
Mumps virus	*Listeria monocytogenes*
Arthropod-borne viruses	
Herpes simplex virus-1 and -2	*Mycobacterium tuberculosis*
Human immunodeficiency virus	*Candida*
Influenza virus types A and B	*Cryptococcus neoformans*
Measles, subacute sclerosing panencephalitis	*Coccidioides immitis*
Varicella-zoster virus	*Histoplasma capsulatum*
Cytomegalovirus	*Blastomyces dermatitidis*
Treponema pallidum	Herpes simplex virus-1
Borrelia burgdorferi	Mumps virus
Leptospirosis	Lymphocytic choriomeningitis virus
Rickettsia rickettsii	Poliovirus
Human monocytic ehrlichiosis	
Anaplasma phagocytophilum	Sarcoidosis
Behçet's disease	Leptomeningeal carcinomatosis
Migraine	
Vasculitis	
Postinfectious encephalomyelitis	
Nonsteroidal anti-inflammatory agents	
Orthoclone	
Azathioprine	
Trimethoprim–sulfamethoxazole	
Isoniazid	
Intravenous immunoglobulin	

for *Toxoplasma gondii* or amebae (e.g., histolytica). Gram stain and bacterial culture should be performed because a partially treated bacterial infection or infection with *Listeria monocytogenes* may occasionally present with a predominance of lymphocytes. Acid-fast smears, culture, and polymerase chain reaction (PCR) (non-US Food and Drug Administration [FDA]-approved) should be done to rule out mycobacterial infections, and India ink stain or determination of cryptococcal antigen in the CSF should be performed.

The CSF should also be sent for routine fungal and mycobacterial cultures. With the increasing use of the nucleic acid detection tests, viral cultures from CSF are not useful and should not be performed routinely. Viral cultures are laborious and time-consuming, and they need to be performed in four different cell lines that are then evaluated daily for cytopathic effect. The findings are then confirmed by a neutralizing or an immunofluorescence antibody test. The overall sensitivity of virus isolation from the CSF of patients with aseptic meningitis is between 3% and 40%. In a recent review of more than 20 000 CSF viral cultures, $\leq$0.1% recovered species were nonenteroviruses and non-Herpes, suggesting that when nucleic acid amplification testing is performed, viral cultures have no additional benefit. If indicated, simultaneous viral cultures are obtained from throat washings and stool specimens.

CSF should be sent for PCR, which is available for the detection of a range of pathogens, particularly viruses. This technique is highly sensitive and specific, with results available within 24 hours, requiring only small volumes of CSF. PCR is the best assay for the detection of HSV-1, HSV-2, varicella-zoster virus (VZV), human herpesvirus 6 and 7, CMV, Epstein–Barr virus (EBV), enteroviruses, respiratory viruses, and HIV in CSF samples. CSF IgM antibody tests for WNV are positive usually by the seventh to eighth day of infection. PCR for *Chlamydia pneumoniae* can also be performed from a CSF sample. Respiratory viruses, *C. pneumoniae*, and *Mycoplasma pneumoniae* can also be detected from throat samples and enterovirus nucleic acid from stool samples; however, these cannot confirm the etiology of the meningitis. The use of PCR for the diagnosis of infectious origins of aseptic meningitis has resulted in increased identification of the enterovirus, which allows the discontinuation of antimicrobial therapy, decreases hospital length of stay and costs, and enables patients to return to their usual environments.

The use of multiplex PCR facilitates assay of multiple viruses on the same sample. The sensitivity and specificities of this technique are similar to those of the single PCR. Examination of the peripheral blood reveals a WBC count that is usually normal or may be less than 5000/mm^3. The differential is also normal, although occasionally a left shift of polymorphonuclear leukocytes has been observed. Eosinophilia has been described in parasitic infections and in drug and serum sickness reactions. Leukopenia associated with thrombocytopenia may suggest *Anaplasma* and *Rickettsia* infection, and nonspecific changes in hepatic enzymes may be found in viral infections. Sedimentation rate may be normal or elevated. Blood cultures should always be performed, because *L. monocytogenes*, *Brucella*, and rarely some typical pathogens, such as *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*, may present with a predominance of lymphocytes in the CSF. Infectious endocarditis from either bacteria or fungi can be considered in the appropriate clinical setting when a patient has positive blood cultures.

If fungal disease is suspected, serologic studies should be performed for cryptococcal antigen and *C. immitis*. *Histoplasma capsulatum* urinary antigen should be tested. PCR for *M. pneumoniae* is also warranted. Venereal Disease Research Laboratory (VDRL) test should be performed on CSF. PCR tests have been developed using a variety of syphilitic antigens. They are quite specific but do not distinguish live from dead organisms. When rickettsial diseases are suspected (i.e., Rocky Mountain spotted fever or Lyme disease), appropriate serologic tests should be performed, but therapy should not be delayed while tests are pending. If rabies is suspected, an immunofluorescence test on conjunctival scrapings or subcutaneous neck fascial biopsy is the best method for establishing the diagnosis. Other serologic tests include antinuclear antibody (ANA) to rule out systemic lupus erythematosus. Given the appropriate clinical setting, HIV testing may be warranted. The virus in CSF may be detected through PCR. Low CSF lactate levels may distinguish aseptic meningitis from bacterial meningitis, though pretreatment with antibiotics may reduce the clinical accuracy.

If vesicular lesions are present, immunofluorescent staining for HSV-1, HSV-2, and VZV and viral culture from the lesion should be performed. If lesions other than vesicular lesions are found, careful examination by dark field may reveal evidence of *T. pallidum*. Petechial lesions should be

stained and cultured for bacteria and stained with immunofluorescence antibody for *Rickettsia rickettsii*. Throat and stool cultures should be obtained for confirmation of enteroviral infection.

A chest roentgenogram specifically looking for diffuse infiltrates, cavitation, and pleural or pericardial involvement may suggest mycoplasma, mycobacterial, or fungal infection in that order. Evidence of a mass lesion in this setting suggests carcinoma and possibly meningeal carcinomatosis. With physical findings of focal involvement, an MRI scan should be performed to look for evidence of an intracranial infection or malignancy.

THERAPY

The diagnosis and treatment of the aseptic meningitis syndrome is a challenge, because differentiating between infectious and noninfectious etiologies can be difficult. For patients with a suspected bacterial etiology or partially treated meningitis, antibiotic therapy should be promptly initiated. In case of aseptic meningitis in an elderly or immunocompromised patient or in case of an unclear picture, antibiotic therapy should be empirically initiated and discontinued if the patient improves symptomatically and cultures are negative. If the patient deteriorates without a clear diagnosis, a repeat lumber puncture may be indicated. Although the management of patients with aseptic meningitis of viral origin includes supportive care in most cases, specific therapy exists for some viral pathogens. Acyclovir may be used to treat meningitis caused by HSV and VZV, and ganciclovir is used for CMV infection. Acyclovir, 10 mg/kg every 8 hours, is used for HSV and VZV; ganciclovir, 5 mg/kg twice a day, is the regimen for CMV. The newer oral antiviral compounds valacyclovir and famciclovir have a 5-fold higher bioavailability than acyclovir, allowing less frequent dosing.

No antiviral therapeutic agent for enteroviruses has demonstrated improved outcome in controlled clinical trials. The administration of gamma globulin helps patients with agammaglobulinemia and chronic enteroviral meningitis as well as neonates with enteroviral sepsis and meningitis. Pleconaril is an orally administered antiviral agent that inhibits enteroviral replication by binding the viral capsid. This drug may reach much higher concentrations within the CNS, suggesting its potential use to treat CNS infection. However, pleconaril induces CYP3A enzyme activity and has not been FDA approved because of its potential for drug interactions. Two large studies of aseptic meningitis due to enterovirus revealed that pleconaril shortened the course of illness compared with placebo, especially when administered early during the course of the disease. However, subgroup analysis showed only a modest benefit in patients with more severe disease. There is no specific treatment for WNV infection. At the moment, only supportive care is available in humans, although intravenous immunoglobulin (IVIG) and WNV-specific IVIG have been studied in mice and interferon and ribavirin have been studied in vitro.

Most viral meningitides are benign and require no therapy. For bacterial, fungal, and spirochetal disease, antimicrobial therapy directed against the offending agent is required (see specific chapters) and should not be delayed while awaiting the results of CSF assay. Treatment with doxycycline in association with two other agents may be indicated for patients suspected of having *Brucella*, and doxycycline or chloramphenicol is used for Rocky Mountain spotted fever. Specific therapy with ampicillin plus gentamicin is suggested when *L. monocytogenes* is the suspected agent, especially in elderly and immunocompromised hosts.

Because the differential diagnosis of aseptic meningitis syndrome is so broad, the initial evaluation of the patient in conjunction with the results of CSF studies will determine whether the patient requires antimicrobial therapy pending culture results from blood and CSF PCR. Patients who are toxic appearing, in the extremes of life, or with serious underlying disease should be hospitalized and treated empirically until a clear diagnosis is made. Isolation precautions for contagious diseases should be instituted.

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76. Acute viral encephalitis

David N. Irani

INTRODUCTION

Viral infections of the central nervous system (CNS) are uncommon but potentially devastating clinical events. As a group, these infections range from benign, self-limited forms of meningitis to full-blown and often fatal cases of acute encephalitis to chronic, persistent diseases. *Encephalitis* literally refers to inflammation of the brain parenchyma, and such a host response is common with many viral infections that spread to this site (Figure 76.1). In contrast, *meningitis* results when infection and the associated inflammatory response are limited to the leptomeninges and the subarachnoid space. In reality, the two syndromes often occur together – hence the term *meningoencephalitis*. A diagnosis of acute viral encephalitis or acute viral meningoencephalitis is suggested by various signs and symptoms indicative of brain parenchymal invasion (mental status and behavioral changes, seizures, and focal neurologic deficits) accompanied by fever. Such patients require emergent evaluation for what can be a life-threatening infectious illness that sometimes has a treatable cause.

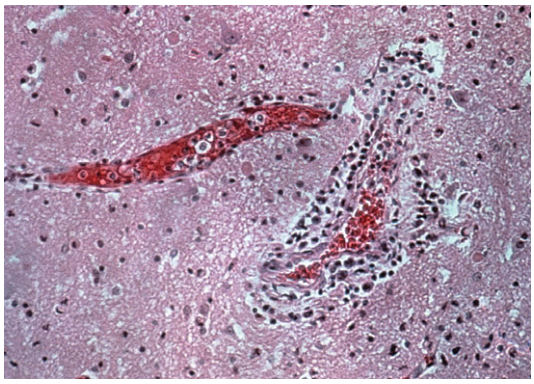

Figure 76.1 Mononuclear inflammatory cells accumulate around blood vessel in a fatal case of Japanese encephalitis. These perivascular "cuffs" are a characteristic histopathologic finding in the central nervous system (CNS) during acute viral encephalitis. Hematoxylin & eosin, 100×. (Courtesy of Richard T. Johnson, MD, Department of Neurology, The Johns Hopkins University School of Medicine.)

ETIOLOGY

More than 100 different viruses can infect the human CNS, but a much smaller number cause the vast majority of viral encephalitis cases. The most relevant pathogens come from the following viral families: Herpesviridae, Picornaviridae, Retroviridae, Paramyxoviridae, and arthropod-borne RNA viruses including the Togaviridae, Flaviviridae, Bunyaviridae, and Reoviridae families (Table 76.1). The acquired immunodeficiency syndrome (AIDS) epidemic, the therapeutic use of immunosuppression in transplant recipients or patients with autoimmune disease, and the immune defects that occur in oncology patients as a by-product of chemotherapy have all resulted in the identification of new infectious disease processes that can cause signs and symptoms consistent with acute encephalitis. Many immunocompromised hosts now require discrimination between an ever-expanding list of potential infectious and noninfectious causes of an acute encephalitis-like clinical picture (Table 76.2).

EPIDEMIOLOGY

The viruses that cause acute encephalitis vary widely in their epidemiology. In many cases, the identification of a particular causative agent can be aided by clues derived from the surrounding environment (geography, season) as well as from a careful review of the patient's background (sexual behavior, intravenous drug use, travel, occupation, arthropod or animal contacts, vaccine history, and exposure to ill persons). One important point is that many viruses causing acute encephalitis are transmitted to humans via infected mosquitos or ticks and thus produce

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Table 76.1 Significant causes of acute viral encephalitis in humans

Herpesviridae	*Reoviridae*
Herpes simplex virus	Colorado tick fever virus
Varicella-zoster virus	*Picornaviridae*
Cytomegalovirus	Echovirus
Epstein–Barr virus	Coxsackievirus
Human herpesvirus 6	Poliovirus
B virus	Enterovirus 71
Bunyaviridae	*Retroviridae*
California serogroup viruses	Human immunodeficiency virus,
La Crosse virus	type 1
Jamestown Canyon virus	*Papovaviridae*
Snowshoe hare virus	JC virus
Togaviridae (alphaviruses)	*Orthomyxoviridae*
Eastern equine encephalitis virus	Influenza virus
Western equine	*Paramyxoviridae*
encephalitis virus	Measles virus
Venezuelan equine	Mumps virus
encephalitis virus	Nipah virus
Flaviviridae	Hendra virus
Japanese encephalitis virus	*Miscellaneous viruses*
St. Louis encephalitis virus	Adenovirus
West Nile virus	Lymphocytic
Tick-borne encephalitis virus	choriomeningitis virus
Dengue fever encephalitis virus	Rabies virus

Table 76.2 Nonviral causes of an acute encephalitis-like clinical presentation

Infectious	Noninfectious
Bacterial	**Parainfectious/autoimmune**
Acute bacterial meningitis	Reye's syndrome
Brain abscess	Postinfectious
Parameningeal infection	encephalomyelitis
Subdural empyema	Postvaccination
Venous sinus thrombophlebitis	encephalomyelitis
CNS Lyme disease	**Neoplastic**
Neurosyphilis	Primary or metastatic
Whipple's disease	brain tumor
Bacterial toxin-mediated process	Paraneoplastic disorder
Fungal	Neoplastic meningitis
Fungal meningitis	**Cerebrovascular**
Fungal brain abscess	Acute ischemic stroke
Parasitic	Subdural hematoma
Toxoplasma gondii abscess	CNS vasculitis
Cerebral malaria	**Systemic**
Human African trypanosomiasis	Metabolic encephalopathy
Amebic	Connective tissue disease
Naegleria fowleri	Drug intoxication
meningoencephalitis	**Epileptic**
Acanthamoeba	Seizures/postictal state
meningoencephalitis	**Traumatic**
	Acute head injury

disease in the summer or early fall months when the vectors are prevalent. The more common viral encephalitides have notable epidemiologic features associated with them (Table 76.3).

PATHOGENESIS

Most viruses gain entry into the CNS either through hematogenous or intraneural spread. Bunyaviridae, Flaviviridae, and Togaviridae seed the CNS from the bloodstream after subcutaneous inoculation by the insect vector and replication in local tissues. Other neurotropic viruses enter the host via the respiratory tract (e.g., adenovirus, measles, influenza) or the gastrointestinal tract (e.g., enteroviruses). Rabies virus reaches the CNS via intra-axonal transport in sensory nerves that innervate the skin. The pathogenesis of herpes simplex virus (HSV) encephalitis remains incompletely understood, but virus passage along the olfactory and trigeminal nerve tracts from ganglia where it can reactivate from latency likely explains the classic temporal lobe localization. Host factors play a role in both the susceptibility to and the severity of viral encephalitis. Chronic enteroviral meningoencephalitis occurs mostly in patients with agammaglobulinemia, whereas acute measles, cytomegalovirus (CMV), and varicella-zoster virus (VZV) encephalitis usually occurs in patients with impaired cellular immunity.

Once inside the CNS, encephalitic viruses cause pathology either due to a direct cytopathic effect or as a result of immune-mediated injury. The tropism of these pathogens for various parenchymal cell populations varies during acute encephalitis, but those directly infecting neurons often cause particularly severe disease (Figure 76.2). The ensuing histopathologic changes reflecting the host response include the perivascular infiltration of mononuclear inflammatory cells (Figure 76.1), a reactive astrocytosis, the formation of glial nodules, and neuronophagia. Cytotoxic T cells and phagocytic macrophages may actually be the effectors of much of the resulting neural injury. It is also likely that soluble immune factors (cytokines, chemokines, nitric oxide, etc.) contribute to disease pathogenesis in complex ways, both to the benefit and the detriment of the infected host. While factors such as the interferons (α, β, and γ) and their regulatory transacting proteins may act to limit CNS virus replication, others such as interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α may have injurious properties in humans and clearly make viral encephalitis worse in animal models of these diseases.

Table 76.3 Clinical and epidemiologic characteristics of major causes of viral encephalitis in the United States

Family/virus	Affected hosts	Peak season/ pattern	Geography/ incidence	Clinical presentation	Epidemiologic clues
Herpesviridae					
HSV	All ages	Year-round; endemic	Ubiquitous (~2500 cases/yr)	Focal neurologic deficits; seizures; bizarre behavior	
VZV	Healthy and immunocompromised adults; infants	Year-round; endemic	Ubiquitous	Ataxia; stroke-like episodes; can have an accompanying myelitis	Recent primary varicella rash or herpes zoster dermatomal rash
CMV	Immunocompromised adults; infants	Year-round; endemic	Ubiquitous	Periventricular lesions on brain MRI; accompanying lumbosacral polyradiculitis	Known HIV+ individuals; post-transplant recipients (especially bone marrow recipients)
Retroviridae					
HIV	All ages	Year-round; endemic	Ubiquitous (3000–4000 cases/y)	Subacute cognitive deficits; psychomotor slowing	High-risk sexual practices; intravenous drug use
Papovaviridae					
JC virus	Immunocompromised adults	Year-round; endemic	Ubiquitous (400–800 cases/y)	Focal neurologic deficits; multifocal MRI lesions	HIV+ individuals; post-transplantion or immunotherapy
Togaviridae					
Eastern equine encephalitis virus	Young and elderly	Summer and fall; endemic/sporadic	East and Gulf Coasts (5–10 cases/y)	Fulminant deficits; seizures; coma	Outdoor occupation or activities; proximity to marshes or standing water
Western equine encephalitis virus	Young and elderly	Summer and fall; endemic/sporadic	Midwest and Western States (10–15 cases/y)	Nonfocal deficits; headache	Outdoor occupation or activities; travel or habitation in rural areas
Flaviviridae					
West Nile virus	All ages (but most cases in the young and the elderly)	Summer and fall; epidemic	Nationwide (2000–4000 cases/y over the last few years)	Nonfocal deficits; headache; ~20% with a poliomyelitis-like illness	Outdoor exposure (urban or rural); most cases are concentrated in a few states each season
St. Louis encephalitis virus	Young and elderly	Summer and fall; epidemic	Nationwide (~100 cases/y; range 2–1967 cases/y)	Nonfocal deficits; headache	Outdoor exposure; endemic in rural areas in the West; sporadic urban outbreaks in the Eastern States
Bunyaviridae					
La Crosse virus	Young	Summer and fall; endemic and small case clusters	Midwest and Eastern States (75–100 cases/y)	Often asymptomatic; can cause seizures	Outdoor activities; suburban cases occur near wooded areas
Picornaviridae					
Echoviruses Coxsackieviruses Polioviruses Unclassified viruses (EV-68–EV-71)	Young, especially agammaglobulinemic children	Summer and fall; epidemic	Nationwide (~1000 cases/y)	Accompanying viral exanthem, conjunctivitis, myopericarditis, herpangina, hand-foot-and-mouth disease	Known community epidemic of picornavirus
Rhabdoviridae					
Rabies	All ages	Year-round; endemic	Nationwide (10–15 cases/y)	Prior animal bite or scratch; autonomic symptoms in ~80%; paralysis in ~20%	Animal contact

Abbreviations: HIV = human immunodeficiency virus; CMV = cytomegalovirus; MRI = magnetic resonance imaging; HSV = herpes simplex virus; VZV = varicella-zoster virus.

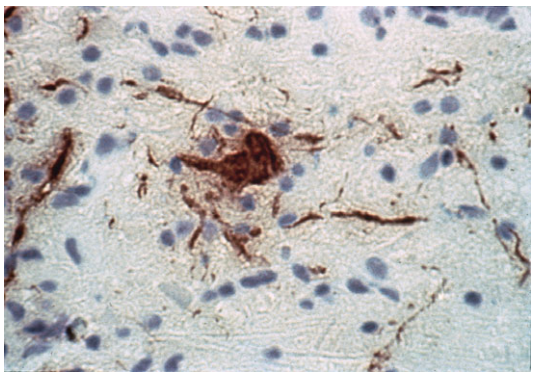

Figure 76.2 Immunohistochemical identification of viral antigens within neurons in a fatal case of Japanese encephalitis. Viruses tropic for neurons often cause severe forms of acute encephalitis. Immunoperoxidase with hematoxylin counterstain, 125×. (Courtesy of Richard T. Johnson, MD, Department of Neurology, The Johns Hopkins University School of Medicine.)

In postinfectious encephalitis, disease occurs via immune-mediated mechanisms rather than through direct cytopathic effects and manifests as multifocal perivascular demyelination. Although poorly understood, it is assumed that the elicited antiviral immune response somehow triggers pathogenic antimyelin autoimmunity through a process such as molecular mimicry. Viruses implicated in this type of encephalitis include measles, mumps, rubella, VZV, and Epstein–Barr virus (EBV). This form of encephalitis usually manifests itself within weeks of the triggering infection.

CLINICAL MANIFESTATIONS

Although the severity of deficits can range from very mild to extreme, most patients with acute viral encephalitis develop a progressive constellation of complaints that evolves over a period of several days and prompts them to seek medical attention. Manifestations typically include fever, symptoms of meningeal inflammation (headache, neck stiffness, nausea, and vomiting), and signs indicative of brain parenchymal involvement (seizures, behavioral changes, weakness, and an altered sensorium often progressing to coma over time). None of these signs or symptoms are pathognomonic of a particular virus, although an occasional extraneural feature may point to a specific pathogen when present. These might include parotitis with mumps infection, pharyngitis and lymphadenopathy with EBV, and a dermatomal rash with VZV. Nonspecific neuroendocrine complications of viral encephalitis may include inappropriate antidiuretic hormone secretion and diabetes insipidus.

More importantly, certain viral pathogens exhibit strong predilections to infect particular regions of the CNS, resulting in characteristic focal neurologic deficits. Although CMV typically involves periventricular areas, rabies the limbic system, VZV the cerebellum, and Japanese encephalitis virus (JEV) the basal ganglia, the prototypic example of such a focal infection is HSV infection of the temporal and inferior frontal lobes of the brain. Accordingly, patients with herpes simplex encephalitis (HSE) commonly present with a hemiparesis, visual field cut, aphasia (if the dominant temporal lobe is involved), and complex-partial or generalized seizures. Because the mortality of untreated HSE exceeds 70%, and because morbidity and mortality can be significantly reduced with the prompt initiation of antiviral therapy, it is imperative that all patients with a fever and such focal neurologic deficits be promptly evaluated for this infection and started on empiric antiviral therapy until the results of specific diagnostic tests are available. Recent experimental data show that different neuronal subpopulations differ in their susceptibility to encephalitic viruses based on differential innate immune responses.

DIAGNOSIS

Routine laboratory studies (serum chemistries, peripheral cell counts, etc.) have limited value in the diagnosis of acute viral encephalitis. Acute and convalescent serum samples can be sent for the measurement of specific antibodies against a number of viral pathogens to identify an etiologic agent (discussed below). In the acute stages of the illness, however, the main diagnostic tools are neuroimaging studies to confirm structural involvement of the CNS and a lumbar puncture (LP) to identify suspicious inflammatory changes in the cerebrospinal fluid (CSF) and to seek molecular evidence of a particular viral pathogen within the intrathecal space.

Electroencephalography and brain imaging studies

The electroencephalogram (EEG) may occasionally aid in the diagnosis of an acute focal encephalitis such as HSE. Periodic lateralized epileptiform discharges in the temporal lobe can be identified

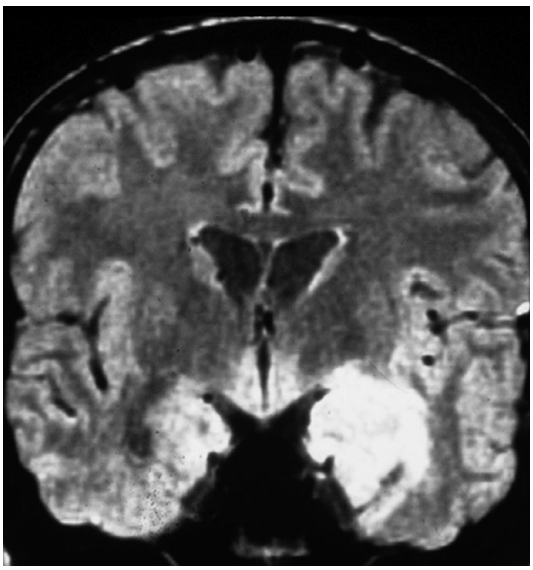

Figure 76.3 Coronal fluid-attenuated inversion-recovery magnetic resonance imaging (MRI) from a patient with polymerase chain reaction (PCR)-proven herpes simplex encephalitis (HSE). Hyperintense signal is seen in the medial portion of both temporal lobes as well as in the inferior frontal lobes in a distribution that is highly characteristic of this disease.

within the first days after symptom onset. Although of low specificity, encephalitis-induced EEG abnormalities can precede cranial computed tomography (CT) changes that may not be seen until several days later. Electroencephalographic evidence of seizures during the course of infection mandates the use of antiepileptic therapies. Furthermore, although diffuse slowing of background EEG activity or epileptiform features are common in the acute stages of viral encephalitis, the emergence of slow background activity at follow-up is often associated with a less favorable clinical outcome.

Brain imaging is essential in the evaluation of suspected viral encephalitis, and a contrast-enhanced cranial magnetic resonance imaging (MRI) scan is now the diagnostic procedure of choice. Conventional fluid-attenuated inversion-recovery (FLAIR) MRI sequences allow for the early radiographic detection of disease in the medial temporal lobes indicative of HSE (Figure 76.3). Likewise, thalamic lesions that are hyperintense on T2-weighted images are characteristic of Japanese encephalitis, and focal abnormalities in the basal ganglia have been associated with eastern equine encephalitis virus (EEEV)-induced disease. Recent comparative studies now demonstrate that diffusion-weighted MRI may be superior to more conventional sequences for the early detection of brain abnormalities in both HSE and West Nile virus (WNV) encephalitis. Thus, it seems likely that newer, more sensitive imaging modalities will continue to augment our ability to diagnose encephalitis patients, even though the main tools will always be the specific identification of viral pathogens using other molecular techniques.

In cases where MRI findings are equivocal, alternative brain imaging modalities such as single-photon emission computed tomography (SPECT) examination may sometimes be useful to identify areas of hyperperfusion. In one small study of patients with acute viral encephalitis, unilateral hyperperfusion as measured by SPECT was an independent predictor of poor outcome. Still, the optimal application of this technique requires further investigation.

Cerebrospinal fluid analysis

Examination of the CSF is mandatory in all suspected cases of acute viral encephalitis. Routine CSF studies in these diseases will generally show a mononuclear cell pleocytosis of not more than 1000 cells/mm^3, with cell counts usually ranging from 30 to 200 cells/mm^3. Up to a third of patients with HSE and WNV encephalitis will have more than 50% neutrophils at the time of their initial LP. Although the total protein content may be normal in the first week of disease, levels are usually elevated thereafter, and 15% to 20% of encephalitis patients have CSF protein concentrations of greater than 100 mg/dL. Hypoglycorrhachia is relatively uncommon in viral encephalitis, but CSF glucose levels can sometimes be low with infections caused by lymphocytic choriomeningitis virus. Viral cultures of CSF are invariably negative in cases of encephalitis, but new molecular diagnostic modalities have been successfully used to identify specific pathogens. It cannot be overemphasized, however, that even in advance of a positive molecular assay for HSV, all patients with a fever, focal neurologic deficits, and a CSF pleocytosis should be treated for presumptive HSE until an alternative diagnosis is confirmed.

Pathogen-specific assays

Serologic assays are available for most neurotropic viruses, including the Herpesviridae, Bunyaviridae, Togaviridae, Flaviviridae, Picornaviridae, Papovaviridae, and Rhabdoviridae, and many of

these tests can be applied to both serum and CSF samples. Unfortunately, viral-specific antibodies can be difficult to detect early in disease, and the process of comparing acute to convalescent serum titers is of limited utility when the initial therapeutic decisions are made.

Polymerase chain reaction (PCR)-based amplification techniques have recently been used to detect the nucleic acids of a number of neurotropic viruses in the CSF of patients with viral encephalitis. In particular, PCR assays can now routinely detect most Herpesviridae and Picornaviridae, as well as JC virus and certain Togaviridae and Flaviviridae. In HSE, the sensitivity and specificity of PCR for the detection of HSV-specific DNA sequences is 95% and 98%, respectively, compared to the previous gold standard of direct brain biopsy. Positive results have been reported as early as a day after onset of symptoms and may persist for as long as 1 week after the initiation of antiviral therapy. Occasionally, HSV PCR can be negative early in disease, and serial testing of CSF samples is advised if the clinical suspicion remains high despite an initial negative assay. Beyond just the detection of viral nucleic acids in clinical samples, PCR is now being used to measure viral loads, to monitor the duration and adequacy of antiviral therapy, to identify determinants of drug resistance, and even to explore the etiology of brain diseases of uncertain causes. Future applications of nucleic acid detection methods for clinical samples such as CSF are likely to incorporate rapid methods that can screen a sample for many pathogen-specific sequences in a single reaction.

Brain biopsy

The utility of diagnostic brain biopsy in the management of suspected encephalitis remains controversial. Proponents advocate that direct tissue analysis may sometimes confirm an alternative treatable disorder in a proportion of PCR-negative cases, whereas those not in favor of its use argue that the yield of the procedure is unacceptably low. However, when a diagnosis remains elusive in a patient with a deteriorating clinical course, brain biopsy continues to play an important role.

THERAPY

General supportive care

Because effective antiviral treatments are not yet available for many neurotropic viruses, attention must be focused on preventing and treating the many complications that can arise in a critically ill patient. Neurologically, seizures and elevated intracranial pressure may necessitate the use of anticonvulsants as well as interventions such as hyperventilation and osmotic agents. Systemically, the possibility of pneumonia, deep vein thrombosis, pulmonary embolism, gastrointestinal stress ulcers, decubitus ulcers, musculoskeletal contractures, and malnutrition all must be sought with rigor to limit disease morbidity and mortality.

Antiviral therapy

There are few effective antiviral regimens for the treatment of patients with acute viral encephalitis. Nevertheless, several drugs have demonstrated activity against members of the herpesvirus family (Table 76.4).

HERPESVIRIDAE

Acyclovir remains the mainstay of treatment for the acute encephalitis caused by HSV. A previously used agent, vidarabine, has much more limited clinical benefit. In adults with HSE, treatment with 10 mg/kg of acyclovir intravenously every 8 hours for 21 days reduces overall mortality from over 70% to below 20%, and importantly, nearly 40% of treated patients recover to the point of returning to normal function. In contrast, clinical trials comparing acyclovir with vidarabine in neonatal HSV encephalitis have failed to show significant differences in outcome, and morbidity and mortality remain high. Relapses have occurred after the administration of acyclovir in a few cases outside of large clinical trials, and most are associated with persistent fever, suggesting an inadequate duration of therapy. Still, such treatment failures have also been attributed to viral drug resistance and postinfectious encephalomyelitis. Drug-resistant HSV occurs with thymidine kinase alteration or deficiency. Resistant strains have been described in cases of refractory HSE among HIV-infected individuals and should be considered in the setting of a worsening clinical picture and/or CSF persistence of HSV DNA despite appropriate therapy with acyclovir. Intravenous foscarnet is recommended in these cases.

In the era of the AIDS epidemic, CMV encephalitis has become a more common disease. It is invariably preceded by viremia and retinitis, and many patients have already received some antiviral therapy and may harbor drug-resistant virus

Table 76.4 Treatment regimens for acute viral encephalitis caused by Herpesviridae

Virus[a]	Drug of choice	Major toxicities	Alternate regimen[b]	Major toxicities
HSV	Acyclovir, 10 mg/kg IV q8h for 14–21 d	Nephrotoxicity, vomiting, diarrhea, mental status changes	Foscarnet, 60 mg/kg IV q8h or 90 mg/kg IV q12h for 14–21 d	Nephrotoxicity, electrolyte disturbances, nausea, fever
CMV	Induction: ganciclovir, 5 mg/kg IV q12h for 21 d, plus Foscarnet, 60 mg/kg IV q8h or 90 mg/kg IV q12h for 21 d	Bone marrow suppression, rash, fever Nephrotoxicity, electrolyte disturbances, nausea, fever	Cidofovir, 5 mg/kg IV qwk, plus Probenecid, 2 g PO 3 h before cidofovir dose, 1 g 2 h immediately after dose, and 1 g 8 h after dose	Nephrotoxicity, rash, cardiomyopathy
CMV[c]	Maintenance: ganciclovir, 5 mg/kg IV qd, plus Foscarnet, 90 mg/kg IV qd	As above As above	Valganciclovir, 900 mg PO qd	Nephrotoxicity, bone marrow suppression, rash, fever
VZV	Acyclovir, 10 mg/kg IV q8h for 10–14 d	As above	Foscarnet, 60 mg/kg IV q8h for 14–21 d	As above
EBV	Acyclovir, 10 mg/kg IV q8h for 14 d	As above	Ganciclovir, 5 mg/kg IV q12h for 21 d	As above

[a] HSV = herpes simplex virus; CMV = cytomegalovirus; VZV = varicella-zoster virus; EBV = Epstein–Barr virus; IV = intravenously; PO = orally.
[b] Alternate regimens are indicated in the setting of known drug resistance (rare in immunocompetent hosts, but not uncommon in immunocompromised patients who have received extended prior antiviral therapy).
[c] Continue maintenance therapy in HIV-infected patients until CD4 count >100 cells/mm^3 for >6 months.

by the time the encephalitis develops. Unfortunately, aggressive antiretroviral therapy is the optimal way to prolong survival in AIDS-related CMV encephalitis. Ganciclovir, one of the mainstays in the treatment of CMV retinitis, has yielded inconsistent results for brain involvement, and its use is limited by significant myelosuppression. Foscarnet crosses the blood–brain barrier more readily, attaining virustatic concentrations in CSF. It, therefore, is an alternative to ganciclovir despite significant renal and electrolyte effects. Unfortunately, although the combination of ganciclovir and foscarnet may transiently stabilize or improve the condition of most HIV-positive patients with acute CMV encephalitis, the regimen does not have an appreciable effect on survival, which averages only 3 months in this setting.

High-dose parenteral acyclovir has been used in the treatment of VZV encephalitis, although the efficacy of antiviral drugs has yet to be proven in this disease. Immunocompetent patients with VZV encephalitis often have an associated granulomatous arteritis of the brain, and a brief course of corticosteroids is often empirically added for its anti-inflammatory effects. Encephalitis is a rare complication of EBV infection. The therapeutic benefit of acyclovir in EBV encephalitis remains unproven as well, but it should be strongly considered given the lack of alternative regimens and the relatively low toxicity of acyclovir.

PARAMYXOVIRIDAE

Infection with measles virus is associated with several distinct CNS syndromes, including two forms of acute encephalitis. One is a classic post-infectious encephalomyelitis that causes acute demyelination via immunologically mediated mechanisms. Corticosteroids are widely used in this situation, but are of unproven benefit in randomized studies. An inclusion-body encephalitis occurs in 5% to 10% of immunocompromised hosts within 1 to 6 months after exposure to measles, and anecdotal reports suggest that intravenous ribavirin has some effectiveness when administered early in the course of this disease. Subacute sclerosing panencephalitis is a chronic disease that occurs in about 1 per million normal hosts, usually years after measles exposure, and typically progresses to death. Intraventricular interferon-α, intravenous or intraventricular ribavirin, and oral isoprinosine, either alone or in various combinations with each other, have been reported to increase disease remission rates in small case series. The rare nature of this disease, however, has precluded controlled trials and the development of a clearly established treatment regimen.

PAPOVAVIRIDAE

Several compounds have been employed for the treatment of JC virus, the etiologic agent of progressive multifocal leukoencephalopathy (PML), without success. Still, the recent identification of the 5HT2A subtype of serotonin receptors as a

receptor for JC virus infection of glial cells has raised hope that the atypical antipsychotic agents – ziprasidone, risperidone, and olanzapine – that serve as selective blockers of this receptor subtype might have some efficacy against this otherwise uniformly fatal disease.

PICORNAVIRIDAE

Enteroviruses as a group are the most common cause of acute viral encephalitis, and although most patients with these infections recover uneventfully, they can be life-threatening in infants and immunocompromised hosts. Pleconaril is a novel compound that integrates into the capsid of both enteroviruses and rhinoviruses and inhibits their replication. It shortens the duration of symptoms in enteroviral meningitis, and analysis of its compassionate use in more life-threatening situations suggests that 60% to 70% of patients have a favorable clinical and virologic response to therapy. Older studies report that the intraventricular administration of gamma globulin may be beneficial in the treatment of picornaviral encephalitis in agammaglobulinemic children.

BUNYAVIRIDAE, FLAVIVIRIDAE, TOGAVIRIDAE, AND REOVIRIDAE

Because effective antiviral therapies for the arthropod-transmitted encephalitides are lacking, treatment for these diseases is also generally supportive. Still, because both polyclonal antisera and monoclonal antibodies against a viral envelope glycoprotein could protect mice from otherwise fatal WNV encephalitis, a randomized, double-blind, placebo-controlled phase II trial of a novel WNV-specific monoclonal antibody was attempted in humans. Unfortunately the study was terminated in 2012 due to inadequate patient enrollment. Small molecules that inhibit replication of these viruses are being sought but remain in early stages of preclinical development.

OUTCOME

Because cases of acute viral encephalitis range from benign, self-limited illnesses to full-blown and highly cytolytic infections, the clinical outcome for patients with these diseases varies widely. The prognosis in HSE is variable despite the availability of antiviral therapy; younger age ($\leq$ 30 years), a higher level of consciousness at presentation (Glasgow Coma Scale score >10), and a shorter duration of disease before the initiation of acyclovir ($\leq$ 4 days) all predict an improved chance of survival. Even among survivors in whom treatment is initiated soon after disease onset, nearly two-thirds have long-term neurologic deficits. For patients with WNV encephalitis, recent epidemiologic studies have shown that nearly 20% die in the acute stages of infection and another 50% to 60% have residual damage that requires chronic institutionalization or extended care in the home. Fortunately, most cases of enteroviral meningoencephalitis have a better prognosis, and these patients usually recover without major sequelae. Worldwide, annual outbreaks of Japanese encephalitis cause extensive morbidity and mortality, and several new viral encephalitides (Nipah and Hendra viruses, enterovirus 71) have appeared in tropical or subtropical regions. Some of these new viruses are quite neurovirulent, and the possibility that these infections might spread to more temperate regions means that ongoing efforts to monitor, prevent, and treat these diseases must continue for the foreseeable future.

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77. Intracranial suppuration

Brian Wispelwey and Scott K. Heysell

BRAIN ABSCESS

A brain abscess begins as a localized area of cerebritis that develops into a collection of pus surrounded by a well-vascularized capsule. Brain abscesses are uncommon, with occurrence rates of 0.18% to 1.3% in large autopsy series. They most commonly result from contiguous septic foci, but hematogenous spread from a distant source and neurosurgical procedures or trauma represent other risk factors. No predisposing factor can be found in approximately 20% of cases (Table 77.1).

The age distribution of patients with brain abscess varies with its cause. A brain abscess from an otogenic focus typically occurs in patients younger than 30 and shows a male predominance. Brain abscess secondary to sinusitis typically occurs in men in their second to third decade of life.

Table 77.1 Clinical settings associated with brain abscess

Spread from a contiguous focus
Otitis media, mastoiditis; 40% of all brain abscesses
Sinusitis, frontal
Dental infections (≤10%), typically with molar infections; abscesses usually frontal but may be temporal
Meningitis; rarely complicated by brain abscess (must be considered in neonates with *Citrobacter diversus* meningitis, of whom 70% develop brain abscess)
Hematogenous spread from a distant focus of infection
Empyema, lung abscess, bronchiectasis, cystic fibrosis, wound infections, pelvic infections, intra-abdominal sepsis
Trauma
After penetrating head trauma, brain abscess develops in about 3%, more commonly after gunshot wounds
Neurosurgical procedures; complicated by brain abscess in only 6 to 17 per 10 000 clean neurosurgical procedures
Cryptogenic
Asymptomatic pulmonary arteriovenous malformation (AVM), a consideration in cases of cryptogenic brain abscess
Cyanotic congenital heart disease is present in 5% to 10% of brain abscesses and is the most common predisposing factor in some pediatric series

Pathogenesis

The location of a brain abscess is dependent on its predisposing cause. Abscess from a contiguous focus usually occurs in the cortical area of the brain near its causal site. The most common foci of contiguous infections are otitis or sinusitis. Infection from a contiguous site can spread either directly through intervening tissues, bone, and meninges or indirectly through retrograde thrombophlebitis of the diploic or emissary veins. An abscess may also result from an otogenic infection by spread through pre-existing channels such as the internal auditory canal or cochlear, and vestibular aqueducts. The majority of otogenic brain abscesses are located in the temporal lobe, followed by the cerebellum. Approximately 90% of cerebellar abscesses are secondary to an otogenic infection. Brain abscesses due to sinusitis are almost always found in the frontal lobe.

Brain abscesses secondary to hematogenous dissemination are often multiple and are located in the territory of the middle cerebral artery at the gray–white junction. They have a distant focus of infection, which is most often within the chest. These abscesses are poorly encapsulated and have a high mortality.

Brain abscesses rarely accompany bacteremia if the blood–brain barrier is intact. For example, despite the presence of persistent bacteremia in bacterial endocarditis, brain abscess is rare (nine brain abscesses reported in 218 cases of infective endocarditis).

Causes

Organisms isolated from brain abscesses are outlined in Table 77.2. Although a single organism is detected in the majority of bacterial brain abscesses, nearly 30% are of mixed infection.

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Table 77.2 Pathogens in brain abscess

Agent	Frequency (%)
Streptococci (*S. intermedius*, including *S. anginosus*)	60–70
Bacteroides and *Prevotella* spp.	20–40
Enterobacteriaceae	23–33
Staphylococcus aureus	10–15
Fungi[a]	10–15
Streptococcus pneumoniae	<1
Haemophilus influenzae	<1
Protozoa, helminths[b] (vary geographically)	<1

[a] Yeasts, fungi, *Aspergillus*, agents of mucor, *Candida*, cryptococci, coccidiodoides, *Cladosporium trichoides*, *Pseudallescheria boydii*.
[b] Protozoa, helminths, *Entamoeba histolytica*, schistosomes, paragonimus, cysticerci.

Streptococci, Enterobacteriaceae, and anaerobes are most commonly found. In contrast, *Staphylococcus aureus* is commonly isolated in pure culture.

Fungal brain abscesses have increased in incidence due to the prevalent use of immunosuppressive agents, corticosteroids, and broad-spectrum antibiotics. *Candida* species are the most common fungi in autopsy series. Risk factors for invasive *Candida* infection include the use of corticosteroids, broad-spectrum antimicrobials, and hyperalimentation. Cerebral aspergillosis occurs in 10% to 20% of all cases of invasive aspergillosis, although the brain is rarely the only site of infection. Most cases occur in neutropenic patients with underlying hematologic malignancy. Fungi of the *Zygomycetes* most often cause rhinocerebral mucormycosis, particularly in patients with diabetes mellitus and ketoacidosis, hematologic malignancies, or patients on immunosuppressive therapy. Isolated cerebral mucormycosis is most commonly seen in injection drug users. *Scedosporium apiospermum* is a common mold found in soil. Brain abscess with this organism is often associated with near drowning, trauma, or immunosuppression. While numerous other etiologic agents of fungal brain abscess exist, it is also important to highlight the recent rise in *Cryptococcus gatti* brain abcesses in immunocompetent hosts with epidemiologic exposure in the Pacific Northwest. Patients usually have outdoor exposure and may have a delayed time to diagnosis given that cryptococcal infection is not frequently considered among an otherwise immunocompetent population.

There are several protozoa and helminths that produce brain abscess. The most common is *Toxoplasma gondii*, which typically causes an intracerebral mass or encephalitis in immunosuppressed hosts. While clinically more descript as an inflammatory lesion rather than suppuration, the larval form of *Taenia solium*, causative of neurocysticercosis, is of considerable burden in Central and South America. Also found among immunocompetent hosts, cysticercosis is the most common cause of acquired seizure in the developing world.

Infections more often found in patients with defects in cell-mediated immunity include *T. gondii*, *Nocardia asteroides*, *Cryptococcus neoformans*, mycobacteria, and *Listeria monocytogenes*. Neutrophil defects are associated with an increased incidence of infections caused by Enterobacteriaceae, *Pseudomonas*, and fungi. Patients with acquired immunodeficiency syndrome (AIDS) may develop focal central nervous system (CNS) lesions as a result of a variety of pathogens (Table 77.3).

Clinical manifestations

The clinical course of patients with brain abscess varies dramatically. In approximately 75% of patients, symptoms are present for fewer than 2 weeks. Importantly, the prominent symptoms are secondary to mass effect, not infection (Table 77.4). Headache, the most common symptom, may be hemicranial or generalized. Varying degrees of altered mental status are present in most patients. Furthermore, fever may be absent in as many as 50% of all cases.

Brain abscesses in certain anatomic locations may cause additional symptoms. For example, cerebellar abscesses are often associated with nystagmus, ataxia, vomiting, and dysmetria. Frontal lobe abscesses induce headaches, drowsiness, inattention, and decline in mental function. Temporal lobe abscesses are associated with early ipsilateral headaches and, if in the dominant hemisphere, aphasia. Intrasellar abscesses simulate pituitary tumors. Brainstem abscesses often cause facial weakness, headache, fever, hemiparesis, dysphagia, and vomiting.

Laboratory findings

Most laboratory tests are not diagnostic for brain abscess (Table 77.5). Lumbar puncture is contraindicated in patients with known or suspected brain abscess. Not only are cerebrospinal fluid (CSF) findings nonspecific, but patients may herniate after the procedure. In one series, 41 of

Table 77.3 Causes of parenchymal CNS lesions in patients with AIDS

Toxoplasma gondii
Most common focal lesion
Occurs in about 10% of all AIDS patients
>1 lesion seen on MRI with surrounding edema, mass effect, and ring enhancement
Most common location is the basal ganglia; most *Toxoplasma* IgG positive
Primary lymphoma
Occurs in about 2% of AIDS patients
Lymphoma is B cell in origin
Lesions are hyperdense or isodense on CT with edema, mass effect, and variable enhancement
Caused by Epstein–Barr virus
Progressive multifocal leukoencephalopathy
Occurs in 2% to 5% of AIDS patients
Lesions occur at gray–white junction and adjacent white matter; usually hypodense without mass effect
Caused by JC virus (Papovavirus)
Less common
Cryptococcus neoformans[a]
Histoplasma capsulatum[a]
Coccidioides immitis[a]
Other fungi – *Aspergillus*, *Candida*, agents of mucormycosis
Mycobacterium tuberculosis[a]
Mycobacterium avium complex
Cytomegalovirus[b]
Metastatic malignancy, notably Kaposi's sarcoma
Acanthamoeba
Bacterial brain abscess of *Listeria*, *Nocardia*, *Salmonella*
Syphilis[a]

Abbreviations: CNS = central nervous system; AIDS = acquired immunodeficiency syndrome; MRI = magnetic resonance imaging; CT = computed tomography; IgG = immunoglobulin G.
[a] More commonly meningitis.
[b] More commonly encephalitis.

140 patients deteriorated within 48 hours after lumbar puncture, and 25 died. Similar results have been reported in other studies.

Imaging studies are most useful in making a diagnosis of brain abscess. Computed tomography (CT) can be used to evaluate all cranial structures, including the paranasal sinuses, mastoids, and middle ear. It can detect edema, hydrocephalus, shift, or imminent ventricular rupture. Contrast enhancement is essential. A brain abscess appears as a hypodense center with an outlying uniform ring of enhancement following the injection of contrast. This is surrounded by a variable hypodense region of brain edema.

Magnetic resonance imaging (MRI) is the diagnostic procedure of choice for brain abscess. It appears more sensitive than CT for detecting cerebral edema and is more accurate in differentiating the central necrosis of brain abscess from other fluid accumulations. Gadolinium enhancement can provide further structural detail. On T1-weighted images, enhancement of the abscess capsule occurs, while on T2-weighted images, the surrounding zone of edema has high signal intensity, and the capsule appears as hypointense at the abscess margin. Diffusion-weighted MRI can additionally be used to differentiate neoplasm from abscess as pus leads to restricted diffusion, but false positivity can be observed in cystic or necrotic cerebral metastases. Positron emission tomography (PET) or magnetic resonance spectroscopy may further refine sensitivity and specificity and are routinely available in many settings.

Table 77.4 Clinical manifestations of brain abscess[a]

Headache	70%	Nuchal rigidity	≈25%
Fever	50%	Papilledema	≈25%
Altered mental status	>50%	Focal neurologic findings	≈50%
Seizures	25–35%		

[a] Fewer than half have classic triad of fever, headache, and neurologic deficits.

Table 77.5 Laboratory tests and imaging studies

Laboratory tests[a]
WBC: moderate leukocytosis present in about 50% (only 10% WBC >20 000) and normal WBC in 40%
Moderate increase in ESR
Chest x-ray film is useful in detecting the origin of hematogenous brain abscess
EEG abnormal in most patients, lateralizes to side of lesion
Imaging studies
CT scan: useful in evaluating the brain, sinuses, mastoids, and middle ear
MRI: appears more sensitive early in illness and in detecting cerebral edema
^{99m}Tc very sensitive; useful where CT or MRI not available

Abbreviations: WBC = white blood cell count; ESR = erythrocyte sedimentation rate; EEG = electroencephalograph; CT = computed tomography; MRI = magnetic resonance imaging.
[a] Lumbar puncture is contraindicated in patients with known or suspected brain abscess.

Therapy

Most patients with bacterial brain abscess require surgical management. The two available procedures are aspiration and excision. No prospective randomized trial has been performed to compare these procedures. While aspiration causes less

tissue damage than excision, and stereotactic aspiration is particularly valuable for deep-seated abscesses, aspiration during early cerebritis stage may risk hemorrhage and all abscesses >2.5 cm require open excision. In one series, no abscess larger than 2.5 cm resolved without surgical therapy. Ventriculostomy is occasionally required if there is evidence of marked increased intracranial pressure due to obstructive hydrocephalus, ventricular rupture, or other uncontrolled mass effect. Medical therapy alone can be considered in the cerebritis stage prior to development of the abscess capsule, or when the abscess is small or inaccessible.

Approach to the patient with suspected brain abscess

Patients who present with altered consciousness, focal CNS signs, or seizures usually are candidates for contrast-enhanced CT or MRI. Lumbar puncture usually is postponed until a space-occupying CNS lesion is excluded. If rapid clinical progression is occurring, blood cultures for bacteria and fungi may be done and empiric antimicrobial therapy begun before neuroimaging. In every case, management should be done in conjunction with a neurosurgeon. A probable focus in the paranasal sinus or middle ear should prompt consultation also with an otolaryngologist. Empiric treatment depends on the presence or absence of immunosuppression, particularly AIDS.

Antibiotics for the treatment of brain abscess should be administered intravenously, be active against the most likely pathogens, reach adequate concentrations in the abscess fluid, and have bactericidal activity. A third-generation cephalosporin, such as cefotaxime, 3 to 4 g every 8 hours, or ceftriaxone, 2 g every 12 hours, is recommended as first-line empirical therapy of community-acquired brain abscess due to its coverage of streptococci as well as its broad gram-negative spectrum of activity. This antibiotic should be used in conjunction with metronidazole, 7.5 mg/kg (often rounded out to 500 mg) every 6 hours, which attains high concentrations in brain abscess pus and has bactericidal activity against strict anaerobes. A high proportion of deep wound infections after neurosurgical procedures are due to methicillin-resistant *Staphylococcus aureus* (MRSA), *Staphylococcus epidermidis*, and multiresistant Enterobacteriaceae. Therefore, recommended empiric antibiotics for brain abscess after a neurosurgical procedure include meropenem or cefepime plus vancomycin. Empiric antibiotic therapy should be modified or extended based on culture results, clinical status, and radiologic findings (Table 77.6).

Table 77.6 Antimicrobial therapy for brain abscess

Antimicrobial agent	Total daily dose
Cefotaxime	8–12 g
Ceftazidime	6–12 g
Ceftriaxone	4 g
Chloramphenicol	4–6 g
Metronidazole	30 mg/kg
Nafcillin	9–12 g
Penicillin G	24 million U
Vancomycin	2 g

See text for discussion of relevant combinations.

Most patients require surgery. If the patient remains stable and the abscess is accessible and encapsulated, aspiration (CT guided, if possible) is desirable to make a specific bacteriologic diagnosis and narrow the antimicrobial regimen. If for any reason, excision or aspiration is delayed or not performed, medical therapy with empiric antibiotic therapy should be instituted immediately. Subsequent management depends on clinical and radiographic (CT) parameters. Later neurologic deterioration, enlargement of an abscess after a 2-week interval, or failure of the abscess to decrease in size after 3 to 4 weeks of antibiotics are indications for further surgery. The duration of microbial therapy remains unsettled. Many authorities treat parenterally for approximately 6 to 8 weeks. Duration cannot be determined by resolution of all CT or MRI abnormalities. A cured brain abscess may continue to appear as nodular contrast enhancement on CT scans for 4 weeks to 6 months after completion of successful therapy.

AIDS patients and other immunocompromised patients

Patients with advanced HIV infection or AIDS and who have CNS lesions on MRI or contrast-enhanced CT consistent with toxoplasmosis are usually begun on empiric therapy with pyrimethamine and sulfadiazine. Pyrimethamine is given to adults as a single loading dose of 75 to 100 mg followed by 25 to 50 mg daily. Folinic acid is given, 10 mg daily, to decrease bone marrow suppression from pyrimethamine. Sulfadiazine is

given, 1 g orally every 6 hours. If sulfadiazine is not available, clindamycin is an acceptable substitute at 600 mg intravenously (IV) every 6 hours. Low-grade fever and a gradual onset also prompt this approach. The limitation of empiric therapy is that radiologic distinction between toxoplasmosis and other lesions is not accurate. Progressive deterioration, an atypical CT or MRI, or failure to show clinical and imaging improvement during 2 weeks of therapy generally warrants biopsy or aspiration. Some physicians also use a negative *Toxoplasma* serology to prompt early neurosurgical intervention. Patients taking trimethoprim–sulfamethoxazole (TMP–SMX) prophylaxis for pneumocystosis may be at a lower risk of toxoplasmosis and are therefore more likely to have another diagnosis. Newer diagnostic modalities, such as single-photon emission computed tomography (SPECT), may allow immediate differentiation between *Toxoplasma* and other pathologic processes. (See Chapter 101, Differential diagnosis and management of HIV-associated opportunistic infections.)

The range of pathogens for brain abscess is so broad in other immunocompromised patients that empiric therapy has limited value. Early neurosurgical intervention is usually indicated. An exception may be the neutropenic patient in whom fungal abscess is likely, in which case addition of antifungal coverage to antibacterial treatment should be considered. An amphotericin B preparation such as amphotericin B deoxycholate at 0.6–1.0 mg/kg daily or liposomal amphotericin B at 5 mg/kg daily will adequately cover brain abscesses from *Candida* species and most endemic fungi. Voriconazole at 4 mg/kg every 12 hours is preferred if an *Aspergillus* species is suspected, and successful combination therapy of voriconazole with an amphotericin B preparation or an echinocandin has been demonstrated.

Corticosteroids

The role of corticosteroids in the treatment of brain abscess remains controversial. They should be restricted to patients who have progressive neurologic deterioration or impending cerebral herniation and radiologic evidence that the abscess is causing significant cerebral edema and mass effect. The use of corticosteroids may delay the entry of antibiotics into the CNS, impair the clearance of bacteria, inhibit capsule formation, and alter the appearance of follow-up radiologic imaging.

Table 77.7 Adverse prognostic factors in brain abscess

Delayed or missed diagnosis
Poor localization, especially in the posterior fossa (before CT)
Multiple, deep, or multiloculated abscesses
Ventricular rupture (80–100% mortality)
Fungal cause
Inappropriate antibiotics

Abbreviation: CT = computed tomography.

Prognosis

Several factors are associated with a poor prognosis (Table 77.7). In addition, characteristics such as patient's age, abscess diameter, and metastatic lesions also influence outcome. Neurologic sequelae develop in 30% to 55% of patients, and in 17% they are incapacitating. Seizures develop in a variable percentage of patients (12% to >50%).

SUBDURAL EMPYEMA

Subdural empyema is the most common sinusitis-associated intracranial infection. The frontal sinus is most frequently implicated, and the most common location of a subdural empyema is the frontal lobe. Other causes of subdural empyema include meningitis, otitis media, prior head trauma, infection of an existing subdural hematoma, or neurosurgical procedure. Subdural empyemas have a male predominance and most often occur in the second decade of life in otherwise healthy individuals. An intracerebral abscess occurs concomitantly in 6% to 22% of cases, and an epidural abscess in 9% to 17%.

Causes

Subdural empyemas are most often monomicrobial; however, polymicrobial infections are common. Organisms found in paranasal sinus cultures often do not correlate with subdural cultures. Aerobic and anaerobic streptococci are the most frequently isolated pathogens. Staphylococci are cultured less often, followed in frequency by aerobic gram-negative bacilli and nonstreptococcal anaerobes (Table 77.8). For example, *Propionibacterium acnes* has been reported following penetrating head trauma and after neurosurgery with the use of dural allograft. Sterile cultures occur in a substantial number of cases, possibly due to the prior administration of antibiotics or difficulties in culturing anaerobic organisms.

Table 77.8 Pathogens in subdural empyema

Aerobic streptococci	32%
Anaerobic streptococci	16%
Staphylococcus aureus	11%
Coagulase-negative staphylococci	5%
Aerobic gram-negative bacilli	8%
Anaerobes	5%
No organism isolated	34%

Table 77.9 Clinical presentation of subdural empyema

Headache	
Altered mental status	≈50%
Fever (>39°C [102.2°F])	Majority
Focal neurologic findings Hemiparesis, ocular palsies, dysphagia, cerebellar signs	In all, eventually
Seizures	25%–80%
Meningismus	≈80%

Clinical presentation

Due to a lack of anatomical constraints to limit the spread of infection in the subdural space, the clinical manifestations can progress rapidly (Table 77.9). Headache and fever are common early symptoms. Altered mental status, focal neurologic deficits, meningismus, papilledema, and vomiting may also result. Seizures are common and occur in 25% to 80% of cases.

Diagnosis

Diagnosis is made by imaging with contrast-enhanced CT or MRI. A subdural empyema appears as a crescent-shaped area of hypodensity adjacent to the falx cerebri or below the cranial vault. With contrast enhancement, an intense line can be seen between the subdural collection and the cerebral cortex. Edema can cause effacement of the basilar cisterns and flattening of the cortical sulci. MRI is more sensitive in detecting subdural empyemas, particularly at the base of the brain, in the posterior fossa, or along the falx cerebri. On MRI, T1-weighted images may reveal mass effect and a hypointense subdural lesion, which in turn is hyperintense on T2-weighted imaging. On diffusion-weighted imaging, subdural empyemas have high signal intensity, in contrast to sterile subdural effusions, which have low signal intensity.

Therapy

Surgical intervention using either a burr hole or craniotomy to drain the subdural empyema is an important part of therapy. Drainage is useful to both relieve mass effect and obtain cultures to guide antimicrobial therapy. Exploration of a sinus or otologic focus of infection should also be done.

A reasonable empiric antibiotic regimen for a community-acquired subdural empyema would be a third-generation cephalosporin plus metronidazole. Depending on the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) or the likelihood of coagulase-negative staphylococci, the addition of vancomycin could be considered. Further antimicrobial therapy should be directed against pathogens revealed by Gram stain, culture of aspirated material, and knowledge of the primary site of infection. Parenteral antibiotics are continued for 3 to 6 weeks depending on the clinical response and associated conditions.

Prognosis

Prognosis is related to the degree of neurologic impairment at presentation. Mortality is approximately 7% in patients who are alert and well oriented, 21% in patients who are lethargic or comatose but respond purposefully, and 56% in patients who are unresponsive. Neurologic sequelae in the form of hemiparesis and aphasia are common, and up to 40% of patients may have seizures.

CRANIAL EPIDURAL ABSCESS

Cranial epidural abscesses (Figure 77.1) were traditionally the sequelae of sinusitis, mastoiditis, and otitis media. Currently, one of the most common causes of an intracranial epidural abscess is a neurosurgical procedure. The organisms responsible for epidural abscesses are similar to those that cause subdural empyemas.

The dura is essentially adherent to the inner lining of the skull, which constrains the epidural space and limits spread of purulence. Because of this, epidural abscesses are typically slow growing and have an indolent course. Headache may be the only presenting symptom. Over time, complications such as subdural empyema, brain abscess, or meningitis may result. It is the manifestations of these complications that may be the first indication of an intracranial process.

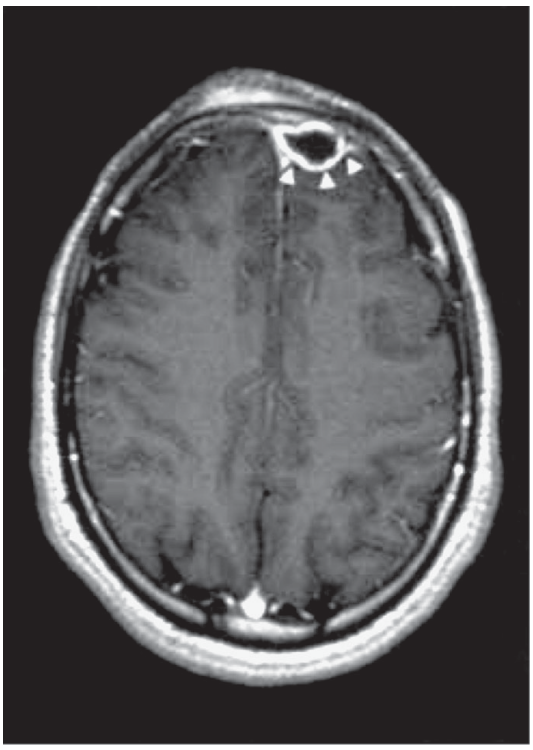

Figure 77.1 Epidural abscess associated with frontal sinus disease. Postgadolinium axial T1W-MRI showing thick-walled enhancing epidural collection close to the inner table of the frontal bone (*arrowheads*) with adjacent soft tissue swelling. (From Bradley WG. *Neurology in Clinical Practice*, 4th edn., Copyright © 2004 Butterworth-Heinemann, an imprint of Elsevier.)

Contrast-enhanced CT or MRI may be used to diagnose an intracranial epidural abscess. Lentiform or crescentic collections overlying a cerebral convexity and/or in the interhemispheric fissure are seen. Treatment is the same as for subdural empyema.

SUPPURATIVE INTRACRANIAL THROMBOPHLEBITIS

Cavernous sinus thrombosis most commonly results from spread of infection from the sinuses, especially the sphenoid sinus. Infections of the middle third of the face, dental abscesses, otogenic infections, and orbital cellulitis are other sources of cavernous sinus thrombosis (see Chapter 16, Periocular infections). Lateral sinus thrombosis is a serious complication of both acute and chronic otitis media. Infection of the superior and inferior petrosal sinuses may also result from otitis media or mastoiditis. Suppurative thrombophlebitis of the superior sagittal sinus may develop after infection of the face, scalp, or subdural or epidural space or after meningitis.

Pathogenesis

Suppurative thrombophlebitis occurs intracranially because of the close proximity of the dural venous sinuses to other structures in the skull. The transverse sinus receives several important supratentorial veins from the temporal and occipital lobes, as well as many infratentorial veins. The superior petrosal sinus, which receives venous channels from the tympanic structures, also drains into the transverse sinus. The sigmoid sinus, which lies close to mastoid cells, is the inferior continuation of the transverse sinus.

The dural venous sinuses and cranial veins are valveless, and blood flow is determined by pressure gradients. Bacteria that enter the facial veins are carried through the cavernous sinuses to the petrosal sinuses and finally the internal jugular vein. Conditions that increase blood viscosity, such as trauma, dehydration, malignancy, and pregnancy, increase the likelihood of developing thrombosis. However, predisposing conditions are not identified in every case.

Causes

The causative pathogen in suppurative intracranial thrombophlebitis depends on the site of the original infection (Table 77.10). *Staphylococcus aureus* is the most common pathogen in cavernous sinus thrombosis, but other gram-positive cocci such as *Streptococcus* species, gram-negative bacilli, and anaerobes can be seen. The most common bacteria in lateral sinus thrombosis include gram-negative bacilli and anaerobes. Mixed infections are frequent.

Clinical presentation

The clinical presentation depends on the location of disease (Table 77.11). Cavernous sinus thrombosis can present with periorbital edema, chemosis, visual loss, restricted eye movement, and proptosis. Orbital cellulitis and orbital apex syndrome can present similarly. In contrast, preseptal cellulitis is confined to structures anterior to the orbit. Suppurative cavernous sinus thrombosis can spread via intercavernous sinuses to the contralateral cavernous sinus within 24 to 48 hours. The thrombus may also extend to other dural venous sinuses, adjacent vascular structures, or

Table 77.10 Suppurative intracranial thrombophlebitis: organism by site of infection

Sinusitis	Streptococci Staphylococci Anaerobes
Soft-tissue infections of the face	*Staphylococcus aureus*
Otitis, mastoiditis	Streptococci *Haemophilus influenzae* Gram-negative bacilli Staphylococci

the brain parenchyma. Metastatic spread of septic emboli may occur and most commonly involves the lung.

Classic symptoms and signs of lateral sinus thrombosis include severe headache, otalgia, spiking fevers, mastoid swelling, and tenderness. However, patient presentations may be highly variable and are influenced by the common occurrence of concurrent intracranial complications and preadmission antibiotics. Symptoms and signs of raised intracranial pressure may result if the thrombosis significantly impairs CSF resorption or cerebral venous outflow. These include headache, nausea, vomiting, 6th nerve palsy, and papilledema. Nuchal rigidity has been reported to occur in 8% to 61% of patients. Unlike meningitis, the nuchal rigidity associated with lateral sinus thrombosis is often unilateral with negative Kernig and Brudzinski signs.

Diagnosis

On contrast-enhanced CT scan, the most accurate diagnostic finding of sinus thrombosis is the empty delta sign. This consists of a darkened area of thrombus in the vessel lumen, surrounded by the contrast-enhanced sinus wall. The thrombus formed within the lumen of the sinus may present different attenuations according to its developmental stage, and artifacts from adjacent bone structures are factors that may decrease the sensitivity of CT. Contrast-enhanced CT has a sensitivity of ~80% for the diagnosis of dural sinus thrombosis. On MRI, an acute thrombus (days 0 to 3) appears isointense on T1-weighted images and hypointense on T2-weighted images. In the subacute phase (days 3 to 15), there is increased intensity of the thrombus in both T1- and T2-weighted images. MR venography (MRV) is more sensitive than contrast-enhanced CT or MRI and demonstrates the loss of signal and then absence of flow in the sinus. CT venography may

Table 77.11 Symptoms of suppurative thrombophlebitis

Cavernous sinus thrombosis	Photophobia, ptosis, diplopia, proptosis, chemosis, weak extraocular muscles, papilledema, altered mental status, meningismus, decreased visual acuity, involvement bilaterally; same findings in opposite eye
Septic lateral sinus thrombosis	Headache >80%, earache, vomiting, vertigo associated with otitis, fever and abnormal ear findings, increased facial sensation/pain, 6th nerve palsy
Superior sagittal sinus	Altered mental status, motor deficits, papilledema, nuchal rigidity, seizures >50%
Inferior petrosal sinus	Gradenigo's syndrome (ipsilateral facial pain and lateral rectus weakness)

be as accurate as MRV. It is less impaired by motion artifact because of a rapid acquisition time. It more frequently depicts sinuses of smaller cerebral veins with low flow than MRV does. However, its disadvantages include significant exposure to ionizing radiation and the need for IV contrast material.

Therapy

Initial IV treatment with antibiotics that have a broad spectrum of activity and good CSF penetration should be used. Surgical removal of the source of infection should also be undertaken. Mortality rates from lateral sinus thrombosis have improved but are still approximately 10%.

Anticoagulation is controversial, and its major risk is intracranial hemorrhage. One study found anticoagulation with antimicrobial therapy may reduce mortality of cavernous sinus thrombosis, but only if used early in disease. It has not been proven to be beneficial in lateral sinus thrombosis.

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78. Spinal epidural abscess

Mark J. DiNubile

Epidural abscess represents a potentially crippling but treatable cause of back pain. Although relatively infrequent, the incidence appears to be increasing. Early diagnosis and aggressive therapy are essential for optimizing outcomes. Even with an indolent presentation, patients can still suffer catastrophic neurologic complications related to delays in recognition and appropriate intervention.

CLASSIFICATION

Epidural abscesses can be separated anatomically into infections involving the spinal or cranial epidural space. Cranial epidural abscesses are discussed in Chapter 77, Intracranial suppuration.

Spinal epidural infections comprise both acute and chronic presentations. This categorization correlates with certain clinical and laboratory manifestations, bacteriology, anatomic details, pathology, and pathogenesis (Table 78.1). The nontuberculous bacterial spinal epidural abscess constitutes the major focus of the current presentation. Tuberculous, fungal, and parasitic abscesses of the spinal epidural space evolve more insidiously than pyogenic bacterial epidural abscesses. Other than iatrogenic candidial infections, these etiologies are more frequently encountered in tropical and subtropical resource-constrained regions of the world. Metastatic carcinoma and lymphoma represent common alternative diagnoses that can exactly mimic epidural infections.

Another differential feature with therapeutic implications concerns the source of epidural infection. Microbes most commonly access the epidural space by hematogenous dissemination from a distant, sometimes trivial, infectious focus. A substantial minority of cases arise from contiguous spread, usually from vertebral osteomyelitis. Epidural abscesses of hematogenous origin are typically located in the dorsolateral thoracic or lumbar area, where the epidural space is widest. Abscesses that form secondary to adjacent osteomyelitis usually involve the epidural space anteriorly or circumferentially. In some cases, it is hard to determine whether the epidural space represents a primary or secondary site of infection.

Table 78.1 Characteristic findings in acute versus chronic spinal epidural abscess

	Acute	Chronic
Duration of symptoms	Less than 2 wk	More than 2 wk
Fever	Often present	Low grade or absent
Systemic toxicity	Sometimes	Infrequently
Source	Hematogenous (often from minor skin infection)	Direct extension from vertebral osteomyelitis
Back pain	Always	Always
Localized spinal tenderness	Very common	Nearly universal
Root weakness	Common	Common
Peripheral leukocytosis	Usually present	Usually absent
Erythrocyte sedimentation rate	Greatly elevated	Greatly elevated
CSF leukocytes[a] (per mm^3)	Usually 50–1000	Often <50
CSF protein >100 mg/dL	Almost always	Almost always
Anatomic location	Usually posterior to spinal cord	Commonly anterior to spinal cord
Gross pathology	Purulent exudate	Granulation tissue

Abbreviation: CSF = cerebrospinal fluid.

[a] Frank pus may be encountered if a lumbosacral epidural abscess is entered during attempted lumbar puncture. If this occurs, the spinal needle must not be further advanced because introducing the needle into the subarachnoid space may precipitate meningitis. The aspirated purulent material should be sent immediately in the airless capped syringe for appropriate studies, including Gram stain and aerobic/anaerobic cultures.

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CLINICAL PRESENTATION AND COURSE

The classical manifestations of spinal epidural abscess were partitioned by Heusner in 1948 as progressing through four sequential but overlapping stages: (1) spinal ache (or back pain); (2) root (or radicular) pain; (3) weakness; and ultimately (4) paralysis. The actual time between the onset of back pain and development of neurologic deficits can be highly variable. The unpredictable but potentially rapid evolution from backache to neurologic tragedy forces physicians to consider this entity in the differential diagnosis of all patients with new or changing back pain, particularly when fever and localized spinal tenderness coexist. Presenting complaints include paresthesias (sometimes described as "electric" in character), paresis, incontinence, constipation, or urinary retention. Atypical presentations include headache or meningismus (with cervical involvement), pleuritic or abdominal pain (with thoracic infection), and hip pain (with lumbar disease).

In patients with epidural abscesses, an inapparent primary source of infection, such as endocarditis, adjacent osteomyelitis, or a distant visceral abscess, may be present. Initially occult infectious foci may ultimately dictate the length of antimicrobial treatment or mandate additional procedures. Not unexpectedly, bacteremia is more often documented in acute hematogenous than chronic locally advancing infections. Especially when *Staphylococcus aureus* is the pathogen, the infection may be multifocal due to seeding of distant sites during a primary or secondary bacteremia.

The dreaded neurologic complications of epidural abscess can arise from either pressure causing compression of the spinal cord or vascular compromise causing ischemic necrosis. Cord compression may be more common, but septic thrombophlebitis is likely responsible for sudden unforeseen deterioration.

RISK FACTORS

Patients with a history of back injury are predisposed to seed the injured area during transient bacteremia and therefore constitute a special risk group for vertebral osteomyelitis and/or epidural abscess. Penetrating trauma may seed the adjacent bone and epidural space. Suspicion of epidural infection should be raised when a patient with diagnosed osteomyelitis or after recent back surgery, epidural injection, or lumbar puncture reports worsening localized back discomfort.

All patients with bacteremia or candidemia incur some risk of metastatic seeding. Patients with cutaneous infections, infected catheters, dental manipulations, decubitus ulcers, urinary tract infections, or endocarditis can develop a secondary epidural focus through hematogenous spread, even in the absence of previously recognized back injury. The risk appears highest in the aftermath of *S. aureus* bacteremia and is not totally eliminated by the 2 to 4 weeks of antibiotic therapy usually given to such patients. Epidural infection may manifest itself weeks to months later. Under most circumstances, back pain developing or worsening in the year following an episode of *S. aureus* bacteremia should be presumed to represent metastatic infection until proved otherwise.

Injection drug users may develop infections of the epidural space. Diabetic patients, patients receiving long-term parenteral nutrition, and patients undergoing hemodialysis also appear to be at increased risk for epidural infection. Infections can arise from epidural injections or catheters due to breach of the anatomic barriers or even contamination of the injected material.

MICROBIOLOGY

Staphylococcus aureus remains the predominant pathogen recovered from all types of epidural abscesses, often originating from an unnoticed and otherwise inconsequential primary skin focus. Injecting drug use, chronic hemodialysis, and indwelling vascular catheters predispose to *S. aureus* bacteremia associated with metastatic seeding.

A comprehensive clinical history including the epidemiologic circumstances may provide the only clues to otherwise unsuspected pathogens. Gram-negative osteomyelitis, discitis, and epidural infection can complicate injection drug use, where Enterobacteriaceae and *Pseudomonas aeruginosa* need to be considered among the possible pathogens. Gram-negative rods and occasionally enterococci can spread from urinary tract or pelvic infections to the lumbar spine and/or epidural space through vascular anastomoses in Batson's plexus. Less commonly isolated bacterial species include streptococci (especially the *S. milleri* group), coagulase-negative staphylococci (usually postoperatively or after open trauma), anaerobes (from either the oral or intestinal flora), *Brucella*, and *Salmonella* species.

Tuberculous spondylitis (Pott's disease) is frequently associated with epidural abscess and

may be the presenting or sole manifestation of reactivation tuberculosis. Chronic osteomyelitis due to tuberculosis is often clinically and radiologically indistinguishable from disease caused by pyogenic bacteria, although the course is generally more protracted. Histopathology typically reveals fibrous connective tissue studded with caseating granulomata containing multinucleated giant cells. Acid-fast bacilli (AFB) can often be demonstrated by appropriate stains or molecular techniques. Despite paraspinal collections, operative intervention is not routinely required for Pott's disease in the absence of significant or progressive neurologic involvement.

Nosocomial candidemia can be complicated by osteomyelitis with or without epidural infection, and may present as a delayed complication of catheter-related candidemia despite antifungal therapy. Unusual etiologies of epidural abscess have involved *Actinomyces*, *Nocardia*, nontuberculous mycobacteria, *Cryptococcus*, *Blastomyces*, *Aspergillus*, *Exserohilum*, *Rhizopus*, cysticercosis, and *Echinococcus*.

DIAGNOSIS

Every patient who complains of new or progressive back pain, fever, and local spine tenderness must be quickly assessed for the possibility of spinal epidural abscess. A normal sedimentation rate makes an epidural abscess unlikely.

Not all the symptoms and signs classically attributed to an epidural abscess are present in every patient. With a protracted course, fever and systemic complaints may be absent. Children especially may exhibit atypical features. In several series, roughly half the reported patients with spinal epidural abscesses were initially given unrelated diagnoses. In oncology and intensive care patients, the symptoms of epidural infection may be obscured by or misattributed to other coexisting problems.

Conventional radiology of the spine is rarely conclusive; osseous destruction can be inapparent even in the presence of vertebral osteomyelitis early in the process. Although fever is generally unimpressive with chronic epidural abscess, these patients will have abnormal spine radiographs more consistently than patients with acute infection. Findings on bone, gallium, and indium scans and even computed tomography (CT) are typically equivocal and thus can delay definitive diagnostic testing and subsequent treatment.

Whether acute or chronic, all patients with suspected epidural space infection require magnetic resonance imaging (MRI) of the spine, CT myelography, or a conventional myelogram on an urgent basis. Gadolinium-enhanced MRI is currently the preferred diagnostic procedure where available. Spinal puncture for myelography when necessary should be performed at a site as far as safely possible from the area of suspected abscess. The needle should be advanced slowly, with frequent aspirations; if pus is encountered, the needle should be withdrawn and the aspirated material sent for appropriate tests. If myelographic contrast material is to be injected into the subarachnoid space, CSF should be obtained beforehand for stains and cultures, glucose and protein levels, total and differential cell counts, and cytology. Otherwise, lumbar puncture should be avoided unless meningitis is in the differential diagnoses. If nonsurgical management is planned, CT-guided aspiration of the epidural collection may be attempted to obtain specimens for stains and culture (as well as to drain the epidural collection).

TREATMENT

Traditional management of spinal epidural abscess involves immediate surgical drainage and prolonged antibiotic therapy. Operative evacuation of the abscess allows for decompression as well as procurement of pus and tissue samples for microbiologic processing. Exposure of the entire length of the abscess with adequate drainage, debridement, and irrigation has been standard practice in most situations, and can usually be accomplished via a simple laminectomy. Neurologic improvement is often evident soon after decompression.

In acute or rapidly progressing cases, antibiotic therapy ought to be initiated promptly and often empirically after blood and other readily accessible sites of infection are sampled for stains and cultures. An antistaphylococcal agent should be routinely included in any empirical antibiotic regimen. With the spread of nosocomial and now community-acquired methicillin-resistant *S. aureus* (MRSA), coverage with antistaphylococcal β-lactam agents has become inadequate for empiric therapy. Antibiotics active against gram-negative and strictly anaerobic bacteria should be added to the regimen when these organisms are suspected based on clinical grounds or epidemiologic context. For example, a patient with a lumbar epidural abscess of suspected urinary tract origin would need broader coverage for

gram-negative pathogens. For infections associated with injection drug use, coverage for *P. aeruginosa* and mouth anaerobes needs to be considered. Many authorities would initiate empiric treatment of all epidural abscesses with broad-spectrum coverage, including vancomycin, metronidazole, and ceftriaxone (or ceftazidime, if *P. aeruginosa* is a suspect). Gram-stained specimens often provide rapid information that can lead to modifications of the planned antibiotic regimen before culture results return.

The initial regimen should be refined once results of stains, cultures, and susceptibility tests from blood, aspirates, or operative samples are available. Aerobic and anaerobic cultures from appropriately processed specimens usually identify the pathogen(s) unless substantial antibiotic treatment has preceded sampling. The dosing guidelines given here are for adults with normal renal and hepatic function. Confirmed methicillin-susceptible *S. aureus* infections have traditionally been treated with nafcillin, 2 g intravenously (IV) every 4 hours (or cefazolin, 1 g IV every 8 hours) in patients not allergic to β-lactam agents. Clindamycin, 600 mg IV every 8 hours, and vancomycin, initially administered as at least 15 mg/kg IV every 12 hours and adjusted to maintain trough levels of 15 to 20 μg/mL, remain the standard alternatives for seriously penicillin-allergic patients. Vancomycin, daptomycin, or linezolid are appropriate when MRSA is recovered or strongly suspected. Community-acquired MRSA may be sensitive to other agents (such as clindamycin, quinolones/rifampin, or trimethoprim–sulfamethoxazole) but susceptibility to these agents should be documented by testing the isolate in the clinical microbiology laboratory before any of these drugs are considered.

Substantial clinical experience supports extended-spectrum quinolones for the treatment of osteomyelitis, discitis, and epidural abscesses. In susceptible staphylococcal infections associated with osteomyelitis, an oral regimen of rifampin 600 mg daily combined with either ciprofloxacin 750 mg twice daily or levofloxacin 750 mg once daily would be a reasonable option to complete a prolonged antibiotic course after successful acute management.

For susceptible gram-negative infections, trimethoprim–sulfamethoxazole, an advanced-generation cephalosporin, or a quinolone may be used. Trimethoprim–sulfamethoxazole is not active against *P. aeruginosa*, which mandates treatment with an antipseudomonal β-lactam derivative or ciprofloxacin, guided by sensitivity results and sometimes combined with an aminoglycoside antibiotic. Carbapenems or colistin may be necessary for multidrug-resistant gram-negative bacilli. Metronidazole is the drug of choice for most anaerobic infections. Quinolones, trimethoprim–sulfamethoxazole, and metronidazole can be given orally to patients tolerating medication by mouth. The incidence of iatrogenic complications (as well as cost) could be dramatically reduced by discontinuing nonessential intravenous lines and administering antibiotic therapy by mouth when appropriate.

The optimal duration of antibiotic therapy has not been determined in controlled studies. Recommendations range from 4 to 8 weeks. Therapy for at least 6 weeks is typically prescribed, especially when vertebral osteomyelitis coexists or adequate surgical drainage was not accomplished.

Selected patients with epidural abscess can be managed conservatively without surgery. Nonsurgical management is more consistently successful in stable patients who present with localized back or radicular pain without objective neurologic signs such as weakness, urinary retention, or incontinence. However, in the majority of cases, a drainage procedure is still considered a critical component of the standard of care under most circumstances both to establish a microbiologic diagnosis and to decompress the thecal sac.

The optimal procedure requires individualizing the approach for the particular location and extent of the infection. In surgical candidates, decompression and drainage are usually accomplished by posterior laminectomy for dorsal abscesses or by partial or complete anterior or anterolateral corpectomy for ventral abscesses in adults. Complete exposure of the involved segments may be contraindicated in patients with extensive craniocaudal abscesses or spinal instability. Less invasive procedures have been increasingly employed for complicated multilevel infection. Multi-segment interlaminar fenestration can replace laminectomy in selected cases with impending anterior instability due to lumbar spondylitis, sometimes accompanied by intraoperative ultrasound to guide decompression despite the narrow bony window. Minimally invasive operative procedures or percutaneous CT-guided needle aspiration may be a compromise approach in some patients despite a theoretical concern about inadvertently seeding the subarachnoid space and inducing meningitis during the procedure.

Table 78.2 Potential candidates for medical management of spinal epidural abscess without immediate operative intervention

No significant or progressive neurologic dysfunction
or
Poor surgical candidate
or
Complete paralysis for >72–96 h
AND
Diagnosis is secure, and causative organism has been identified

Medical management alone is an appropriate option for neurologically stable patients who exhibit no significant neurologic deficits or have a contraindication to surgery (Table 78.2). Qualifying candidates for medical therapy are not infrequent. Unfortunately, some patients will suffer neurologic progression despite appropriate antibiotics, which can ensue abruptly and unpredictably without warning. The resultant paresis or paralysis may be irreversible, even if surgery is then performed urgently. In addition to mass effect, vascular compromise from septic arterial or venous thrombosis with cord infarction may play a key pathophysiologic role in these tragic cases.

All patients with epidural abscess, whether managed conservatively or not, must be evaluated by careful and repeated physical examinations at least daily for signs of neurologic deterioration. The role for periodic imaging during the course is not defined.

PROGNOSIS

Spinal epidural abscess was often lethal before the antibiotic era. Nonetheless, morbidity rates remain disappointingly high. Up to a third of survivors have persistent deficits and unsatisfactory outcomes.

Presenting symptoms of back pain or radiculopathy are associated with better functional outcomes, regardless of symptom duration, than more severe neurologic findings at presentation. For patients presenting with frank motor deficits, duration of symptoms ("acute" versus "chronic" presentations) appears to have prognostic implications, with better outcomes when treatment is initiated within 72 hours of onset of weakness. The severity of the neurologic defect at the time of the drainage/decompression procedure is a critical predictor of the ultimate neurologic result. Other prognostic indicators include patient age, the degree of cord impingement on imaging studies, and operative findings of granulation tissue as opposed to purulent fluid.

SUMMARY AND CONCLUSIONS

Epidural abscess is a potentially devastating infection. Early diagnosis and combined aggressive medical–surgical intervention are essential for most patients because neurologic function may deteriorate quickly, leaving irreversible deficits.

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DISCLOSURES

The author is an employee of Merck and owns stock and stock options in the company. A penultimate version of the paper was reviewed by Merck. The opinions expressed in this report represent the views of the author and do not necessarily reflect the formal position of Merck.

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79. Myelitis and peripheral neuropathy

Jeffrey M. Percak and Rodrigo Hasbun

Myelitis and peripheral neuropathy complicate many infections. This chapter discusses major infectious etiologies of myelitis (Table 79.1), peripheral neuropathy (Table 79.2), polymorphic syndromes (Table 79.3), and neuropathic syndromes seen in human immunodeficiency virus (HIV) infection (Table 79.4). Further, an algorithm (Figure 79.1) suggests an approach to the clinical and laboratory diagnosis of myelitis and peripheral neuropathy.

MYELITIS

Myelitis refers to inflammation of the spinal cord. Myelitis may be infectious or noninfectious and primary – directly attacking cord structures – or secondary – adjacent processes altering cord function. Primary myelitis can present as one of three discrete clinical patterns: (1) anterior poliomyelitis, (2) leukomyelitis, or (3) transverse myelitis. Poliomyelitis is inflammation involving gray matter; leukomyelitis is confined to white matter. Transverse myelitis, inflammation of an entire cross section of the spinal cord, can affect more than one spinal segment. A number of infectious agents are known to cause or to be associated with myelitis. Myelitis can also occur after infection or vaccination as in the acute disseminated encephalomyelitis (ADEM) syndrome.

There are five cardinal manifestations of spinal cord disease: pain; motor deficits; sensory deficits; abnormalities of reflexes and muscle tone; and bladder dysfunction. The distribution of neurologic deficits depends on the spinal segment(s) affected. Local pain occurs at the site of the lesion and can assume a radicular quality if the nerve roots are involved. Paresthesias have greater localizing value than radicular pain. Weakness is present in virtually all spinal cord disorders, and in myelitis may progress over hours, days, or weeks. Spinal shock is characterized by absent plantar reflexes, and areflexia and atonia below the level of the lesion. More slowly progressive lesions are associated with hyperreflexia and hypertonia. Bladder dysfunction is usually not an early sign of spinal cord disease, although if spinal shock develops, flaccid bladder paralysis ensues with urinary retention and overflow incontinence. Chronic myelopathies cause a spastic bladder and result in urgency, frequency, and incontinence.

Acute primary infectious transverse myelitis must be distinguished from infectious secondary myelopathies and other noninfectious causes of myelitis such as multiple sclerosis or systemic lupus erythematosus. Magnetic resonance imaging (MRI) of the spinal cord must be performed early to exclude a compressive lesion.

Tropical spastic paraparesis/HTLV-1-associated myelopathy

Human T-cell lymphotropic virus type 1 (HTLV-1) is a retrovirus associated with adult T-cell leukemia/lymphoma and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). Approximately 15 to 20 million people are infected worldwide with endemic areas in the Caribbean, southern Japan, Africa, and Italy. Among first time US blood donors, the prevalence in 2009 was 5 per 10 000, half that seen in 2000. In perhaps 4% of those infected, HTLV-1 causes a chronic meningomyelitis with focal destruction of gray matter as well as demyelination of white matter primarily within the posterior columns and corticospinal tracts. Neurologic disease usually begins in the fifth decade; women are more commonly affected than men (~2.5–3:1). Patients typically note bilateral lower extremity weakness and stiffness but may also have difficulty walking and back pain. Neurogenic bladder may develop and neuropathy may be found. Physical examination shows spastic paraparesis, hyperreflexia, extensor plantar reflexes, and reduced vibratory sensation and proprioception. Typically the disease is slowly progressive and

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Table 79.1 Myelitis

Syndrome/ disease	Organism	Symptoms, signs, and neurologic findings	CNS	PNS	Cord	Other findings	Risk factors
Anterior polio myelitis syndrome	Poliovirus 1, 2, 3	*Onset:* Acute *Clinical patterns:* Spinal and bulbar paralysis *Common features:* Asymmetric flaccid paralysis (AFP)	√		√	"Minor illness" (3–4 d) influenza-like syndrome "Major illness" (5–7 d) aseptic meningitis, myeloencephalitis	Absence of protective immunity and travel in endemic areas
	Nonpolio Coxsackie A, B Echovirus Enterovirus West Nile virus (WNV)	*Onset:* Acute *Clinical patterns:* Similar to polio but milder disease *Asymptomatic infection:* Common except at extremes of age and in immunosuppressed	√		√	CNS phase aseptic meningitis, encephalitis, encephalomyelitis	Seasonal incidence in temperate climates (summer), year-round in tropical climates WNV: Vector borne (*mosquito*) and transmitted by breast milk, blood transfusions, and organ transplants
Ascending myelitis syndrome (leukomyelitis)	HIV-1	*Onset:* Acute/subacute *Clinical patterns*:	√	√	√		See below
	HTLV-1	*Onset:* Subacute/chronic *Clinical patterns*: tropical spastic paraparesis (TSP) or HAM			√	"Rosette cells" in CSF lymphocytes Coinfection with HIV in IVDUs	Injecting drug use Prior residence in endemic areas
	Herpesviruses: CMV, EBV HSV, VZV	*Onset:* Acute *Clinical patterns:* Ascending pattern w/initial plexitis Asymmetric commonly		√	√	Primarily seen in immunosuppressed	Related to epidemiology of primary infection
	Herpes B virus (Monkey B)	*Onset:* Subacute (5–30 d) *Clinical pattern:* Aseptic meningitis Ascending encephalomyelitis	√		√	Prodromal illness: Early (*vesicles*); Intermediate (*numbness, weakness, hiccups*)	Macaque monkey bite or exposure to tissues Laboratory workers exposed to contaminated cell cultures
Transverse myelitis syndrome	*Primary* myelitis VZV Dengue Spirochetes[a] Schistosomiasis Post-meningococcal	*Onset:* Acute (after prodrome) *Clinical patterns:* Sensory motor level Initial spinal shock Hyperreflexia below level of lesion			√		Related to epidemiology of primary infection
	Secondary myelitis*:* Bacteria, fungi, mycobacteria	*Onset:* Acute/subacute *Clinical patterns:* Radicular-spinal cord syndrome Cauda equina syndrome			√	Related to primary infection and organisms	Injecting drug use Hematogenous osteomyelitis Back surgery: Intraoperative contamination
Acute demyelinating encephalomyelitis (ADEM)	*Mycoplasma*, Lyme, Enteroviruses, EBV, CMV, VZV, dengue, measles, hepatitis A, Semple Rabies vaccine	*Onset:* Acute *Clinical patterns:* Pyramidal and extrapyramidal symptoms, hemiplegia, ataxia, cranial neuropathies, myelitis paresthesias, polyradiculopathy, altered mental status	√		√		Related to epidemiology of primary infection

[a] Spirochetes include: *Borrelia* species (*B. burgdorferi* – Lyme, *B. recurrentis* – relapsing fever), *Leptospira* spp., *Treponema pallidum*.

Abbreviations: CMV = cytomegalovirus; CNS = central nervous system; CSF = cerebrospinal fluid; EBV = Epstein–Barr virus; HAM = HTLV-1-associated myelopathy; HIV = human immunodeficiency virus; HSV = herpes simplex virus; HTLV = human T-cell lymphotropic virus; IDUs = injecting drug users; IVDU = intravenous drug use; PNS = parasympathetic nervous system; VZV = varicella-zoster virus; WNV = West Nile virus.

Table 79.2 Peripheral neuropathy

Syndrome/ disease	Organism/ antibiotic	Symptoms, signs, and neurologic findings	CNS	PNS	Cord	Other findings	Risk factors
Polyneuritis: Acute (AIDP) Guillain–Barré Landry Miller-Fisher Chronic (CIDP)	1. Idiopathic 2. Infection-associated	*Onset*: Acute/subacute and chronic *Common features:* Progressive, symmetric weakness Distal→proximal limbs Truncal→cranial muscles Paresthesias, hypotonia, areflexia *Clinical patterns:* Ascending, descending, bulbar	√	√		Variable autonomic dysfunction (ileus, cardiac)	Preceding viral illness or vaccination, prior episode Infection-associated: Viral (EBV, HIV, dengue, hepatitis) Bacterial (*Campylobacter*) Chlamydia (*C. psittaci*) Mycoplasma (*M. pneumoniae*) Spirochetes (Lyme borreliosis)
Neuropathy due to bacterial toxins	*Corynebacterium diphtheriae*	*Onset:* Acute/subacute *Clinical patterns:* Bulbar symptoms Ascending peripheral neuropathy	√	√		Pharyngitis with pseudomembrane Myocarditis Endocarditis	Absence of protective immunity, epidemic respiratory diphtheria, contaminated wound
	Clostridium botulinum	*Onset:* Acute/subacute (dose-related) *Clinical patterns:* Bulbar symptoms Myasthenia-like weakness	√	√		Autonomic dysfunction (dry tongue, ileus, urinary retention) Decreased vital capacity	Food sources Contaminated wounds (IDUs) Sinusitis in cocaine snorters
	Clostridium tetani	*Onset:* Acute/subacute (dose-related) *Clinical patterns:* Localized, cephalic, generalized	√	√	√	Autonomic dysfunction Hypertensive crises Decreased vital capacity	Absence or loss of protective immunity Puncture/contaminated wounds Infected neonatal cord stumps
Medication *Acute* Antibacterials	Aminoglycosides Polymyxins	*Onset:* Acute (concentration-related) *Clinical patterns:* Neuromuscular blockade	√	√		Decreased vital capacity Generalized paralysis	Excessive or unadjusted dosage for lean body mass
Subacute Anti-TB Antiretrovirals Antibacterials	Isoniazid ddI, ddC, d4T Chloramphenicol Metronidazole Nitrofurantoin	*Onset:* Subacute (dose and duration) *Clinical patterns:* Symmetric Distal paresthesias and weakness Progressive loss of distal DTRs		√			Isoniazid: Lack of pyridoxine Nucleoside antiretrovirals: Pre-existing neuropathy Excessive or unadjusted dosage Antibiotics: Cumulative dosage
Vasculitis	Polyarteritis nodosa (PAN) Wegener's	*Onset*: Subacute *Clinical patterns:* Mononeuritis multiplex *Common features*: Asymmetric weakness, paresthesias, loss of DTRs in affected areas		√		PAN: Asymptomatic micro-aneurysms Wegener's: sinusitis, pulmonary and renal lesions, +/– eosinophilia	PAN: Chronic active hepatitis B Wegener's: Unknown etiology
Leprosy	*Mycobacterium leprae*	*Onset:* Insidious/acute *Clinical patterns:* Mononeuritis multiplex Polyneuropathy *Common features:* Anesthetic lesions, enlarged nerves		√		Deformity Nerves most commonly affected: Median, ulnar, peroneal	General Genetic susceptibility Prior residence in endemic areas Neuropathy Tuberculoid Reversal reaction

Abbreviations: AIDP = acute inflammatory demyelinating polyneuropathy; CIDP = chronic inflammatory demyelinating polyneuropathy; CNS = central nervous system; DTRs = deep tendon reflexes; EBV = Epstein–Barr virus; HIV = human immunodeficiency virus; IDUs = injecting drug users; PNS = peripheral nervous system.

Table 79.3 Polymorphic neurologic syndromes associated with infections

Syndrome/ disease	Organism	Symptoms, signs, and neurologic findings	CNS	PNS	Cord	Other findings	Risk factors
HIV-associated	HIV-1	*Onset:* Acute, subacute, and chronic *Clinical patterns*: Acute*:* GBS, Bell's palsy, mononeuritis multiplex Subacute/chronic: Vacuolar myelopathy: progressive spasticity; Ascending myelitis (leukomyelitis); Sensory peripheral neuropathy (CIDP)	√	√	√	*Acute* infection: aseptic meningitis, infectious mononucleosis syndrome *Late disease:* concurrent HIV encephalopathy	IVDU, sexual transmission, exposure to contaminated blood or body fluids
Dengue-associated	Dengue virus	*Onset:* acute or postinfectious *Clinical patterns:* Myelitis (transverse), Guillain–Barré syndrome, mono- or poly-neuropathy, brachial neuritis, ADEM, encephalitis	√	√	√	Fever, headache, myalgia, arthralgia, rash, headache, leukopenia, thrombocytopenia, elevated liver transaminases	Mosquito exposure in endemic region
Mycoplasma-associated	*Mycoplasma pneumoniae*	*Onset:* acute *Clinical patterns:* Ascending myelitis (leukomyelitis), polyradiculitis	√	√	√	Commonly associated with encephalitis	Recent upper respiratory infection in child or young adult
Neuro-brucellosis	*Brucella* spp.	*Onset:* Subacute/chronic *Clinical patterns:* Radiculitis, myelitis, CNS palsies	√	√	√	Encephalitis, meningitis, mycotic aneurysm; Leukoclastic vasculitis, thrombocytopenia and splenomegaly in children	Unpasteurized milk products, occupational exposure to livestock and cattle parturition
Neuro-borreliosis	*Borrelia burgdorferi*	*Onset:* Acute and chronic *Clinical patterns:* Acute: Bell's palsy, aseptic meningitis, encephalitis, transverse myelitis Chronic: weakness, paresthesias	√	√	√	*Acute*: Erythema chronicum migrans	Tick-bite Travel or residence in endemic areas
Neurosyphilis	*Treponema pallidum*	*Onset:* Acute and chronic *Clinical patterns:* Acute syphilitic meningitis Chronic asymptomatic Chronic symptomatic (meningovascular, behavioral, tabes dorsalis, myelopathy)	√	√	√	Dementia Gumma (cord/meninges) Uveitis, optic atrophy Deafness	Asymptomatic (abnormal CSF) and symptomatic neurosyphilis occurs after early syphilis. Higher risk with HIV infection with or without standard treatment of primary syphilis
Tuberculosis	*Mycobacterium tuberculosis*	*Clinical patterns:* Meningitis, vasculitis, cord infarction, granulomatous myeloradiculitis, intramedullary tuberculoma, cord compression from vertebral collapse	√		√	Pulmonary disease, meningitis, fever	Travel to or residence in high prevalence region, homelessness, incarceration, institutionalization, contacts with known tuberculosis
Schistosomiasis	*Schistosoma* spp.	*Clinical patterns:* Transverse myelitis, subacute myeloradiculopathy, encephalitis	√		√	Fever, abdominal pain, hepatosplenomegaly	Travel to or residence in endemic region

Table 79.3 *(continued)*

Syndrome/ disease	Organism	Symptoms, signs, and neurologic findings	CNS	PNS	Cord	Other findings	Risk factors
VZV-associated	VZV	*Onset:* Acute *Clinical patterns:* Bell's palsy, Ramsey Hunt syndrome Sensory radiculitis (CNS and PNS) Ascending and transverse myelitis	√	√	√	Dermatomal vesicles Encephalitis Uveitis, corneal ulcer	Immunosuppression (with recrudescent VZV)
Herpes simplex-associated	HSV	*Onset:* Acute and recurrent *Clinical patterns:* HSV-1: Bell's palsy; HSV-2: sacral radiculitis (Elsberg syndrome)	√	√	√	Ascending necrotizing myelitis Mollaret's meningitis	AIDS Primary genital HSV

Abbreviations: ADEM = acute demyelinating encephalomyelitis; CNS = central nervous system; CSF = cerebrospinal fluid; HSV = herpes simplex virus; HIV = human immunodeficiency virus; PNS = peripheral nervous system; VZV = varicella-zoster virus; IVDU = intravenous drug use; GBS = Guillain–Barré syndrome; CIDP = chronic inflammatory demyelinating polyneuropathy.

Table 79.4 Etiology of neuropathic syndromes in HIV infection

Autoimmune/idiopathic
Acute inflammatory demyelinating polyneuropathy (*AIDP – Guillain–Barré syndrome*)
Chronic inflammatory demyelinating polyneuropathy (*CIDP*)
Vasculitis
Bell's palsy
Ataxic dorsal radiculopathy
Mononeuritis multiplex from hepatitis B virus (HBV)-associated cryoglobulinemia
Opportunistic infections
Cryptococcal meningitis: bulbar palsies
Herpesviruses polyradiculopathy, sacral radiculitis, Bell's palsy
Epstein–Barr virus
Cytomegalovirus (CMV)
Varicella-zoster virus (VZV)
Herpes simplex type 1 (HSV-1) type 2 (HSV-2)
Neurosyphilis: polyradiculopathy
Tuberculous meningitis: bulbar palsies
Drug toxicity or nutritional
Antiretroviral nucleoside analogs
Dideoxycytosine (ddC)
Dideoxyinosine (ddI)
Stavudine (d4T)
Niacin analog: isoniazid (INH) without B6
Neurotoxic antibiotics: aminoglycosides, chloramphenicol, metronidazole, nitrofurantoin, polymyxins
Vitamin deficiencies: folate, pyridoxine, B_{12}

may ultimately leave patients wheelchair dependent; the upper extremities are usually not affected. HAM/TSP may be preceded, more commonly in children, by infective dermatitis, a dermatologic condition associated with HTLV-1 and characterized by recurrent erythematous, scaly, and crusted rash of the scalp, face, neck, axilla, and groin. In one series, 47% of children and adolescents with infective dermatitis went on to develop HAM/TSP.

In patients with HAM/TSP, the cerebrospinal fluid (CSF) may demonstrate a lymphocytic pleocytosis, elevated CSF immunoglobulin IgG, and oligoclonal banding, and demonstrable anti-HTLV-1 antibodies. Diagnosis is established clinically in the presence of HTLV-1 seropositivity and characteristic CSF findings. Distinguishing between incidental HTLV-1 infection and patients with true HAM/TSP may be difficult. Recent studies suggest that anti-Gag, anti-Env, and anti-Tax antibodies may help distinguish patients with true HAM/TSP from persons with asymptomatic HTLV-1 infection. No effective antiretroviral or adjunctive therapies have been established to date.

Herpesviruses

All herpesviruses have been implicated in acute transverse myelitis, especially in the setting of immunosuppression. Herpes simplex virus (HSV) types I and II, varicella-zoster virus (VZV), cytomegalovirus (CMV), and Epstein–Barr virus (EBV) have all been associated with a nonspecific myelitis, although ascending necrosis of the cord appears to be most typical. Associated clinical findings of concurrent CMV retinitis, peripheral outer retinal necrosis due to VZV, or vesicular skin lesions characteristic of herpes simplex or VZV are helpful in suggesting the diagnosis.

Patients may have fever and characteristically have rapidly progressive neurologic deficits.

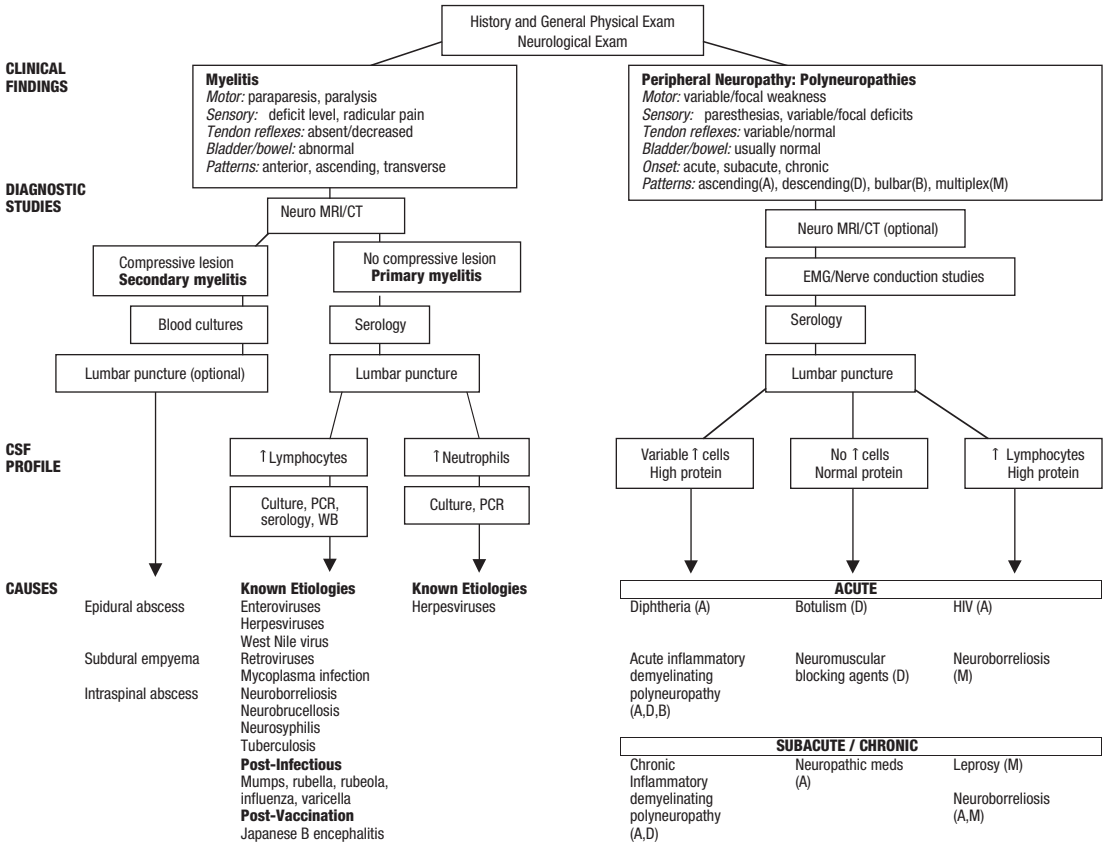

Figure 79.1 Algorithm for clinical and laboratory evaluation of acute myelitis and peripheral neuropathy. Abbreviations: CSF = cerebrospinal fluid; CT = computed tomography; EMG = electromyogram; MRI = magnetic resonance imaging; PCR = polymerase chain reaction; WB = Western blot.

CSF with lymphocytic pleocytosis, elevated protein, and normal glucose is typical. Early empiric therapy with intravenous acyclovir, ganciclovir, or foscarnet may preserve cord function pending definitive diagnosis in immunocompromised patients presenting with acute transverse myelitis of unknown origin. Valacyclovir and valganciclovir are attractive agents in suppressing herpes simplex and CMV myelitis, respectively, in immunosuppressed individuals. Oral ganciclovir is ineffective because of limited bioavailability.

Macacine herpesvirus 1, formerly known as *Cercopithecine herpesvirus* and commonly known as herpes B virus or *Herpesvirus simiae*, is a naturally occurring virus among primates of the genus *Macaca*. It can cause fatal encephalitis in humans with associated ascending myelitis following a bite, cage scratch, or other exposure. Patients may develop vesicular lesions at the site of the bite before developing neurologic manifestations. Human B-virus infections are diagnosed by viral culture and serology, which must be performed in certified laboratories. The Centers for Disease Control and Prevention (CDC) should be consulted in cases of suspected human B-virus infection. In addition to thorough washing, prophylactic oral acyclovir or valacyclovir should be considered after an at-risk exposure. Intravenous acyclovir or ganciclovir should be considered with evidence of any disease (e.g., vesicles), and intravenous ganciclovir used in cases with central nervous system (CNS) symptoms.

Enteroviruses

The enteroviruses are well-known causes of infectious myelitis, of which poliovirus has been the most historically significant. Poliovirus infection may present with fever, meningismus, and muscle spasms followed by acute flaccid paralysis from infection of anterior horn cells. Largely due to effective vaccination programs, poliovirus is now unusual, but sporadic cases of myelitis due to other enteroviruses – such as Coxsackie

A and B, echovirus, and enteroviruses 70 and 71 – still occur. Myelitis due to nonpolio enteroviruses, generally less severe than that due to poliovirus, causes weakness rather than paralysis. Enterovirus 71 – the causative agent of hand-foot-and-mouth disease – is an important exception and may mimic poliovirus in severity. In some cases of viral myelitis, it may be difficult to distinguish between postinfectious, immune-mediated cord injury and direct viral invasion. Detection of virus in CSF is supportive of direct viral invasion. Enteroviruses can be recovered from CSF as well as from blood, pharynx, and stool. The most reliable diagnostic test is the CSF enteroviral polymerase chain reaction (PCR).

West Nile virus

Since the appearance of West Nile virus (WNV) in the United States in 1999, more than 30 000 WNV disease cases have been reported to the CDC. Although most WNV infection is asymptomatic or self-limited, neuroinvasive disease (NID) also occurs. Acute flaccid paralysis occurred in 4% of cases reported to the CDC in 2011 and is one of the most serious presentations of NID and mimics poliomyelitis with injury to spinal cord anterior horn cells. Acute flaccid paralysis commonly accompanies WNV encephalitis, appears abruptly, and often results in asymmetric lower extremity weakness.

Areflexia, loss of bladder and bowel function, and signs of denervation may develop. CSF typically demonstrates pleocytosis; diagnosis is aided by serologic and CSF testing for WNV IgM, or serum or CSF PCR. Although no agents are currently licensed to treat WNV disease, emerging case reports and animal studies suggest a potential benefit of intravenous immunoglobulins with high WNV antibody titers; this practice warrants further investigation.

Dengue

Neurologic complications of dengue are increasingly recognized, with recent estimates that neurologic disease may complicate 1% to 5% of infections. An array of neurologic manifestations has been encountered, including meningitis, encephalitis, Guillain–Barré syndrome (GBS), mono- and poly-neuropathies, ADEM, and myelitis. Pathogenesis is likely multifactorial and varies for each clinical syndrome encountered. It seems likely that direct neurologic invasion and autoimmune reactions each play a role in myelitis. CSF may demonstrate pleocytosis and elevated protein. Diagnosis is supported by serologic studies and further aided by CSF antibody testing or PCR, though CSF antibody testing is not very sensitive. Care is supportive. Many patients with neurologic complications of dengue infection recover, though perhaps a quarter of patients may have residual deficits.

HIV

Vacuolar myelopathy is a diagnosis of exclusion. Although of distinctive neuropathology, it often coexists with the acquired immunodeficiency syndrome (AIDS)-associated dementia complex, also known as HIV encephalopathy or encephalitis. Vacuolar myelopathy was found in up to 50% of AIDS patients undergoing autopsy before the highly active antiretroviral therapy (HAART) era. In severe cases patients develop spastic paraparesis of the lower extremities with or without involvement of the arms, mimicking HTLV-1 myelopathy. The weakness, which may be asymmetric, evolves over weeks. Coexisting neuropathy is often present. A discrete sensory level is unusual. Sphincter dysfunction occurs late in the course of the disease.

Other viral causes of myelitis

Other viruses associated with myelitis include Japanese encephalitis virus, tick-borne encephalitis virus, and chikungunya virus. Acute flaccid paralysis may occur in rabies infections before proceeding to fatal encephalitis.

Syphilis

Although there are many manifestations of neurosyphilis, four major types of spinal cord disease are associated with *Treponema pallidum* infection: tabes dorsalis, syphilitic meningomyelitis, spinal vascular syphilis with infarction of the (most commonly anterior) spinal arteries, and gummas of the meninges and cord. Because of its varied presentations, syphilis should be considered in the differential diagnosis of nearly all diseases of the spinal cord. The serum rapid plasma reagin (RPR) titer is usually above 1:32 in neurosyphilis, and the CSF usually shows a lymphocytic pleocytosis, elevated protein, and normal glucose; HIV infection with or without HAART may impact these parameters. The CSF Venereal Disease Research Laboratory (VDRL) test is specific but generally insensitive. CSF fluorescent

treponemal antibody test and *T. pallidum* PCR may also aid diagnosis. Steroids may be added to intravenous penicillin to prevent cord edema, ischemia, or Jarisch–Herxheimer reaction associated with treatment.

Mycoplasma pneumoniae

CNS complications of *M. pneumoniae* infection are probably the most frequent extrapulmonary manifestation of infection. Although encephalitis is the most common neurologic complication, meningitis, polyradiculitis, ADEM, and transverse myelitis also occur. The exact pathogenesis of CNS disease is unknown, but it may be secondary to direct invasion, elaboration of neurotoxins, autoimmune complexes, molecular mimicry, or vasculitis. A recent respiratory tract infection, especially in a child or young adult, should suggest the diagnosis. Diagnosis can be confirmed with positive CSF *M. pneumoniae* PCR or by retrospectively observing a 4-fold rise in antibody titers. If active infection is present, antibiotic therapy may be effective. Tetracycline penetrates the CNS more effectively than macrolides but is contraindicated in young children. Steroids, plasmapheresis, and intravenous immunoglobulin (IVIG) have also been advocated but remain controversial.

Brucellosis

Approximately 2% to 5% of patients with brucellosis have neurologic complications, though a recent study of hospitalized patients in an endemic country with brucellosis confirmed neurobrucellosis in 37.5% of patients with neurologic symptoms. Although meningitis with cranial nerve palsies and vasculitis are the most common neurologic manifestations, direct involvement of the brain or cord can result in encephalitis or myelitis, respectively. Myelopathy typically involves the corticospinal tracts and produces a pure upper motor neuron syndrome without sensory findings. Secondary myelitis can occur from granulomatous spondylitis and epidural abscess.

Radiculopathy due to chronic inflammation of intrathecal nerve roots complicates neurobrucellosis in an eighth of patients. CSF usually reveals a lymphocytic pleocytosis, elevated protein, and hypoglycorrhachia. CSF cultures are positive in fewer than 50% of cases. Cultures of blood and tissue fluids may become positive in 2 to 4 days with modern automated liquid culture systems, particularly when specimens are first processed to release intracellular organisms. PCR methods are reportedly more sensitive than culture. Serum tube agglutination (TA) testing can support a diagnosis of brucellosis. CSF TA testing can help confirm a diagnosis of neurobrucellosis; however, there is no commonly agreed upon titer cut-point for CSF TA titers. Treatment of neurobrucellosis requires multidrug therapy, though there is no consensus for an optimal regimen or duration. Surgical exploration and decompression may be warranted for symptomatic epidural abscess. Adjunctive steroids early in meningitis may reduce complications from vasculitis.

Tuberculosis

While meningitis is the most common neurologic manifestation of tuberculosis, myelopathy may be seen as well. Myelopathy may occur secondary to spinal cord or nerve root compression from Pott's disease, to compression from epidural or intramedullary tuberculomas, to vasculitis with cord infarction, or to granulomatous myeloradiculitis from hematogenous seeding of the CNS. Necrotizing tuberculous granulomas may directly affect spinal arteries. Vasculitis can lead to cord infarction. Most patients with tuberculous myelitis have concurrent meningitis, but coincident pulmonary tuberculosis is less common. Tuberculosis diagnosis and treatment are addressed in detail elsewhere.

Schistosomiasis

Neuroschistosomiasis should be considered in the differential diagnosis of acute myelopathy in regions where *Schistosoma* species are prevalent. A Brazilian study found that 6% of patients with nontraumatic acute myelopathy had spinal schistosomiasis. Half of patients admitted to a Malawian spinal cord rehabilitation center had spinal schistosomiasis.

Myelitis is most common with *S. mansoni* and *S. haematobium* infection. Schistosoma ova spread hematogenously and invade the CNS where the host inflammatory response, including granuloma formation, can lead to acute myelopathy. The lower thoracic and lumbar cords are most commonly affected. Patients may present with lower extremity weakness, cauda equina syndrome, or lumbar or radicular pain. Spinal artery infarction may be found. Diagnosis is challenging; schistosomal ova are found in stool or urine

in fewer than half of cases of neuroschistosomiasis. CSF findings may be nonspecific, but may show eosinophils and elevated protein levels. Visualization of schistosomal forms in biopsy specimens provides definitive diagnosis. Treatment is with steroids, to reduce inflammatory response, followed by praziquantel, though optimal treatment doses and duration are not established.

Toxocara spp.

Toxocara canis and *T. catis* are round worms and the cause of visceral larva migrans and have occasionally been reported as a cause of myelitis. Patients present with typical symptoms of myelitis; lower extremity weakness is most common. MRI findings often reveal a single inflammatory lesion. Symptoms generally improve after albendazole therapy.

Other parasitic diseases found to cause spinal cord disease include gnathostomiasis, *Taenia solium*, *Toxoplasma gondii*, and *Echinococcus granulosus*.

Fungal diseases

Fungal infections rarely cause spinal cord disease, and present most commonly among immunosuppressed persons. Secondary myelopathy from epidural abscess, granuloma, or vertebral compression fracture is most commonly from *Aspergillus*, *Cryptococcus*, or *Candida* species. *Blastomyces* and *Coccidioides* also causes spinal and paraspinal disease. Fungal myelopathy may result from direct iatrogenic inoculation; cauda equina syndrome was noted in 17% of patients in an outbreak of *Exserohilum rostratum* from contaminated glucocorticoid injections. Iatrogenic paraspinal aspergillus infection has also been described.

ACUTE DISSEMINATED ENCEPHALOMYELITIS

While the focus of this chapter thus far has been myelitis, discussion of infectious causes of spinal cord disease should include acute disseminated encephalomyelitis (ADEM) as well. ADEM may be considered as one among a spectrum of similar diseases including transverse myelitis, multiple sclerosis, and neuromyelitis optica. At least three-quarters of cases are associated with antecedent infection or vaccination. While the pathogenesis is not definitively established, it appears that infectious antigens may stimulate myelin-reactive T-cell populations by molecular mimicry. A number of infectious agents have been implicated as precipitants of ADEM, including viruses – influenza, enteroviruses, EBV, CMV, varicella, measles, mumps, rubella, hepatitis A – and bacteria including *M. pneumoniae*, *Borrelia burgdorferi*, leptospira, and β-hemolytic streptococci. Semple rabies vaccine is the most definitively associated vaccine-related trigger; other vaccines believed to be associated with ADEM include live measles vaccine (though measles virus-induced encephalitis occurs about 10 times more frequently than vaccine-related ADEM); Japanese encephalitis; tetanus, diphtheria, pertussis, and hepatitis B vaccines; and vaccinia.

Children are affected more commonly than adults. Presentations are acute, evolving over hours and usually peaking around 4 to 5 days, and exhibit a variety of neurologic findings, including pyramidal and extrapyramidal symptoms, hemiplegia, ataxia, cranial neuropathies, optic neuritis, paresthesias, and altered mental status. Spinal cord involvement occurs in about a quarter of patients. Peripheral nerve involvement such as acute polyradiculopathy is more common among adults, where it is reported in as many as 40% of cases. Fever and systemic symptoms are typically absent, as cases tend to be postinfectious rather than concurrent with infection.

Diagnosis is challenging, in part because of differences in definitions found in the literature. The International Pediatric MS Study Group suggests the following criteria to diagnose (pediatric) ADEM: "a first polyclonal, clinical CNS event with presumed inflammatory demyelinating cause," "encephalopathy that cannot be explained by fever," "no new clinical and MRI findings emerge three months or more after the onset," and "brain MRI is abnormal during the acute (three-month) phase." Spinal cord disease has variable enhancement on MRI but large lesions, most often in the thoracic region, are common. Diagnosis is clinical based on history, symptoms, neuroimaging, and exclusion of other diagnoses; no biomarkers of disease have been found. CSF findings are nonspecific, but a mild lymphocytic pleocytosis and elevated protein may be seen. Though no prospective, randomized trials have been done, most patients are treated with steroids; IVIG and plasmapheresis are generally reserved for refractory or fulminant cases. These treatments should only be considered after effectively excluding acute infections.

NEUROPATHY

As there are many patterns of neuropathy of both infectious and noninfectious etiologies, the approach to the patient with peripheral neuropathy begins with identification of the pattern of illness. The history should focus on the duration of symptoms and their relation to antecedent or comorbid illnesses. An acute onset is highly suggestive of an inflammatory, immunologic, vascular, or toxic cause. Because infectious diseases are known to mediate disease via all of these mechanisms, most neuropathies due to infectious diseases will present acutely or subacutely. Chronic neuropathies of infectious origin, although less common, do occur, particularly Hansen's disease (leprosy) and Lyme borreliosis. In general, an acute onset suggests a more favorable prognosis and should prompt a timely search for the underlying cause to prevent permanent neurologic sequelae. Etiologic clues may be suggested by recent or current systemic illness, such as pharyngitis in diphtheritic neuropathy, *Campylobacter* gastroenteritis in GBS, or epidemiologic exposures such as tick bites or sexual activity. Travel and residence history is also of diagnostic importance in suggesting an entity such as Lyme borreliosis.

The four major anatomic patterns of neuropathy are *mononeuropathy*, *mononeuropathy multiplex*, *polyneuropathy*, and *plexopathy*. Neuropathies are further classified according to the type of functional nerve involvement: *purely motor*, *sensory*, *autonomic*, or *mixed*. In classifying the neuropathy, the physical exam should address the following questions: Does the involvement include more than one functional nerve type? Is involvement symmetric or asymmetric, distal or generalized, ascending or descending? Is there a sensory level? Do motor and sensory deficits overlap, and do they match subjective complaints? Are deep tendon reflexes and other reflexes (e.g., Babinski, genitoanal) normal? Is sphincter function normal? Is there evidence of denervation (e.g., fasciculation, atrophy)? Are there associated skin lesions? Establishing the pattern of illness and rate of onset lets the neuropathic syndrome be identified and points to specific causes. Discussed next are some of the major infectious causes of peripheral neuropathy.

Hansen's disease (leprosy)

Hansen's disease (leprosy) is a chronic mycobacterial infection in which *Mycobacterium leprae* primarily affects the peripheral nervous system and secondarily involves skin and other tissues. *M. leprae* is shed from skin and mucous membranes and while the mode of transmission is not definitively established, appears to be transmitted from person to person by respiratory droplets.

Worldwide, Hansen's disease is one of the most common causes of peripheral neuropathy. Although a rare disease in the United States, new cases are still diagnosed, most frequently in immigrants. Of the ~228 000 cases reported globally to the WHO in 2010, 95% were reported by 17 countries; over half were from India.

Clinical Hansen's disease ranges a broad spectrum resulting from complex interactions between the organism and the patient's immune system. The cardinal manifestations of Hansen's disease are anesthetic skin lesions, palpably enlarged peripheral nerves, and, in lepromatous patients only, visible acid-fast bacilli on skin biopsy or slit skin smear that do not grow in conventional mycobacterial cultures.

Although skin lesions vary in appearance, anesthesia of the involved skin is the characteristic feature in typical Hansen's disease. Lepromatous disease can result in symmetric anesthesia of the colder areas of the body (e.g., pinnae, dorsa of hands and feet), whereas nerve involvement in indeterminate and tuberculoid disease is typically asymmetric.

The peripheral nerves most commonly involved are the facial, ulnar, median, common peroneal, and posterior tibial nerves. Superficial nerves, such as the ulnar and posterior auricular nerves, are accessible to palpation and are often enlarged and tender. Neuropathic injury to the hands and feet is a significant cause of disability; a complete motor and sensory exam should be performed before beginning therapy. Proprioceptive deficits are uncommon but have been described. Where the disease is rare, such as in the United States, skin biopsy of the most active margin should be performed. Specific details about therapy and prevention of neuropathy can be found in Chapter 142, Leprosy.

HIV-associated neuropathies

Neuropathy is the most common neurologic disorder associated with HIV. Many causes of neuropathy have been described in HIV-infected persons (Table 79.4). Predominantly sensory neuropathy is the most common neuropathy seen in AIDS and is one of the most debilitating aspects of advanced HIV infection. Its exact cause is unclear, although pathology studies suggest an

immune complex vasculitic etiology. Patients often note painful paresthesias of the distal extremities, primarily of the soles of the feet. On exam, patients with progressive HIV neuropathy will exhibit a generalized decrease in sensation in the affected areas and atrophy of the intrinsic muscles of the feet. Deep tendon reflexes of the ankles are eventually lost, but patellar reflexes may be exaggerated by coexisting myelopathy. When reflexes are affected, nerve conduction studies are consistent with distal axonal degeneration. Reversible causes of neuropathy should be excluded. Treatment of HIV predominantly sensory neuropathy is generally unsatisfactory.

Herpesvirus-associated peripheral neuropathies: CMV, HSV, VZV, EBV, and B-virus

CMV infection of the peripheral nerves, essentially unknown prior to AIDS, is often associated with active CMV infection in other systems, particularly retinitis. The capacity of CMV to invade both endothelial and Schwann cells accounts for its varied clinical manifestations. Polyradiculopathy, the most dramatic of these syndromes, is caused by CMV more often than by other herpesviruses. It is characterized by subacute ascending motor weakness, areflexia, incontinence or urinary retention, paresthesias, and variable sensory dysfunction. Patients often report pain in the back and legs. Inflammation of lumbar nerve roots, dorsal root ganglia, and spinal cord result in characteristic CSF findings mimicking bacterial meningitis: pleocytosis with white blood cell counts from 5 to more than 3000 with a polymorphonuclear predominance, hypoglycorrhachia, and elevated protein. Enhancement of the cauda equina on MRI has been reported. PCR of CMV viral DNA in the CSF is the diagnostic method of choice.

Herpes simplex type 2 can cause sacral radiculitis (Elsberg syndrome) manifested by urinary retention, constipation, erectile dysfunction, sensory loss in a sacral dermatome, and buttock pain. Lumbar spine MRI may show sacral root edema and enhancement, and the CSF HSV-2 PCR is positive. In AIDS patients, the infection can progress to ascending necrotizing myelitis.

Herpes simplex type 1 causes the majority of Bell's palsy episodes. Steroids combined with antivirals such as acyclovir or valacyclovir improve outcomes. Antivirals should not be given without steroids, as meta-analysis revealed worse outcomes with antivirals alone.

VZV can also cause polyradiculopathy in AIDS patients. VZV classically involves the dorsal root ganglia, but spread of inflammation into the cord can reach anterior horn cells, resulting in pain and paralysis. VZV has also been associated with transverse myelitis and myositis. Zoster-associated disease may occur without a vesicular rash (*Zoster sine herpete*). The diagnosis is established with a positive CSF VZV DNA PCR.

Treponema pallidum-associated neuropathy

CNS syphilis may also present as subacute polyradiculopathy in HIV infection. The CSF contains lymphocytes, and the CSF VDRL test is typically positive.

Mononeuropathy multiplex

Mononeuropathy multiplex is a syndrome of simultaneous or sequential neuropathy of noncontiguous nerve trunks evolving over days to years. Characterized by patchy, asymmetric motor and sensory nerve dysfunction, mononeuropathy multiplex is possibly the result of ischemic injury from viral or other infection of the endothelium of the vasa nervorum and immune complex disease. Mononeuritis multiplex may be seen in HIV infection even before immunosuppression has occurred. Some cases are associated with cryoglobulinemia in persons infected with hepatitis B, in which the course is often benign and may not require specific therapy. Recently, parvovirus B19 has been associated with mononeuritis multiplex; case reports have been described with Q fever as well. Lyme is a common cause of radiculopathy and cranial neuropathies in areas endemic for *B. burgdorferi*. In patients with advanced HIV infection and CD4 counts $\leq$50 mm^3, CMV is the most likely cause.

Inflammatory demyelinating neuropathies

Guillain–Barré syndrome (GBS), a heterogeneous syndrome of demyelinating diseases of peripheral nerves with multiple variants, has well known association with infectious diseases such as EBV, CMV, VZV, HIV, *M. pneumoniae*, psittacosis, Lyme, dengue, and particularly *Campylobacter jejuni*. In over half of patients a mild respiratory or gastrointestinal tract illness precedes the onset of GBS by 1 to 3 weeks. Molecular mimicry and cross-reactive antibodies between infectious agents may play a role in the pathogenesis of some variants.

When an inflammatory demyelinating polyneuropathy persists beyond 8 weeks, or recurs, *chronic inflammatory demyelinating polyneuropathy* (CIDP) is considered. CIDP is associated with multiple predisposing factors, and is also seen in patients infected with HIV. Like GBS, CIDP has multiple variants, but usually presents as weakness with varying degrees of sensory loss. Physical exam reveals proximal muscle weakness. Weakness of the neck flexors is particularly suggestive. As in GBS, CSF albuminocytologic dissociation is common. The presence of leukocytes should raise suspicion of HIV infection. Electrodiagnostic studies and neuroimaging studies are also helpful. Multiple diagnostic criteria, including the Koski criteria and criteria from the European Federation of Neurological Societies and the Peripheral Nerve Society (EFNS/PNS), have been published.

Plasmapheresis is effective short term but deterioration after stopping plasmapheresis is common. Glucocorticosteroids are commonly used, although most supporting evidence is from nonrandomized trials. IVIG is superior to placebo in improving disability, and comparable to plasmapheresis and steroids. Immunomodulatory drugs such as azathioprine and methotrexate have been used; additional research is needed to determine whether these may provide significant benefit.

Lyme neuroborreliosis

Borrelia burgdorferi infection can result in acute and chronic peripheral neuropathies. Acute disseminated disease is usually characterized by peripheral and/or cranial neuropathies and meningoencephalitis, usually 4 to 12 weeks after a tick bite. Plexitis, mononeuropathy multiplex, and myelitis also occur with acute infection. Facial palsies occurred in 8% of cases reported to the CDC from 2003 to 2005, and radiculopathy in 3%. In endemic areas, facial palsy with a history of tick bite is sufficient to warrant empiric therapy. Peripheral nerve involvement usually presents asymmetrically as motor, sensory, or mixed radiculoneuropathy. Presentation may vary by borrelial species; meningoradiculitis and radicular pain (Bannwarth's syndrome) is more common in Europe where multiple borrelial species are found and associated most frequently with *B. garinii*. Long-standing, untreated Lyme borreliosis can cause intermittent distal paresthesias and radicular pain. Physical examination may be normal, but nerve conduction studies demonstrate axonal neuropathy. Diagnosis and specific antibiotic therapy are discussed in Chapter 164, Lyme disease.

Neuropathies due to bacterial toxins

DIPHTHERIA

Diphtheria is rare in the United States but is still seen in unimmunized children and in adults with waning immunity. All adults are advised to have a diphtheria booster vaccine every 10 years (in combination with tetanus with or without acellular pertussis); travelers to areas with diphtheria outbreaks or endemic diphtheria are advised to either have completed a primary immunization series or received a booster dose within the last 10 years.

Neurological, cardiac, and renal complications of diphtheria are due to its potent toxin, which acts on elongation factor, a protein critical for mammalian protein synthesis. The toxin causes noninflammatory demyelination of cranial and peripheral nerves through its toxic effect on Schwann cells.

In upper respiratory tract diphtheria, locally produced toxin causes paralysis of the pharyngeal and laryngeal muscles. The patient may speak with a nasal voice and report dysphagia and nasal regurgitation. As disease progresses, within days the trigeminal, facial, vagal, and hypoglossal nerves are affected ("*bulbar phase*"), and loss of ocular accommodation is followed in 1 to 2 months by a generalized sensorimotor polyneuropathy ("*systemic phase*"), frequently complicated by myocarditis and injury to other organs.

BOTULISM

Clostridium botulinum is a ubiquitous, spore-forming, anaerobic gram-positive rod that lives in soil and aquatic habitats. It produces a potent neurotoxin, termed BoNT, capable of binding irreversibly and blocking acetylcholine release at the neuromuscular junction.

Manifestations of clinical botulism include (1) *infant botulism* in babies between 1 and 6 months of age occurring after ingestion of *C. botulinum* spores and the most commonly encountered form; (2) *adult infectious botulism* or *adult intestinal toxemic botulism*, also caused by ingestion of spores; (3) *foodborne botulism*, involving ingestion of BoNT and often occurring as small foodborne outbreaks; (4) *wound botulism*, from proliferation of *C. botulinum* in a contaminated anaerobic wound, or paranasal sinus in cocaine snorters; (5) *inadvertent botulism*, a complication of

therapeutic uses of purified botulinus toxin; and (6) *bioterrorism*, where BoNT is dispersed by aerosol or contaminates food and water supplies.

Neuromuscular symptoms of botulism vary with patient age, by whether exposure is from preformed toxin ingestion or from active toxin production in the gut or a wound, and by toxin type. Infants first develop constipation, then hypotonia ("floppy baby syndrome") and ophthalmoplegia. Clinical features include symmetrical cranial neuropathies, autonomic dysfunction, symmetrical "descending weakness" – eye and facial muscles are most sensitive to neuromuscular blockade – in a proximal to distal pattern, and respiratory dysfunction from respiratory muscle paralysis or airway obstruction. Sensory exam is always normal. Wound botulism has the same clinical pattern as foodborne botulism, but may be complicated by concurrent bacterial wound infections. In cases of foodborne exposure the time to onset of disease is usually 12 to 36 hours. Neurologic effects are dose-dependent; people with a common source exposure exhibit differing degrees of neurologic findings depending on the amount of prototoxin ingested. Toxin type also affects the rate and extent of progression of symptoms. Type E has the shortest incubation period, but type A produces more severe illness and requires intubation more frequently (67%).

TETANUS

Tetanus is caused by the toxic action of tetanospasmin, or tetanus neurotoxin (TeNT), produced by the anaerobic spore-forming rod *Clostridium tetani,* which is widely distributed in nature. *C. tetani* is usually introduced into tissues as a spore. Disease only develops under anaerobic conditions, which permit growth of the toxin-producing vegetative form. Tetanus toxin is the next most potent toxin after botulinum toxin. TeNT is a protein with three domains endowed with different functions: neurospecific binding, membrane translocation, and proteolysis for specific components of the neuroexocytosis apparatus. While tetanus neurotoxin acts mainly at CNS synapses, the seven BoNT subtypes act peripherally.

Despite availability of effective and inexpensive tetanus toxoid vaccines, cases of tetanus continue to occur in the United States with fatality rates up to 25%. Primary prevention of tetanus is accomplished by active immunization with vaccines. All adults should complete a three-dose primary vaccination schedule and a tetanus booster every 10 years thereafter. Pregnant women should receive Tdap between weeks 27 and 36 of each pregnancy. *Secondary prevention* refers to post-wound tetanus prophylaxis, and varies with vaccine history and type of wound. All wound patients should receive Td if they have received $\leq$3 tetanus-containing vaccines, if vaccination history is uncertain, if >10 years has elapsed since the last booster in a patient with a minor wound or >5 years since the last booster in a patient with a major wound. Patients should also receive tetanus immunoglobulin if wounds are contaminated with feces, soil, or saliva, or if they have wounds from punctures, avulsions, projectiles, crushing, burns, or frostbite.

The "incubation period" is the time from inoculation to symptom onset, and reflects the quantity of toxin released and distance traveled to the CNS. The "period of onset" – the time between the first symptom and start of spasms – reflects rate of progression of neurologic disease and is the most important prognostic factor for generalized tetanus. Diagnosis is clinical and confirmed by characteristic neurophysiologic findings and absence of serum antitetanus antibody. CSF is normal. Gram stain and anaerobic cultures of the wound may or may not reveal the organism.

There are three clinical presentations of tetanus: (1) local tetanus with muscular contraction at the site of injury, which may persist or progress to the generalized form; (2) cephalic tetanus affecting cranial nerves, mostly the VIIth pair; and (3) generalized tetanus with lockjaw, reflex spasms provoked by external stimuli, opisthotonos, and risus sardonicus. The patient is conscious during spasms and experiences intense pain. Glottal or laryngeal spasm and urinary retention may occur.

The spastic paralysis induced by tetanus toxin is due to the blockade of neurotransmitter release from spinal inhibitory interneurons. When inhibitory signals to motor neurons are blocked, uninhibited motor nerve transmissions continue, resulting in prolonged muscle spasms that can persist for weeks. Autonomic instability also occurs, including labile hypertension, cardiac tachyarrythmias, peripheral vasoconstriction, and profuse sweating. Neuronal cell death may occur from unopposed excitation.

Acute treatment has four components: (1) local wound debridement and systemic antibiotics; (2) systemic (intramuscular) administration of human antitoxin; (3) control of spasms, with associated intensive care support, sedation

with benzodiazepines, and neuromuscular blockade when necessary; and (4) α- and β-adrenergic blockade to prevent secondary autonomic hyperactivity. Details are provided elsewhere. For tetanus survivors, prevention of future risk requires a primary vaccination series for active immunization after the completion of acute therapy.

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80. Reye syndrome

Debra L. Weiner

BACKGROUND

Reye syndrome is an acute noninflammatory encephalopathy with fatty degenerative liver failure. Decrease in aspirin use in children, in response to its association with Reye syndrome, and the identification of medications, toxins, and inborn errors of metabolism (IEMs) that present with Reye-like syndrome manifestations have made the diagnosis of Reye syndrome exceedingly rare.

While recognizing the rarity of Reye syndrome, the diagnosis should be considered in any child with vomiting, altered mental status, and classic laboratory findings, but must be a diagnosis of exclusion (Table 80.1). Early recognition and treatment of Reye and Reye-like syndromes, including possible IEM, is essential to prevent death and optimize the potential for recovery without neurologic impairment.

CDC DIAGNOSTIC CRITERIA

Table 80.1 Diagnostic criteria

- Acute noninflammatory encephalopathy with altered level of consciousness
- Hepatic dysfunction, liver biopsy fatty metamorphosis without inflammation or necrosis, or $\geq$ 3-fold increase in ALT, AST or ammonia
- No other explanation for cerebral edema or hepatic abnormality
- Cerebrospinal fluid white blood cell count $\leq 8/mm^3$, usually lymphocytes. Opening pressure may be elevated particularly in stages 4, 5 but is usually normal
- Brain biopsy-cerebral edema without inflammation or necrosis

PATHOPHYSIOLOGY

Reye syndrome appears to involve mitochondrial injury resulting in inhibition of oxidative phosphorylation and fatty-acid β-oxidation usually in a virus-infected, sensitized host, most commonly with recent upper respiratory tract illness, chickenpox, or diarrheal illness, in association with exposure to mitochondrial toxins, most often salicylates.

Histologic changes include cytoplasmic fatty vacuolization of hepatocytes, astrocyte edema and loss of neurons in the brain, and edema and fatty degeneration of the proximal lobules in the kidneys. Hepatic mitochondrial dysfunction results in hyperammonemia, thought to induce astrocyte edema, which causes cerebral edema and increased intracranial pressure (ICP).

ETIOLOGY

Pathogens

Influenza A and B, and varicella-zoster are the pathogens most commonly associated with Reye syndrome. Other pathogens include parainfluenza, adenovirus, coxsackie, herpes, rubella, measles, cytomegalovirus, Epstein–Barr, HIV, retrovirus, hepatis A and B, mycoplasma, chlamydia, pertussis, shigella, salmonella, and poliomyelitis. Reye syndrome can occur after vaccination with live viral vaccines.

Salicylates

Epidemiologic studies have demonstrated association of Reye syndrome with salicylates, particularly aspirin. More than 80% of patients with Reye syndrome had taken aspirin in the past 3 weeks, and recommendations that children not be treated with salicylates led to an immediate and dramatic decrease in the incidence of Reye syndrome.

Other medications

Valproate, warfarin, zidovudine, didanosine, tetracycline, and some neoplastic drugs have been associated with Reye or Reye-like syndrome.

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Nonsteroidal anti-inflammatory drugs, including sodium diclofenac and mephenamic, are thought to produce or worsen Reye syndrome. Association with acetaminophen and antiemetics was postulated but not substantiated.

Toxins

Insecticides; herbicides; aflatoxins; isopropyl alcohol; paint; paint thinner; margosa (neem) oil; hepatotoxic mushrooms; hypoglycin in ackee fruit (Jamaican vomiting sickness); and herbal medications with atractyloside, a diterpenoid glycoside in extracts of the tuber of *Callilepis laureola* (impila poisoning), and *Bacillus cereus* cereulide toxin have been reported to cause Reye syndrome.

IEMs

Reye-like syndrome is caused by fatty-acid oxidation defects, particularly medium-(MCAD) and long-chain acyl dehydrogenase deficiency (LCAD), urea-cycle defects, amino and organic acidopathies, primary carnitine deficiency, and disorders of carbohydrate metabolism.

EPIDEMIOLOGY

In the United States, cases reported to the Centers for Disease Control (CDC) peaked at 555 in 1979–1980. Between 1987 and 1993, a maximum of 36 cases were reported annually, and since 1994, ≤2 cases annually. Although CDC reporting is no longer mandated, reporting is still required by many local/state health boards.

PRESENTATION

Abrupt onset of pernicious vomiting occurs 12 hours to 3 weeks (mean, 3 days) after symptoms of viral illness have resolved. Diarrhea and hyperventilation may be the first signs in children < 2 years old. Neurologic symptoms usually occur 24 to 48 hours after the onset of vomiting, beginning with lethargy and progressing to irritability, agitation, delirium, seizures, and coma.

Exam findings may include dehydration, hepatomegaly, lethargy, encephalopathy, obtundation, coma, seizures, and paralysis. Notably patients are afebrile with minimal or absent jaundice.

Findings may also include acute respiratory failure, aspiration pneumonia, cardiac arrhythmia, myocardial infarction, cardiovascular collapse, gastrointestinal bleeding, and pancreatitis.

Table 80.2 Clinical staging

- Stage 0 – Alert, abnormal history and laboratory findings c/w Reye syndrome, no clinical manifestations
- Stage 1 – Vomiting, sleepiness, lethargy
- Stage 2 – Restlessness, irritability, combativeness, disorientation, delirium, tachycardia, hyperventilation, dilated pupils with sluggish response, hyperreflexia, +Babinski sign, appropriate response to noxious stimuli
- Stage 3 – Obtunded, comatose, decorticate rigidity, inappropriate response to noxious stimuli
- Stage 4 – Deep coma, decerebrate rigidity, fixed and dilated pupils, loss of oculovestibular reflexes, and dysconjugate gaze with caloric stimulation
- Stage 5 – Seizures, flaccid paralysis, absent deep tendon reflexes, no pupillary response, respiratory arrest
- Stage 6 – Patients who cannot be classified due to treatment with medication that alters level of consciousness

CLINICAL STAGING

Lovejoy described five clinical stages of Reye syndrome 1–5. Hurwitz added a nonclinical stage (i.e., stage 0). The CDC added stage 6 for patients who cannot be classified due to treatment. Stage 0 does not meet the CDC case definition, because it does not meet the clinical criteria (Table 80.2).

LABORATORY ABNORMALITIES

Serum bicarbonate is decreased secondary to vomiting. Blood urea nitrogen (BUN) and creatinine are elevated. Anion gap and venous pH may reveal metabolic acidosis.

Patients may develop syndrome of inappropriate secretion of antidiuretic hormone, or diabetes insipidus.

Glucose, while usually normal, may be low, particularly during stage 5 and in children younger than age 1 year.

Ammonia as high as 1.5 times normal 24 to 48 hours after onset of mental status changes is the most common laboratory abnormality. Ammonia tends to peak 56 to 60 hours after onset of symptoms and may return to normal in stages 4 and 5.

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increase to three times normal but may return to normal by stages 4 and 5. Bilirubin is >2 mg/dL, but usually <3 mg/dL, in 10% to 15% of patients. If the direct bilirubin is >15% or total exceeds 3 mg/dL, consider other diagnoses.

Lipase and amylase are elevated.

Table 80.3 Treatment

Airway, breathing	**Oxygen, endotracheal intubation** as required to maintain airway, control ventilation, and prevent increased ICP. Intubation using rapid-sequence agents that minimize increasing ICP. Nasogastric tube to decompress the abdomen	Continuous cardiorespiratory monitoring of vital signs, oxygen saturation, end-tidal carbon dioxide wave capnography, blood gas
Circulation	Consider restricting fluids to 2/3rds maintenance. **Crystalloids** to restore volume. **Blood products** to correct hematologic deficiencies	Overhydration may precipitate cerebral edema. Dehydration may compromise cardiovascular volume and reduce cerebral perfusion. Goal is normal urine output. Albumin is controversial
Electrolyte derangements	**Sodium, potassium** based on specific abnormalities and/or to prevent abnormalities	If sodium bicarbonate given for acidosis and/or sodium benzoate, sodium phenylacetate for hyperammonemia, fluids may need to be adjusted to account for high sodium loads
Hypoglycemia	**Dextrose** 25%, 1–2 mL/kg IV followed by D10–15 as needed to maintain glucose 100–125 mg/dL	Check glucose, particularly if age <1 year and/or has altered mental status
Acidosis	**Sodium bicarbonate** to correct acidosis is controversial due to potential paradoxical CSF acidosis. For pH < 7.0–7.2, consider 0.5–2 mEq/kg/h to correct pH to 7.25–7.3	Data regarding pH for which bicarbonate should be administered and appropriate dosage are lacking. Avoid rapid correction/overcorrection
Hyperammonemia	**Sodium phenylacetate–sodium benzoate** (Ammonul) **Hemodialysis** should be considered for ammonia > 500–600 μg/dL and for patients whose condition fails to respond to initial course of sodium phenylacetate, sodium benzoate	FDA approved for treatment of hyperammonemia due to urea-cycle defects. Available only from Ucyclyd Pharma, Inc (8125 N. Hayden Road, Scottsdale, AZ 85258; 24-hour phone number USA, Canada, 888–829–2593)
Nausea, vomiting	**Ondansetron** 1–2 mg IV q8h prn vomiting. Give with sodium phenylacetate, sodium benzoate to prevent vomiting. Consider **antacids** for gastrointestinal protection	Prevent vomiting to avoid increasing ICP
Increased intracranial pressure	**Head** midline, head of bed 30° **Ventilation** to maintain **PCO_2 normal** range 35–40 mm Hg Avoid overhydration by restoring fluid deficit with **isotonic fluids** rather than hypotonic fluids, **restrict fluid** to volume necessary to maintain normal urine output, administer **furosemide** 1 mg/kg q4–6h prn fluid overload Prevent increased cerebral metabolic demand, blood flow: **Antipyretic** for fever to prevent the increased cerebral metabolism and blood flow from hyperpyrexia. **Analgesia/sedation** to alleviate agitation and/or perform for painful interventions. **Paralytic** agents to control shivering. **Barbiturate coma, hypothermia** controversial For life-threatening ICP, **mannitol** 20% solution, dose 0.25–0.5 g/kg IV infused over 10–20 minutes up to every 6–8 hours or **hypertonic saline** 3%, dose 3–5 mL/kg over 3–30 minutes	
Seizures	**Phenytoin** 10–20 mg/kg IV loading dose, followed by 5 mg/kg/d IV divided q6h or fosphenytoin as 10–20 mg/kg phenytoin equivalents	
Coagulopathy	**Fresh frozen plasma** (FFP) 10–15 mL/kg q12–24h, **cryoprecipitate** 10 mL/kg q6h, **platelets, vitamin K** 1–10 mg IV, **and/or exchange transfusion. Platelets** should be administered to restore count to >50 000/mm^3 prior to invasive procedures	FFP rapid correction, volume expansion if active bleeding or invasive procedures are required. If fibrinogen <100 mg/dL, consider cryoprecipitate instead of FFP because it has a higher concentration of fibrinogen. Consider vitamin K instead of FFP or cryoprecipitate if correction is not emergent. Exchange transfusion is rarely required

Lactic dehydrogenase (LDH) may be high or low.

Prothrombin time (PT) and activated partial thromboplastin time (aPTT) are prolonged >1.5-fold in over 50% of patients. Levels of factors I (fibrinogen), II, VII, IX, and X may be low because of the disruption of synthetic activities in the liver. Consumption may contribute to low levels of coagulation factors. Platelet counts are usually normal.

Free fatty acids and amino acids (e.g., glutamine, alanine, and lysine) may be elevated.

Urine specific gravity is increased. Eighty percent have ketonuria.

Cerebral spinal fluid white blood cell count, by disease definition, does not exceed 8/mm^3. Opening pressure is usually normal but may be elevated, particularly in stages 3–5.

Brain computed tomography (CT) may reveal cerebral edema, but is usually normal.

Electroencephalography (EEG) may reveal slow-wave activity in early stages and flattened waves in advanced stages.

These derangements are not specific for Reye syndrome and may suggest other etiologies that should be considered.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes meningitis, encephalitis, intracranial bleed, sepsis, gastroenteritis, hepatitis, intussusception with obtundation, adverse drug reactions, toxins, and IEM.

IEM is suggested by age <1 year, recurrence of symptoms, precipitating factors including prolonged fasting and changes in diet, decompensation out of proportion to intercurrent illnesses, failure to thrive, neurologic abnormalities, and family members with similar symptoms and/or unexplained neonatal/infant deaths.

TREATMENT

Early recognition, careful monitoring, and aggressive management of possible Reye syndrome, as well as possible IEM, are critical. Support of airway, breathing, circulation, minimizing metabolic demands, correction of metabolic derangements and coagulopathy, ammonia detoxification, and prevention/treatment of increased ICP are the mainstays of treatment (Table 80.3). Reye syndrome has been successfully treated with liver transplant.

Place central venous and/or arterial lines to monitor hemodynamic status, Foley catheter to monitor urine output. Use ECG to monitor cardiac function and EEG to monitor seizure activity.

PROGNOSIS

Mortality has decreased from 50% to less than 20% as a result of early diagnosis, recognition of mild cases, and aggressive therapy, as well as appropriate diagnosis and disease-specific treatment of Reye-like syndromes, including IEMs. Death is usually due to cerebral edema or increased ICP, but may be due to myocardial dysfunction, cardiovascular collapse, respiratory failure, gastrointestinal bleeding, renal failure, or sepsis.

Patients who survive may recover completely. US data indicate full recovery in 62% of patients with known outcome. Indicators of poor prognosis are:

- Age <5 years (death 42.8% vs. 24.2%; relative risk 1.8, 95% CI 1.5–2.1)
- Rapid progression from stage 1 to 3 and/or presentation stage 4 or 5. Meaningful survival beyond stage 3 unlikely. Full recovery possible stages 0–2
- Central venous pressure (CVP) <6 mm Hg
- Ammonia >45 μg/dL (26 μmol/L) (death 28.6% vs. 8.4%; relative risk 3.4, 95% CI 1.9–6.2). In survivors, higher levels of ammonia are associated with increased likelihood of neurologic sequelae
- Serum glucose <60 mg/dL
- Hypoproteinemia
- Muscle involvement
- Antecedent diarrheal illness.

PREVENTION

Salicylates should be avoided in children. Those with a condition for which salicylates are a mainstay of therapy (e.g., Kawasaki disease) should discontinue salicylate at first signs/symptoms of Reye syndrome.

Influenza vaccine is recommended by the CDC for all children >6 months of age.

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81. Progressive multifocal leukoencephalopathy

Joshua J. Chalkley and Joseph R. Berger

INTRODUCTION

In their seminal report in 1958, Astrom, Mancall, and Richardson described a progressive neurologic syndrome with a characteristic triad of neuropathologic findings, namely, demyelination, giant astrocytes, and oligodendrocytes with abnormal nuclei. They named the disorder progressive multifocal leukoencephalopathy (PML). The viral etiology of this neurologic disease was not determined until later. Until the advent of the acquired immunodeficiency syndrome (AIDS) pandemic, PML remained a vanishingly rare disorder seen almost exclusively in individuals with underlying immunosuppressive disorders. Prior to the advent of highly active antiretroviral therapy (HAART), PML occurred in approximately 1 in 20 of all human immunodeficiency virus (HIV)-infected persons in developed countries. Although the incidence of AIDS-associated PML appears to have declined since the availability of HAART, it has not declined to the extent observed with other opportunistic infections (Sacktor 2002). Currently, AIDS has been estimated to be the predisposing disorder for about 90% of all PML cases. More recently, monoclonal antibodies, such as natalizumab, an α4 β1 integrin inhibitor, and rituximab, a chimeric monoclonal antibody directed against CD20 receptors on B cells, and other immune-altering pharmacologic agents, such as mycophenolate mofetil, have been associated with PML and carry US Food and Drug Administration (FDA) mandated "black box" warnings of this risk.

JC VIRUS AND THE PATHOGENESIS OF PML

In 1965, Zu Rhein and Chou identified viral particles in glial nuclei resembling papovavirus. Subsequently, Padgett isolated polyomavirus from PML brain in glial cell cultures. The virus has a simple DNA genome of 5.1 kilobases in a double-stranded, supercoiled form, encapsidated in an icosahedral protein structure measuring 40 to 50 nm in diameter. The virus was named the JC virus (JCV) after the initials of the person from whom it was first isolated. JCJCV DNA encodes for three capsid (VP1, VP2, and VP3) proteins and five regulatory proteins (agnoprotein, t, T, T, T'135, T'136, and T'165); the latter three are derived by alternative splicing of early viral mRNA. To date, all cases of PML have been associated with JCV; although there are rare reports of other polyomaviruses, in particular, BK virus, being associated with PML-like disorder in immunosuppressed individuals.

JCV uses serotonin receptor 5-HT2A linked to sialic acid for binding to the cell surface. It is not unlikely that other receptors that remain yet to be identified also permit JCV binding. Following binding, the virus enters the cell through clathrin- and eps15-dependent pathways, following which it is transported to the endoplasmic reticulum through caveosomes. From there, it enters the nucleus. Nuclear DNA binding proteins that selectively interact with the regulatory region of the genome are critical to the tropism of the virus. JCV is most likely carried in to the brain by white blood cells. Pathologically, the gray–white junction is the most common location for typical PML. Whether the virus enters the brain by itself or in a cell-associated fashion remains unknown. Some investigators have suggested that the B cell plays a fundamental role in genetically modifying JCV as well as assisting the virus in central nervous system (CNS) entry. T lymphocytes, especially JCV-specific cytotoxic CD8+ T lymphocytes, play an important role in controlling CNS infection with JCV. These cytotoxic T lymphocytes (CTLs) correlate with survival and in the appearance of the immune reconstitution inflammatory syndrome (IRIS). Seroepidemiologic studies demonstrate that the virus is ubiquitous. By the age of 20 years, approximately 50% to 70% of the population or more has been exposed to JCV. The mechanism of spread of JCV remains uncertain. The detection of JCV in tonsillar tissue suggests the possibility of a respiratory or oropharyngeal

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route, but studies of the expression of reactivated JCV in saliva and oropharyngeal secretions by polymerase chain reaction (PCR) have not demonstrated its presence in immunologically normal individuals. No acute illness has been consistently identified with primary JCV infection. Following infection, latent virus can be demonstrated in many extraneural sites, including kidneys, lymph nodes, tonsils, intestines, and lung. Urinary excretion of JCV is detected in as many as one-third of all adults. Differences in the virus isolated from the kidney and that from the brain of patients with PML have led to the designation of the former as "archetypal" virus. It has been proposed that the archetype virus is genetically modified in cells of B-cell lineage to a neurotropic form of the virus that subsequently migrates into the brain as cell-associated virus. A number of lines of evidence support the contention that PML is the result of a reactivated latent or persistent non-CNS infection including the demonstration of IgG directed to JCV in all patients, the demonstration of a neurotropic JCV from blood and tissue months to years before the development of PML in a small group of patients, the presence of JCV-specific antibody within 6 months of the development of PML in a large number of natalizumab-associated PML cases, and the rarity of the illness in children. It is possible that in rare instances, the disease develops after primary infection. Many controversies surround the pathogenesis of PML. The current proposed hypothesis regarding the development of PML is that it is a stochastic event in which several hurdles must be overcome, including: (1) initial infection; (2) establishment of viral latency; (3) mutation of the archetype strain to one that is neurotropic, perhaps within B cells; (4) re-expression of the virus; (5) entry into the brain with establishment of productive infection of oligodendrocytes; and (6) failure of normal immune mechanisms to suppress and/or clear the virus from the brain.

The numbers of AIDS patients developing PML greatly exceed those of patients developing other illnesses having similar degrees of impaired cell-mediated immunity, suggesting that factors related to HIV infection may be amplifying the frequency of the disease. This unique association may be related to the degree and duration of the immunosuppression; alteration of the blood–brain barrier by HIV infection; the upregulation of endothelial adhesion molecules for JCV-infected B lymphocytes due to cytokines elaborated by HIV-infected macrophages and microglial cells in the brain; the B-cell activation associated with HIV; and transactivation of JCV by the HIV tat protein and HIV-induced chemokines.

There appears to be a vastly increased risk of developing PML in patients that receive natalizumab for the treatment of multiple sclerosis (MS) or inflammatory bowel disease or efalizumab, an LFA antagonist once used in the treatment of psoriasis. It has been proposed that these monoclonal antibodies predispose to PML by preventing the surveillance of the CNS by JCV-specific CTLs and by the release of premature B cells which hypothetically may increase the likelihood of genetic modification of the archetype JCV to the neurotropic form as well as amplifying JCV replication within these cells. The risk of PML with these pharmacologic agents greatly exceeds that of others reported to date which have been associated with PML.

PATHOLOGY

As its name implies, the disease is characterized by multiple sites of demyelination with a distinctive microscopic triad of multifocal myelin and

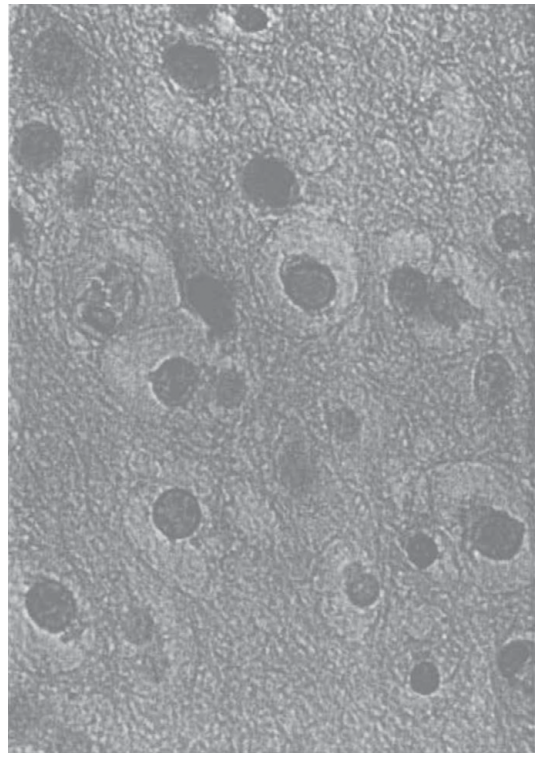

Figure 81.1 An abnormal infected oligodendrocyte with enlarged nuclei.

oligodendroglial cell loss with minimal inflammatory infiltrate; hyperchromatic enlarged oligodendroglial nuclei (Figure 81.1); and enlarged and bizarre appearing astrocytes with irregularly lobulated nuclei. The enlarged oligodendroglia are found mostly at the periphery of the lesion, whereas the atypical astrocytes are generally more centrally located. Ultrastructurally, the viral particles may be detected by electron microscopy. Alternatively, the virus can be detected by immunohistochemical staining or by PCR. The virus appears in three forms: a filamentous form in the nuclei of infected cells and in spherical or paracrystalline forms in either nucleus or cytoplasm. Virions are visualized mostly in oligodendrocytes and rarely in astrocytes. Infection of oligodendrocyte is productive, whereas the astrocyte is nonpermissive for viral replication. JCV has also been associated with other forms of CNS disease including granular cell degeneration of the cerebellum and encephalitis and, on occasion, these pathologies may be observed in association with PML.

EPIDEMIOLOGY

The epidemiology of PML may be divided into several epochs. These include the pre-description era (prior to 1958); the pre-AIDS era (1958–1981); the AIDS era (1981–2005); and the monoclonal antibody era (2005 to present). Prior to 1982, 200 cases of PML had been recorded by the National Center for Health Statistics and an extensive review of the literature published in 1984 was able to find but 230 cases. The overwhelming majority of these cases were the consequence of lymphoid (predominantly B cell) malignancies. Other neoplastic disorders, granulomatous disease, such as tuberculosis and sarcoidosis, and immunosuppressed conditions followed in frequency. In early series, about 5% of patients with PML had no identifiable underlying predisposing disorder, but this is likely to be an overestimate of the true incidence, as illnesses such as idiopathic CD4 lymphopenia had yet to be described. From the beginning of the AIDS pandemic through the introduction of HAART, the numbers of PML deaths has increased dramatically. From 1981 to 1990, 0.73% of AIDS deaths reported to the Centers for Disease Control and Prevention were associated with PML. However, most series suggest that approximately 5% of HIV-infected individuals ultimately develop PML. A striking 20-fold increase in the prevalence of PML was seen between the years 1980 to 1984 and 1990 to 1994 in south Florida with all but 2 of 156 cases of PML in this series occurring in association with HIV. Typically, AIDS patients with PML have significant lymphopenia and low CD4 lymphocyte counts; however, in one series, >10% had CD4 counts in excess of 200 cells/mm^3 at the time of presentation. The introduction of HAART may have led to a decline in the frequency with which PML complicates HIV infection, although this remains to be unequivocally established.

CLINICAL MANIFESTATIONS

The clinical manifestations of PML are varied and depend on the area of the brain involved. In natalizumab-associated PML, the most common abnormalities were behavioral and cognitive abnormalities followed by weakness; whereas, in the HIV-associated PML cases, the most common manifestations have been weakness (generally, hemiparesis), gait disturbance, speech and language disorders, cognitive dysfunction, and visual loss. Ataxia, dysarthria, numbness, headaches, aphasia, seizures, and vertigo are occasionally noted. Rarely, focal cognitive deficits, such as prosopagnosia, apraxia, left-sided neglect, and Gerstmann's syndrome, are observed; however, global deficits such as memory disturbances and personality changes are more common. There may be some differences in clinical presentation of PML based on the predisposing cause. On rare occasion, magnetic resonance imaging (MRI) abnormalities due to PML may be detected in advance of any clinical features; however, symptoms typically intervene within weeks of this observation.

RADIOLOGY

The diagnosis of PML is strongly suggested by the typical appearance on imaging studies. On computed tomography (CT), multiple white matter hypodensities are revealed (Figure 81.2), but MRI is more sensitive. The lesions of PML appear hyperintense on T2 (Figure 81.3) and hypointense on T1. The scalloped appearance of these areas is due to subcortical "U" fiber involvement. Although any area can be affected, there is a predilection for the frontal and parieto-occipital regions, perhaps due to the large volume of white matter in these areas. About one-third of patients have posterior fossa involvement, and 5% have only cerebellar and brainstem lesions. Most patients have bilateral abnormal areas, and the basal ganglia may be affected, chiefly due to involvement

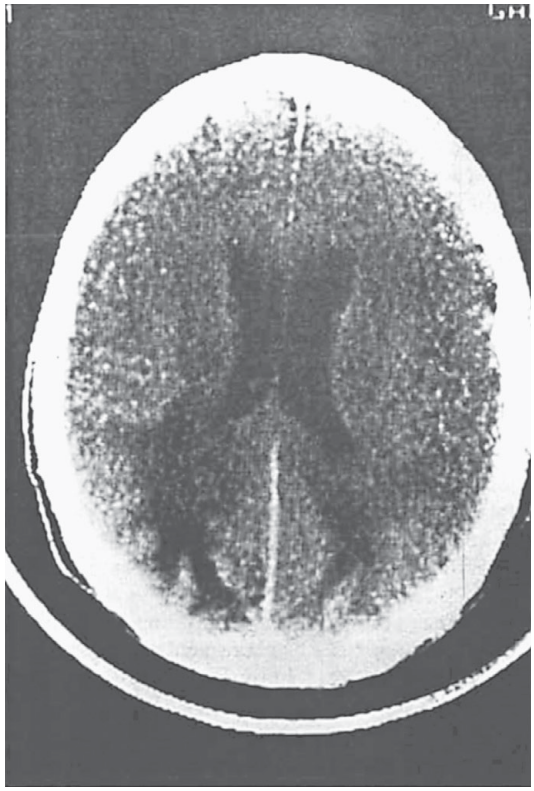

Figure 81.2 Computed tomography scan shows hypodense abnormalities in bilateral occipital lobes.

of myelinated fibers that course through this region. Enhancement had not been considered typical, but in a pre-HAART AIDS PML population, 10% of patients had contrast enhancement on CT scan and 15% had gadolinium enhancement on MRI. In natalizumab-associated PML, 40% to 50% have gadolinium enhancement on MRI.

When PML occurs in association with HIV infection, it must be differentiated from HIV leukoencephalopathy, although this can be difficult on a radiologic basis. The MRI of HIV encephalopathy often shows atrophy and the white matter lesions do not enhance and are typically isointense on T1-weighted imaging. Clinical distinguishing HIV PML characteristics are its rapid course, focal features, and subcortical involvement. In contrast, HIV encephalopathy or dementia has a more protracted course, is of a cortical nature, and only rarely has focal features.

In patients developing PML while under treatment for MS with natalizumab, the white matter lesions of MS must be distinguished from those of PML. This can be difficult but the presence of periventricular lesions, ring, C-shaped or uniform globular enhancement, and Dawson's

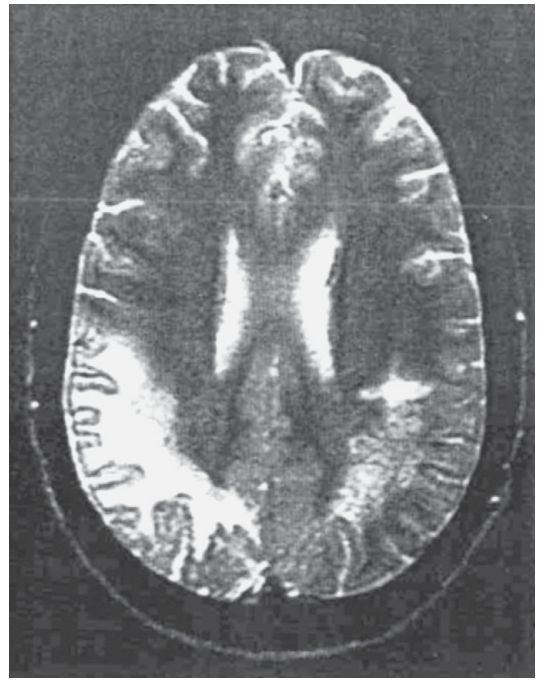

Figure 81.3 This T2-weighted magnetic resonance image shows extensive hyperintense signal abnormalities in the right hemisphere white matter and smaller subcortical lesions on the left.

finger appearance are among the features that suggest MS, whereas subcortical location, faint, irregular contrast enhancement, a sharp border toward the gray matter and an ill-defined border towards the white matter on T2-weighted images, and T1-hypointensity and diffusion-hyperintense lesions are those suggestive of PML.

CEREBROSPINAL FLUID

Routine studies on cerebrospinal fluid (CSF) are not particularly helpful for diagnosing PML. A mild increase in protein as well as an increase in myelin basic protein may be detected in the CSF. In HIV-infected individuals, the presence of oligoclonal bands and increased IgG synthesis (elevated CSF index) is not infrequently observed but is the consequence of HIV rather than JCV. PCR for JCV is an indispensable test for diagnosing PML in persons with the appropriate clinical and radiographic features. CSF PCR has a specificity of 100% and has a sensitivity of 70% to 80%.

DIAGNOSING PML

The 2013 consensus statement for diagnosing PML established two primary approaches. In a patient with appropriate clinical presentation, radiologic

features and the demonstration of JCV in the CSF is sufficient for establishing the diagnosis of PML. The second option when the clinical picture is more obscure or if the CSF PCR is negative is confirmation by brain biopsy with immunohistochemistry and classical pathologic features. Tissue diagnosis with brain biopsy is not without error. Brain biopsy for focal lesions in AIDS patients was associated with 93% to 96% sensitivity along with a 12% postoperative morbidity, and 2% postoperative mortality. The 2013 AAN guidelines for PML diagnosis segregate PML into definite, probable, and possible categories based on the evidence for diagnosis. A diagnosis can be made comfortably in patients presenting with clinical features and MRI pattern consistent with PML coupled with the detection of JCV DNA by PCR in the CSF. In some patients a definitive diagnosis rests on demonstrating the characteristic histopathologic triad at brain biopsy and detecting the virus.

PROGNOSIS

In the absence of a reversible immunosuppressive disorder, the prognosis of PML is typically grim, with death occurring in most patients between 1 and 18 months (mean 4 months) after disease onset. However, there is a significant difference in prognosis depending on the predisposing factors for disease. For instance, PML associated with AIDS pre-HAART was fatal in about 90% to 95% of cases. After the institution of optimized HAART therapy, 1-year survival increased to close to 50%. Natalizumab-associated PML has a much higher survival rate, approximately 80%, although the vast majority of these patients are debilitated by significant neurologic deficits. Certain features seem to be associated with a greater likelihood of long survival (in excess of 12 months), including PML as the heralding illness of AIDS, lesser degree of immunosuppression (CD4 counts >300 cells/mm^3), enhancement on radiographic imaging, and any evidence of clinical recovery. Low CSF JC viral loads have also correlated with longer survival. Additionally, a correlation between low titers of JC viral DNA load in the CSF and prolonged survival has also been demonstrated. The cellular immune response against JCV appears to tightly correlate with a favorable clinical outcome in PML. The presence of JCV-specific CTLs in these patients is likely related to the presence of inflammatory infiltrates in the PML lesions and contrast enhancement seen on imaging studies.

TREATMENT

To date there are no unequivocally successful therapeutic modalities for PML. Most of the extant literature consists of anecdotal reports. Treatment modalities can initially be placed in two categories: patients with AIDS-related PML and those with PML not associated with AIDS. In HIV-associated PML HAART should be initiated, with the goal of normalizing CD4 counts. In non-AIDS-related PML, the initial effort should be made to eliminate the offending immunosuppression in an attempt to allow the host's own immune system to combat the disease. In natalizumab-associated PML these patients should undergo plasma exchange or immunoadsorption to aid in the removal of the drug. The survival of PML in the era of HAART has changed quite considerably, however, with as many as 50% of patients demonstrating long-term survival (>12 months). The benefit of HAART in AIDS-associated PML has not been universally observed, however, as the benefit seems to be chiefly confined to treatment-naïve patients. The remarkable success of HAART in the treatment of AIDS-related PML has had its downside as well.

A syndrome referred to as the immune reconstitution inflammatory syndrome (IRIS) may result in new or worsening neurologic deficits, an increased number or size of lesions observed by neuroimaging, contrast enhancement of these lesions, and brain edema. Fatal outcomes have been reported, and the development of this syndrome with infratentorial PML may be especially dangerous. This occurs in some AIDS patients in whom HAART has been initiated and the CD4 T lymphocyte count has increased as well as in some natalizumab-treated patients who undergo plasma exchange or immunoadsorption.

Nucleoside analogs have been employed because they impede the synthesis of DNA. In vitro studies have clearly demonstrated the ability of cytosine arabinoside (cytarabine, ARA-C), a cytosine analog, to inhibit JCV replication, and anecdotal reports of intravenous and intrathecal administration suggested the value of this therapy in PML. However, a carefully conducted clinical trial of AIDS-related PML failed to show any value of either intravenous or intrathecal administration of ARA-C when compared with placebo. Despite anecdotal reports of the value of other nucleoside analogs in PML, such as adenine arabinoside (vidarabine, ARA-A), none has been convincingly demonstrated to ameliorate the disease course.

Interferons have also had occasional positive results both subcutaneously and intrathecally

when used in conjunction with ARA-C. The antiretroviral activity of the interferons may be the consequence of their ability to stimulate natural killer (NK) cells. In a pilot study of 17 patients with AIDS and PML treated with interferon (IFN)-α2a and zidovudine, two had long-term clinical stabilization, although none improved. A retrospective study compared patients with AIDS-associated PML receiving a minimum treatment of 3 weeks of 3 million units of IFN-α daily with untreated historical controls and suggested that IFN-α treatment delayed the progression of the disease, palliated symptoms, and significantly prolonged survival. However, re-examination of those data indicated that the improved survival could be explained by the concomitant administration of HAART.

The antineoplastic drug camptothecin, a DNA topoisomerase I inhibitor, and its close relative, topotecan, have been demonstrated to block JCV replication in vitro when administered in pulsed doses in amounts nontoxic to cells. The therapeutic effectiveness of topoisomerase I inhibitors for PML has been entirely anecdotal. They display significant systemic toxicity, and their value in the treatment of PML has not been demonstrated in well-controlled trials.

Cidofovir [HPMPC; (S)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine] and its cyclic counterpart have demonstrated selective antipolyomavirus activity. The 50% inhibitory concentrations for HPMPC were in the range of 4 to 7 μg/mL, and its selectivity index varied from 11 to 20 for mouse polyomavirus and from 23 to 33 for SV40 strains in confluent cell monolayers. It had been proposed as an agent for the treatment of PML, and there is anecdotal evidence to support its use in AIDS and with other immunosuppressive conditions. However, several larger observational studies have failed to show any benefit. Better designed trials to address the value of cidofovir for PML are needed before it is widely adopted, particularly in light of the serious side effects that occur with the drug, including ocular hypotony, bone marrow depression, and renal disorders.

Mirtazapine and risperidone have been proposed in the treatment of PML. The JCV uses a subtype of the serotonin receptors, 5-HT2A. Mirtazapine and risperidone specifically block this receptor. Mirtazapine has been used in non-AIDS related PML, but the data are clouded as these patients also received other treatments. To date there are no double-blind placebo-controlled studies using these medications. Similarly, inhibition of the clathrin-dependent endocytosis by drugs such as chlorpromazine have been proposed as therapies, but without any supporting trials.

An analysis of a couple of thousand compounds for JCV inhibition suggested that the antimalarial mefloquine would be beneficial. A trial in which mefloquine was administered as 250 mg four times daily and then 250 mg weekly thereafter failed to show suppression of JCV replication in the CSF.

Perhaps most alluring in the treatment of PML is the therapeutic potential of antisense oligonucleotides which are designed with a specific complementary base sequence that binds selectively to a targeted region of messenger RNA (mRNA) to prevent the translation of the mRNA into protein. Antisense oligonucleotide directed to JCV T antigen may reduce viral expression by 80%. Antisense oligonucleotides that target other sites of the viral genome, such as transcription sites, may prove to be effective therapeutic strategies. As a strong JCV-specific cellular immunity has recently been associated with a favorable clinical outcome of PML, the enrichment of an autologous population of JCV-specific CTL populations using tetrameric MHC class-I/JCV peptide complexes may be demonstrated to be a therapeutic option. An alternate, though equally unproven, approach is to boost immunity to JCV with a vaccine based on a newly discovered JCV-specific CTL epitope.

CONCLUSION

The occasional report of stabilization or remission and the growing understanding of the pathophysiology of the virus provide hope for the future development of curative strategies. The growing number of persons affected with PML has allowed the organization of carefully designed therapeutic trials to address this issue.

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82. Cerebrospinal fluid shunt infections

Elisabeth E. Adderson and Patricia M. Flynn

Cerebrospinal fluid (CSF) shunts are critical for many patients surviving congenital central nervous system (CNS) anomalies, infection, or intracranial hemorrhage. Infection is a common complication of these devices and a leading cause of morbidity and hospitalization. Despite this, there is little consensus on the optimal means to prevent and treat these infections.

PATHOGENESIS

Most CSF shunts are silastic tubes inserted into the cerebral ventricles or subarachnoid space and connected to a pressure-regulating valve on the external skull. The proximal shunt is connected to tubing tunneled under the skin to the peritoneal cavity (ventriculoperitoneal shunt). In situations where intraperitoneal drainage is not feasible, the shunt may drain into the right atrium (ventriculoatrial shunt) or pleural cavity (ventriculopleural shunt).

The reported incidence of CSF shunt infections ranges from 1% to 30%, with an average of ≈10% in recent studies. Risk factors for infection include previous surgical revision, a short interval from the time of placement or revision, younger age (particularly premature neonates), a less-experienced surgeon, previous infection, endoscopic surgery, and the presence of a postoperative CSF leak. Prior cardiac surgery and any surgical procedure within 30 days of shunt insertion are risk factors for shunt infection in infants less than a year of age. Shunt valve design does not appear to influence infection rates.

The majority (40% to 75%) of CSF shunt infections are caused by coagulase-negative *Staphylococcus* spp. (CNS). *Staphylococcus aureus* and gram-negative bacilli are each responsible for between 6% and 35% of infections. *Escherichia coli*, *Klebsiella* spp. and *Pseudomonas aeruginosa* are the most commonly reported gram-negative pathogens. Anaerobic bacteria, especially *Propionibacterium* spp., and fungi are occasionally reported.

Most (50% to 70%) CSF shunt infections occur within 60 days of shunt insertion and 90% occur in the first 6 months after placement. This timing, and the prominent role of bacteria that normally colonize the skin in causation, suggests that most infections result from the intraoperative contamination of shunt devices. One small prospective study found that contamination of surgeons' gloves by normal skin flora such as coagulase-negative *Staphylococcus* and *Proprionibacterium acnes* was universal and occurred within a short time after surgery was commenced. Less commonly, shunt infections may result from direct extension of surgical wound infections. Infections with delayed onset (after 2 to 3 months) and those caused by gram-negative bacilli may originate from an intra-abdominal focus (appendicitis, bowel perforation or surgery, trauma) by retrograde spread or bacteremia. Organisms such as coagulase-negative *Staphylococcus* and *S. aureus* adhere specifically to medical devices or to host proteins that are rapidly deposited on these foreign bodies. Adherent bacteria are enveloped in biofilm, a complex mixture of carbohydrate and proteins that both augments adherence and protects the organism from host immune defenses. Bacteria in biofilm are less susceptible to antimicrobial killing than plankton organisms. In some cases, biofilm acts as a mechanical barrier to reduce the penetrance of drugs. Sessile organisms also have reduced growth rates and metabolic changes that may affect the expression and function of drug targets.

CLINICAL PRESENTATION

The clinical presentation of shunt infections may range from almost asymptomatic colonization of the shunt device to severe ventriculitis, depending on the infecting organism and the patient's underlying medical condition. Illness is frequently nonspecific. It is imperative to exclude CSF shunt infections in patients with unexplained systemic

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illness or symptoms of shunt malfunction, since these infections cannot reliably be distinguished from systemic illnesses or noninfectious causes of shunt malfunction. The most common symptoms include fever, vomiting, lethargy or altered consciousness, and irritability. Fever may be absent initially in up to 40% of patients. Some patients have more obvious presentations, with evidence of wound infection, inflammation along the subcutaneous shunt tract, or signs of meningeal irritation or elevated intracranial pressure. Approximately 10% have symptoms and signs of distal infection, including abdominal pain, guarding, gastrointestinal obstruction, or a palpable peritoneal pseudocyst. Patients with infected ventriculoatrial shunts are generally bacteremic and have more prominent fever and other constitutional symptoms. Ventriculoatrial shunt infections are occasionally complicated by an immune-complex-mediated "shunt nephritis," characterized by hypocomplementemia, hematuria, proteinuria, and renal dysfunction.

DIAGNOSIS

CSF shunt infections are diagnosed by examination and culture of CSF obtained from the shunt reservoir or cerebral ventricles. The CSF white blood cell count is usually elevated (usually 100 to 2500 cells/mm^3, with a range of 0 to >18 000/mm^3); however, a mild pleocytosis is also commonly observed with mechanical shunt malfunction and hypersensitivity reactions to shunt material. There is typically a neutrophil predominance (range 0% to 93%) and CSF eosinophilia of >5% occurs in 15% to 25% of patients. The CSF protein is generally elevated (usually 150 to 400 mg/dL). CSF glucose concentrations are less frequently abnormal, typically ranging from 30 to 60 mg/dL.

Gram stain examination of CSF permits a rapid diagnosis in 70% to 90% of patients. CSF cultures are positive in approximately 85% of patients. Positive cultures are less common in patients who have received antimicrobial therapy prior to CSF sampling. The addition of anaerobic cultures of CSF may increase the yield of *P. acnes*. The likelihood of a positive culture may also be reduced in patients with infections caused by unusual pathogens, including anaerobic bacteria and fungi. Polymerase chain reaction amplification of bacterial DNA may be more sensitive than culture but the specificity of these tests has not been established and they are not widely available. Blood cultures are rarely positive in ventriculoperitoneal shunt infections. In one study, an elevated serum C-reactive protein was helpful in distinguishing shunt infections from mechanical obstruction.

THERAPY

Initial approach to management

In patients with suspected CSF shunt infections, initial management includes obtaining CSF from the shunt reservoir or ventricle for Gram stain, culture, and biochemical analysis. Patients with presentations suggestive of infection should begin antimicrobial therapy while awaiting results of CSF cultures. Patients who have mild illness, no evidence of shunt malfunction, a mild pleocytosis, and negative CSF stains may be observed without empirical therapy. Contamination of diagnostic CSF samples is possible. It is prudent, therefore, to obtain a second CSF sample before instituting antibiotic therapy in cases where antimicrobials have not been administered and the patient's course is not consistent with infection.

Antimicrobial therapy

Empirical antibiotic therapy should be based on the likely pathogen, clinical findings, and the severity of illness. Children with uncomplicated infections may be treated with vancomycin alone, in doses appropriate for intracranial infections (Table 82.1). Combination therapy with vancomycin and an agent effective against gram-negative bacilli (cefepime, ceftazidime, or meropenem) is recommended for initial treatment of adults, children with more severe clinical illness, patients with findings suggestive of intra-abdominal infection, and those with gram-negative bacilli seen on CSF stain. Definitive antimicrobial therapy should be based on the specific organism, in vitro susceptibility testing, and the ability of the antimicrobial agent to cross the blood–brain barrier.

Poor blood–brain barrier penetration is a significant problem with some antimicrobial agents used to treat shunt infections, most notably vancomycin. Serum vancomycin levels should be monitored, aiming for peak concentrations of 30 to 45 μg/mL and trough concentrations of 15 to 20 μg/mL. Effective CSF concentrations of vancomycin, aminoglycosides, and certain other antimicrobial agents can often be more easily achieved by antimicrobial administration into the cerebral ventricles. No prospective randomized trials have

Table 82.1 Recommended doses of intravenous antimicrobial agents

Agent	Age[a]	Total daily dose	No. daily doses
Ampicillin	Neonate <7 days	150 mg/kg	3
	Neonate 8–28 days	200 mg/kg	4
	Children	300 mg/kg	4
	Adults	12 g	6
Cefepime	Neonate <7 days	–	
	Neonate 8–28 days	–	
	Children	150 mg/kg	3
	Adults	6 g	3
Cefotaxime	Neonate <7 days	100–150 mg/kg[a]	2–3
	Neonate 8–28 days	150–200 mg/kg	3–4
	Children	300 mg/kg	4–6
	Adults	8–12 g	4–6
Ceftazidime	Neonate <7 days	100–150 mg/kg[a]	2–3
	Neonate 8–28 days	150 mg/kg	3
	Children	150 mg/kg	3
	Adults	6 g	3
Ceftriaxone	Neonate <7 days	–	
	Neonate 8–28 days	–	
	Children	100 mg/kg	2
	Adults	4 g	2
Meropenem	Neonate <7 days	–	
	Neonate 8–28 days	–	
	Children	120 mg/mL	3
	Adults	6 g	3
Nafcillin	Neonate <7 days	75 mg/kg	2–3
	Neonate 8–28 days	100–150 mg/kg[a]	3–4
	Children	200 mg/kg	4–6
	Adults	9–12 g	6
Oxacillin	Neonate <7 days	75 mg/kg	2–3
	Neonate 8–28 days	150–200 mg/kg[a]	3–4
	Children	200 mg/kg	4
	Adults	9–12 g	6
Penicillin G	Neonate <7 days	150 000 units/kg	2–3
	Neonate 8–28 days	200 000 units/kg	3–4
	Children	300 000 units/kg	4–6
	Adults	24 000 000 units	6
Rifampin	Neonate <7 days	–	
	Neonate 8–28 days	10–20 mg/kg	2
	Children	10–20 mg/kg	1–2
	Adults	600 mg	1
Vancomycin	Neonate <7 days	20–30 mg/kg	2–3
	Neonate 8–28 days	30–45 mg/kg	3–4
	Children	60 mg/kg	4
	Adults	30–45 mg/kg	2–3

[a] Lower doses and increased intervals are advisable for infants weighing <2000 g

Table 82.2 Recommended initial doses and CSF concentrations of intraventricularly administered antimicrobials

Agent/age	Initial dose (MG/DAY)	Peak concentration[a] (MG/L)	Trough concentration[b] (MG/L)
Vancomycin			
Infants and children	2–10	50–80	<10
Adults	5–20		
Gentamicin			
Infants and children	1–4	5–20	<2
Adults	4–8		
Tobramycin			
Infants and children	1–4	5–20	<2
Adults	4–8		
Amikacin			
Infants and children	2–8	25–30	<5
Adults	5–10		

[a] Peak concentrations measured 15 to 30 minutes after administration.
[b] Initial trough concentration measured 24 hours after administration of the first dose.

compared combined parenteral and intraventricular administration of antimicrobials with parenteral therapy alone. Intraventricular administration is commonly made use of, nonetheless, in patients with suboptimal responses to systemic antibiotics and patients for whom shunt removal is not feasible. Some authorities advocate the routine use of intraventricular antimicrobials in infection caused by susceptible organisms. No antimicrobial agents are currently licensed for intraventricular use. Intraventricular vancomycin and aminoglycosides, however, have few reported adverse affects when used at appropriate concentrations (Table 82.2). Preservative-free formulations of these drugs should be reconstituted in sterile normal saline for administration and the extraventricular drain (EVD) clamped for 15 minutes to permit diffusion throughout the ventricular system. An alternative "flush" procedure has been described in which a more dilute antimicrobial solution is infused slowly through one EVD and allowed to drain through a second EVD placed in the contralateral ventricle. Antimicrobial CSF concentrations achieved by intraventricular administration are highly variable and should be monitored periodically to both ensure adequate levels and avoid toxicity. A reasonable approach is to obtain CSF for determination of the antimicrobial "inhibitory quotient" 24 hours after administration of the first dose. Subsequent doses and dosing schedules should be adjusted in order to maintain a CSF antimicrobial trough concentration that exceeds the pathogen's minimum inhibitory concentration by 10- to 20-fold.

Surgical therapy

Three general approaches for surgical management of shunt infection are practiced. Most commonly, antimicrobial therapy is combined with shunt removal and, if required, an EVD placed for CSF drainage until the shunt can be replaced. A one-stage procedure combines antibiotic therapy with immediate replacement of the infected shunt. Finally, some patients have been treated with antibiotics alone without shunt removal. The success rates for each of these management schemes are approximately 88%, 68%, and 33%, respectively. The poor cure rates observed with antibiotic therapy alone are likely to be attributable to the combination of persistent viable bacteria in biofilms and the limited achievable CSF concentrations of many antimicrobial agents. Clinical studies have also described a shorter duration of hospitalization and lower mortality rates with two-stage shunt management, although it is probable that patients with a poor overall prognosis are more likely to be treated with antibiotics alone. These data suggest that patients with CSF shunt infections are optimally treated by removal of infected hardware and antimicrobial therapy followed by delayed shunt replacement. Shunt removal is indicated for wound or shunt tract infections, which should also be treated with local debridement, and in patients with evidence of intra-abdominal infection other than isolated infection of an abdominal pseudocyst without positive CSF cultures. The latter patients are treated by shunt externalization, drainage of fluid collections, and systemic antimicrobials appropriate for intra-abdominal infection. Patients with a short life expectancy, an Ommaya reservoir, and those with infections caused by coagulase-negative *Staphylococcus* spp. that respond promptly to aggressive medical therapy may be considered for conservative management without shunt removal. These patients should have EVD or ventricular reservoirs placed and be treated with systemic and intraventricular antimicrobial agents for a minimum of 14 days after CSF sterilization, with meticulous attention to ensuring CSF antimicrobial concentrations are optimal.

Continuing management

After antimicrobial therapy is initiated, CSF should be sampled every 1 to 2 days for culture and Gram stain until its sterility is confirmed. If cultures remain positive after 48 hours of appropriate systemic therapy, CSF antimicrobial concentrations should be determined and the addition of intraventricular antimicrobial agents should be considered. In infections caused by susceptible gram-positive bacteria, combination therapy with rifampin, which has excellent CSF and biofilm penetration, may be helpful. The possibility that the EVD has become colonized, which occurs in 5% to 10% of cases, should also be taken into account. Routine changes of EVDs, however, have not been proven to reduce the risk of colonization or secondary infection.

The optimal duration of therapy for CSF shunt infections has not been systematically studied. Most infections caused by coagulase-negative *Staphylococcus* spp. and *S. aureus* can be treated for 7 to 10 days after CSF is sterile. Infections caused by gram-negative pathogens are generally treated for a minimum of 10 to 14 days after CSF sterilization. Published studies have described a variety of criteria for the timing of shunt replacement, but most practitioners consider this after the CSF is sterile for 7 to 10 days and CSF protein concentrations fall <200 mg/dL.

OUTCOMES

CSF shunt infections are an uncommon direct cause of death. These infections, however, may be a risk factor for mortality related to underlying medical conditions. Some studies in children have noted an increased incidence of intellectual impairment and learning disabilities in patients with CSF shunt infections compared to those with shunts and no history of infection.

PREVENTION

Strict attention to disinfection of skin and surgical technique at the time of shunt or EVD placement may prevent many shunt infections. In one study, initial double-gloving with inter-operative removal of the outer pair of gloves before handling the shunt catheter reduced infection rates relative to continuous double-gloving. Studies evaluating the implementation of a perioperative care bundle have consistently demonstrated reduced shunt infection rates. Reduced rates of both wound dehiscence and shunt infections were reported in a group of children randomized to wound closure with tissue adhesive compared to the group treated with nonabsorbable sutures. The use of antimicrobial-coated sutures for closure of the galea and fascial incisions has shown similarly promising results. EVDs should be removed at the earliest feasible time. The use of prophylactic

antimicrobial agents at the time of shunt insertion is controversial. Although no randomized controlled trials have compared infection rates, many studies have suggested prophylaxis may reduce shunt infection rates without an increase in infections caused by resistant organisms. A recent analysis of these studies concluded that short-term (<24 hour) antimicrobial prophylaxis should be considered, an approach consistent with general recommendations for the prevention of surgical infections. Most studies have used cefazolin for prophylaxis, with the first dose of 1 g IV for adults and 20 mg/kg for children within 60 minutes before surgical incision, followed by two additional doses at 8-hour intervals. For patients with serious allergies to cephalosporins and in institutions with a high incidence of infections caused by methicillin-resistant *S. aureus*, vancomycin is an alternative (adults, 15 mg/kg within 120 minutes before surgical incision and 12 hours later; children, 10 to 15 mg/kg IV within 120 minutes before surgical incision and every 6 hours for a total of four doses).

Catheters impregnated with antimicrobial agents (clindamycin, minocycline, and/or rifampin) have been developed recently. Incorporation of these drugs has no apparent effect on shunt function and no significant toxicity in animal and limited human studies. Antibacterial activity gradually decays over a period of months, in some cases persisting for more than 90 days after shunt insertion. Most observational and randomized clinical trials of these devices suggest their use has a significant effect in reducing infection rates and may reduce healthcare costs. Additional randomized controlled trials evaluating the long-term efficacy of these catheters and their effect on rates of antimicrobial resistance are needed.

MENINGITIS IN PATIENTS WITH CSF SHUNT INFECTIONS

Rarely, patients with CSF shunts may develop hematogenous bacterial meningitis caused by common pathogens such as *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type b. These infections can generally be treated by systemic antimicrobial agents alone, without removal of the shunt.

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83. Prion diseases

Richard T. Johnson

Transmissible spongiform encephalopathies or prion diseases are chronic neurologic disorders characterized by long incubation periods, progressive noninflammatory disease of brain and spinal cord, a failure of a specific immune response, and a uniformly fatal course. They are transmissible within their natural species and to a limited extent across species barriers. The pathology is characterized by neuronal loss, gliosis, and vacuoles in cytoplasm of neural cells giving the spongiform appearance on microscopic examination. Infectivity copurifies with an isoform of a normal surface glycoprotein expressed primarily in the central nervous system. The function of the normal prion protein is unclear; but the misfolded protein – the prion – induces post-translational conversion of normal prion protein with a helical structure into the infectious isoform rich in β-pleated sheets. This abnormal protease-resistant protein accumulates in brain, leading to disease. To date nucleic acid has not been detected in the transmissible protein fraction.

Prion diseases are recognized in animals (scrapie of sheep, bovine spongiform encephalopathy, and chronic wasting disease of deer and elk) and humans (kuru, Creutzfeldt–Jakob disease [CJD], and the variant of CJD related to bovine spongiform encephalopathy). The human forms of disease can be divided into three groups: (1) sporadic CJD, which represents 85% to 90% of cases, (2) familial CJD due to mutations in the gene coding for prion protein, making up 10% of cases, and (3) transmitted CJD due to iatrogenic transmission, cannibalism in the case of kuru, and, recently, transmission of bovine spongiform encephalopathy to humans.

EPIDEMIOLOGY

Sporadic CJD occurs worldwide at a rate of about 1 per million population per year. Rates are equal in men and woman. The mean age of onset is about 65 years with few cases below 55 or over 80 years of age. No geographic or temporal clustering is evident; conjugal exposure does not increase risk; and no occupations such as meat preparation, medical work, or farming appear related to disease. The assumption is that the great majority of cases of CJD result either from random misfolds of the prion protein which then causes a cascade of misfolding or from an unidentified environmental exposure.

Familial cases of CJD have been related to over 25 point mutations, insertions, and deletions in the gene coding for the prion protein. They show a pattern of autosomal dominant inheritance. In addition, polymorphisms in the gene, particularly a methioine/valine polymorphism at codon 129, influence susceptibility to sporadic and transmitted CJD and determine the phenotype of some hereditary forms.

Transmitted diseases include kuru, which was transmitted through ritual endocannibalism among the Fore tribal group of Central New Guinea, and variant CJD transmitted from bovine spongiform encephalopathy to young people predominantly in the United Kingdom. In addition, iatrogenic CJD has occurred with contaminated operating room tools, by injection of human growth hormone derived from cadaveric pituitaries, and from the use of human dura as grafts in neurosurgery. Although human growth hormone was replaced by safe recombinant growth hormone in 1985 and most neurosurgeons have abandoned the use of human dural grafts, exposure history must still be sought since incubation periods of up to 50 years have been observed for kuru and may be anticipated in iatrogenic transmission.

The outbreak of over 170 000 cows with bovine spongiform encephalopathy in the United Kingdom peaked in 1993 and has been declining since; the ongoing point source epidemic was related to contaminated feed. Only about 200 young adults have died of this variant CJD, which represents the spread of this bovine prion to humans; 80% of these cases have been in the UK. Rare cases of

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bovine and human disease are now being seen in many countries. A disquieting feature of the "mad cow" variant of CJD is that, unlike sporadic CJD, transmission has been observed with blood transfusions.

CLINICAL SYMPTOMS AND SIGNS

Sporadic CJD often begins insidiously with fatigue, loss of dexterity, distortion of vision, insomnia, and other nonspecific complaints. About 40% have early complaints of cognitive decline and 40% have an early onset of movement disorders, particularly cerebellar ataxia. The progression is rapid. Dementia and severe motor abnormalities, particularly startle-sensitive myoclonus, develop within weeks or months. Aphasia, blindness, hemiparesis, and mutism may all develop. The mean survival is only 5½ months, and 90% of patients are dead within 12 months.

The familial cases may have distinctive phenotypes such as Gerstmann–Straussler–Scheinker disease with cerebellar ataxia and fatal familial insomnia with autonomic abnormalities, but most familial cases have presentations similar to sporadic cases. In general, familial cases have onsets at earlier ages and have more protracted courses.

Variant CJD occurs in older children and young adults and has a protracted course; mean age of onset is 29 years and mean survival is 14 months. The clinical presentations are unique often with behavioral abnormalities, depression, and pain. Variant CJD and kuru, both of which are thought to be transmitted orally, present with early cerebellar ataxia and a delay in the development of cognitive changes.

LABORATORY TESTS

Blood counts and chemistries are generally normal. The cerebrospinal fluid is typically acellular, with normal or mildly elevated protein, normal sugar, and no abnormal antibody synthesis or oligoclonal bands. Elevations of spinal fluid 14-3-3 protein or neuron-specific enolase, both normal neuronal proteins, are common in sporadic disease but present in only half of familial or variant cases where progression of disease is slower.

The electroencephalogram (EEG) usually shows nonspecific slowing early in disease, but a pattern of periodic sharp wave complexes, characteristic but not diagnostic of CJD, is common late in disease, particularly after myoclonic jerking has begun. The typical EEG pattern usually does not develop in variant CJD.

Computed tomography of the brain is usually normal except to show atrophy in the late stage of disease. In contrast, magnetic resonance imaging (MRI) may give very typical patterns early in disease using fluid-attenuated inversion-recovery (FLAIR) and diffusion-weighted imaging. A cortical ribbon pattern is common, and a characteristic increased signal in the caudate and putamen is frequent. In contrast, in variant CJD the pulvinar of the thalamus often shows an increased signal.

Spinal fluid 14-3-3 protein, EEG, and MRI are all helpful, but none have perfect selectivity or sensitivity. Sensitivity is increased if tests are repeated during the course of disease.

Uncertainty of diagnosis may necessitate a brain biopsy. Adequate tissue should be obtained for standard histology as well as frozen tissue for immunocytochemistry, Western blots for prion protein, and genetic studies for mutations in the *PRNP* gene. This can be processed free of charge by the National Prion Disease Pathology Surveillance Center (see below). The same center can assist with autopsies and funeral arrangements when local concerns about infectiousness interfere with good medical practice.

DIFFERENTIAL DIAGNOSIS

Early in disease differentiation from Alzheimer's disease and other degenerative diseases may be difficult; particularly in some cases of familial Alzheimer's disease where myoclonus is seen. The rapid course of CJD and the development of focal neurologic findings usually clarify this differential. It is early in disease that MRI changes can be helpful in suggesting the diagnosis.

Causes of subacute dementia such as neurosyphilis, fungal meningitis, and other inflammatory diseases are ruled out by spinal fluid examination. Localized vasculitis usually is accompanied by spinal fluid protein elevation but can pose the most difficult diagnosis to rule out in CJD. Cases of gliomatosis cerebri, intravascular lymphomatosis, and anti-GAD antibody cerebellar ataxia have been reported to clinically simulate CJD and show positive 14-3-3 protein in spinal fluid.

Toxic and metabolic diseases can mimic CJD. Cognitive impairment and myoclonus have been seen with bismuth and lithium intoxication and in Hashimoto's encephalopathy. In these acute intoxications or metabolic disorders seizures and myoclonic jerks often occur at the onset; in CJD myoclonus usually develops after several months, and seizures are rare. A history of

familial disease, travel, drug ingestion, blood transfusions, prior neurosurgical or ophthalmologic procedures, thyroid disease, and toxin exposures should be pursued in all suspected cases.

TREATMENT

No long-term remission or survival has ever been documented with animal or human prion disease. Treatment, therefore, takes two forms: palliative treatment and experimental treatment.

Patients in late stages of CJD are often mute and show limited voluntary motor activity. Agitation is not a common problem, so psychotropic drugs are seldom indicated. If myoclonic jerking is distressing to the patient clonazepam (0.5 to 5 mg three times a day) can be given. Seizures are unusual, but if they occur, treat with routine anticonvulsants. Swallowing may become impaired. Nutrition by feeding tube and hydration by the intravenous route may be considered after discussion with family.

Experimental treatment with amphotericin B, pentosan polysulfate, Congo red, quinacrine, and chlorpromazine has shown some beneficial effect in vitro and limited effects in mice with scrapie. Human experimental trials of several drugs are in progress.

No special isolation precautions are needed at home or in the hospital, except to mark spinal fluid and blood specimens for special handling because of hazard of prion disease. Masks, gowns, and gloves in hospital rooms are not only unnecessary but harmful. Family members suddenly seeing a parent treated as infectious who has been recently babysitting a grandchild are terrorized, and isolation precautions may jeopardize subsequent nursing home or hospice placement.

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RESOURCES

www.cjdfoundation.com (patient support and information).

National Prion Disease Pathology Surveillance Center, Case Western Reserve University, Cleveland OH; www.cjdsurveillance.com, telephone 216-368-0597 (studies of biopsy and autopsy tissue, 14-3-3 analysis on CSF, genetic studies; no charge).

PART XI

The susceptible host

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84. Evaluation of suspected immunodeficiency

Thomas A. Fleisher

The need to evaluate immunologic function has become a part of the standard practice of clinical medicine, resulting at least in part from the secondary immunodeficiency produced by human immunodeficiency virus (HIV) infection. In addition, since the early 1990s the molecular basis of primary immunodeficiency disorders has evolved, with now more than 200 genetic defects identified impacting host defense and an expanded range of clinical phenotypes associated with the resulting immune dysfunction. This chapter presents the general methods available to assess immune function, linking these to the clinical infectious history that is suggestive of specific types of immunodeficiency.

The primary clinical problem that sets the stage for initiating an immunologic evaluation is a history of increased susceptibility to infection. In general, the specific characteristics of the recurrent and/or chronic infections, including organism(s), site(s), frequency, and response to therapy provide critical insights into the most likely type or category of immunodeficiency.

Defects in adaptive immunity involving antibody production (humoral immunity) most typically lead to recurrent infections with high-grade encapsulated extracellular bacteria such as *Haemophilus influenzae* (often untypeable) and *Streptococcus pneumoniae* usually affecting the sinopulmonary tract. The protective immune response depends on the production of antibodies against the capsular carbohydrate antigens present on these organisms. In contrast, the clinical picture of patients with defective T-cell (cellular) immunity typically consists of recurrent infections with opportunistic organisms, examples of which include *Pneumocystis jirovecii* (*carinii*), *Candida* species, and cytomegalovirus. This demonstrates that functional T cells are required to prevent or clear infection with these opportunistic intracellular microorganisms. A more recent focus of study has been the interface between the adaptive and innate immune systems directed at defects in the interferon-γ/interleukin (IL)-12 circuit found in certain patients with persistent nontuberculous mycobacterial (NTM) infection as well as other intracellular pathogens. The critical role of the lymphoid arm of the innate immune system (natural killer cells) in host defense has been clarified based on defects affecting these cells producing clinical phenotypes that include increased susceptibility to the herpesvirus family including Epstein–Barr virus (EBV) and herpes simplex virus (HSV) infections as well as in some cases uncontrolled inflammation. Recently, genetic defects associated with increased susceptibility to cutaneous infections both viral and fungal have been defined such that significant, persistent cutaneous infections justify consideration of specific immunologic defects. Abnormalities in the phagocytic arm of innate immunity involving neutrophils include either decreased cell numbers (infections associated with neutropenia are discussed in Chapter 85, Infections in the neutropenic patient) or cellular dysfunction. The congenital neutrophil defects result in cutaneous and deep-seated abscesses, pneumonia, periodontitis, and osteomyelitis. Typically these infections are caused by catalase-producing bacteria such as *Staphylococcus aureus*, *Serratia marcescens*, and *Nocardia* species as well as fungi such as *Aspergillus* species. The clinical findings point to the critical role of mobile phagocytic cells in normal host defense. Congenital defects in specific complement components of innate immunity can also be associated with recurrent infections although in certain cases these are also linked to the development of autoimmune disease and in others to neisserial infections.

Clinical suspicion of a defect in immune function is primarily generated by the medical history and any patient with a history of increased susceptibility to infection should first be carefully questioned about risk factors for HIV infection. The family history may also prove important because many molecularly defined immune deficiencies are genetically linked. The physical examination can provide clues in the case of specific primary

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immunodeficiencies (e.g., typical facies in the hyperimmunoglobulin E [IgE] [Job] syndrome, scars from abscess drainage sites in chronic granulomatous disease, petechiae in Wiskott Aldrich syndrome). This may also provide clues to the evaluation of secondary immune disorders (e.g., oral hairy leukoplakia or Kaposi's sarcoma in HIV infection).

EVALUATING B-CELL FUNCTION

Clinical findings that suggest an abnormality in antibody production are recurrent or chronic infections with encapsulated bacteria involving the sinopulmonary tract. Gastrointestinal, hematologic, and autoimmune disorders may also be associated with antibody deficiencies (Table 84.1).

The clinical screening of antibody-mediated immune function can be accomplished by measuring the levels of the major immunoglobulin classes, IgG, IgA, IgM, and IgE. The results must be compared with age-matched reference intervals (normal ranges) as these levels change significantly during childhood; the results are typically expressed as 95% confidence intervals. The serum immunoglobulin levels are the net of protein production, utilization, catabolism, and loss.

There are no rigid standards regarding the diagnosis of immunoglobulin deficiency, although an IgG value below 4 g/L (400 mg/dL) in an adult or adolescent generally suggests an increased risk for infection. Hypogammaglobulinemia associated with significant recurrent bacterial infection is a definitive indication for intravenous or subcutaneous immunoglobulin replacement therapy after completing the immunologic evaluation and establishing a diagnosis.

Table 84.1 Evaluation of suspected antibody (B-cell) immunodeficiency

Screening tests
Quantitative immunoglobulins
Specific antibody
Circulating specific antibodies
Post-immunization antibodies
Protein antigens
Carbohydrate antigens
IgG subclasses (+/–utility)
Human immunodeficiency virus testing
Secondary tests
B-cell immunophenotyping (e.g., CD19+, switched/nonswitched, naive/memory B cells)
In vitro B-cell function tests (primarily research)

Measurement of a functional antibody response is often required before immunoglobulin replacement therapy is approved and is particularly useful when the total immunoglobulin levels are only modestly depressed or normal in the face of a strong history of recurrent infection. The simplest means to accomplish this is evaluation for spontaneous antibodies (e.g., anti-blood group antibodies [isohemagglutinins] and antibodies to documented prior immunizations). The definitive method is immunizing and assessing preimmunization versus 3- to 4-week post-immunization antibody levels using both protein antigens (e.g., tetanus toxoid) and polysaccharide antigens (e.g., Pneumovax®). Guidelines for normal responses, which are usually provided by the testing laboratory, typically consist of at least a 4-fold increase in antibody and/or protective levels of antibody following immunization.

An additional and readily available test is quantitation of IgG subclass levels; these are most useful in evaluating the IgA-deficient patient with significant recurrent bacterial infections. However, in many settings detection of an IgG subclass deficiency still requires the demonstration of an abnormality in specific antibody production before immunoglobulin replacement therapy is indicated.

Despite the preponderance of recurrent opportunistic infections resulting from HIV infection, appropriate testing to rule this out should be considered even in the face of recurrent bacterial infection. This type of clinical presentation may be seen more often in children infected with HIV. Testing focused on viral load may be needed to rule out HIV infection in the face of absent or diminished antibody production, because the screening tests depend on detecting anti-HIV antibodies (enzyme-linked immunosorbent assay [ELISA] and Western blot assays).

Additional tests focused on humoral immune function are generally performed in specialized centers and fall into two general categories: evaluation of the number and characteristics of B cells and testing the function of B cells in vitro. The former determines the number of B cells as well as specific surface characteristics of B cells and is generally performed by flow cytometry (immunophenotyping). This is evolving as a useful approach to subcategorize patients with common variable immunodeficiency. The latter involves studies that test in vitro B-cell signaling and immunoglobulin biosynthesis and these are generally confined to research centers.

EVALUATING T-CELL FUNCTION

A clinical history of recurrent opportunistic infections strongly suggests an abnormality in T-cell function. Immunodeficiency involving T cells has the highest prevalence as a secondary defect associated with HIV infection. Thus, initial screening assays should always include testing for HIV infection. In addition, the absolute lymphocyte count (generated from the white blood cell count and differential) and cutaneous delayed-type hypersensitivity (DTH) response to recall antigens have served as standard T-cell function screening tests. The significance of the former relates to the fact that T cells constitute approximately three-fourths of circulating lymphocytes such that conditions that inhibit T-cell development or increase T-cell destruction will typically cause lymphopenia. The DTH response provides an in vivo window of T-cell function in response to a previously encountered antigen. However, failure to respond may either reflect T-cell dysfunction (T-cell anergy) or indicate that the host has not been exposed (sensitized) to the antigen. Consequently, it is prudent to use more than one antigen for testing and increasing issues with availability of recall antigens has resulted in decreasing use of DTH testing. Clinical correlates in the medical history of a DTH response include the cutaneous response to poison ivy and/or other contact hypersensitivity reactions (Table 84.2).

The screening tests for T-cell function are often followed by additional testing to complete the assessment of cellular immunity. This parallels that of B cells with quantitation and characterization (immunophenotyping) of T cells and T-cell subsets by flow cytometry together with in vitro functional testing (e.g., proliferation assays [mitogens, recall antigens, alloantigens], cytokine production, cytotoxicity testing). Both of these approaches are generally available in large medical centers as well as via commercial laboratories.

Table 84.2 Evaluation of suspected T-cell immunodeficiency

Screening tests
Human immunodeficiency virus testing
Lymphocyte count
Delayed-type hypersensitivity skin tests
Secondary tests
T-cell enumeration (e.g., CD3+, CD4+, CD8+, naive/memory T cells)
T-cell proliferation (mitogen, alloantigen, antigen)
T-cell cytokine production
T cell cytotoxicity

EVALUATING DEFECTS IN THE IL-12/23 AND INTERFERON-γ PATHWAYS

Recent data have identified abnormalities in specific components of a cytokine-linked pathway involving T cells and monocytes/macrophages associated with recurrent infections to a limited range of opportunistic organisms, particularly NTM. The infections are typically invasive and fail to respond to long-term multiple-agent antimicrobial therapy. These findings led to a study demonstrating that interferon-γ is an effective adjunct to antimicrobials in treating some of these patients. Specific defects involving various components of this pathway have been identified in approximately one-half of these patients with the current research focus being clarification of the molecular basis of the remaining patients. Additional defects continue to be identified that are associated with the clinical phenotype of recurrent infections involving this more limited range of microorganisms. The laboratory evaluation of patients with persistent NTM is generally performed in specialized centers and is focused on evaluating for defects in the cellular signaling pathways involving IL-12/23 and interferon-γ. Most recently, a secondary defect associated with high titer autoantibodies to interferon-γ has been characterized in association with later-onset NTM infection in previously healthy hosts.

EVALUATING DEFECTS IN NATURAL KILLER CELL FUNCTION

The third arm of the lymphoid system consists of circulating cells distinct from B and T cells, the natural killer (NK) cells. Deficiency in NK cell function (and often numbers) has been described in patients with recurrent herpes and human papillomavirus infections associated with a defect in the transcription factor GATA2. The actual clinical disorder is far more complex with infections including organisms other than viruses as well as a significant risk for malignancy plus other findings. This recently described autosomal dominant disorder continues to be characterized as more patients are identified. The X-linked lymphoproliferative syndrome (XLP) associated with defective NK and NKT cell function produces a disorder characterized by a markedly increased

susceptibility to overwhelming EBV infection often during childhood that can result in an aggressive lymphoproliferative disease. Another category of NK cell (and cytotoxic T cell) defects is found in disorders with uncontrolled inflammatory response initiated by specific infections that can lead to multiple organ damage (hemophagocytic lymphocytic histiocytosis [HLH]). In addition, experimental models point to a role for the NK cell in allograft and tumor rejection. These various disorders point out that the role of NK cells in host defense is an emerging field. Testing of NK cell function includes immunophenotyping NK cells by flow cytometry using a variety of monoclonal reagents and assessing NK cell cytotoxicity using standard in vitro assays.

EVALUATING DEFECTS IN INNATE IMMUNE SIGNALING

An area of intense current investigation involves the identification of disorders associated with defective signaling by Toll-like receptors (TLR). This is a family of 10 receptors that represent a phylogenetically more primitive arm of the immune system-dependent signaling via pattern recognition of unique bacterial, fungal, and viral products. An example of such a process is the activation of monocytes and macrophages by bacterial lipopolysaccharide (LPS) binding to TLR4. This pathway of activating the immune system appears to be one of the first lines in host defense as it does not require prior exposure to the pathogenic organism. Recently, two different clinical phenotypes have been identified with genetic defects involving TLR signaling. In one, there is a genetic susceptibility to serious bacterial infection that presents in childhood and appears to improve during adolescence. One of the hallmark features of these patients is the very limited inflammatory response to overwhelming infection (i.e., limited fever and C-reactive protein [CRP] response). The more recently described defect is associated with the development of herpes simplex encephalitis linked to defects in TLR3 function. Additional alterations in TLR function are likely to be identified, and this represents an evolving field in clinical immunology. Currently, the evaluation of TLR function is confined to a limited number of centers that usually screen by evaluating TLR-induced cytokine production associated with stimulation by a variety of ligands that are specific for one or more of the TLRs.

EVALUATING NEUTROPHIL FUNCTION

The clinical features of neutrophil dysfunction usually include recurrent bacterial and fungal infections of the skin, lymph node, lung, liver, bone, and, in some cases, the periodontal tissue. This clinical presentation is most commonly observed with neutropenia as a result of decreased production, altered localization, or increased destruction of neutrophils (see Chapter 85, Infections in the neutropenic patient). In addition, some primary and secondary abnormalities of neutrophil function also demonstrate patterns of increased susceptibility to infections (Table 84.3).

The clinical pattern of infection often can help to discriminate the underlying problem. Patients with neutropenia and those with the leukocyte adhesion deficiency (LAD) tend to have recurrent cellulitis, periodontal disease, otitis media, pneumonia, and rectal or gastrointestinal abscesses. Although LAD is accompanied by a persistent granulocytosis, there is effectively a tissue neutropenia. This is due to the underlying adhesion defect that prevents the directed movement of phagocytic cells to sites of infection. In contrast, patients with chronic granulomatous disease (CGD) have significant problems with liver and bone abscesses as well as pneumonias with unique organisms, including *Staphylococcus aureus, Serratia marcesens, Burkholderia cepacia, Nocardia* species, and *Aspergillus* species. In addition, CGD patients have exuberant inflammation that may be associated with gastrointestinal and genitourinary complications. More recently CGD patients have been reported infected with the unusual human pathogens *Chromobacterium violaceum* and *Francisella philomiragia*, organisms associated with exposure to brackish water.

Table 84.3 Evaluation of suspected neutrophil deficiency

Screening tests
Multiple sequential neutrophil counts
Review of neutrophil morphology
Secondary tests
CD11, CD18 assessment
Respiratory burst assessment
Nitroblue tetrazolium test
Flow cytometric test
Specific enzyme activity testing
Chemotaxis testing
In vivo (Rebuck skin window)
In vitro (Boyden chamber, soft agar assay)

Finally, these patients tend to have a lower frequency of β-strep and *Escherichia coli* infections than do patients with neutropenia.

Screening studies directed at the evaluation of neutrophil function should start with the leukocyte count, differential, and morphologic review. If neutropenia (determining cyclic neutropenia requires multiple evaluations over time) and morphologic abnormalities are ruled out, the evaluation then should be directed at assays that provide functional information about neutrophils. Included are the flow cytometric assessment of neutrophil adhesion molecules to assess for the expression of CD11a,b,c and CD18 surface antigens (the β 2-integrins that are absent or depressed in LAD-1 patients) as well as CD15s (absent in LAD-2 patients). The neutrophil oxidative burst pathway can be screened using either the nitroblue tetrazolium (NBT) test or a flow cytometric assay (dihydrorhodamine [DHR] test), both of which are abnormal in patients with CGD. Finally, evaluation of neutrophil-directed movement (chemotaxis) can be performed in vitro with a Boyden chamber or a soft agar system as well as in vivo using the Rebuck skin window technique. Abnormalities of chemotaxis have been observed secondary to certain pharmacologic agents as well as the leukocyte adhesion deficiency, Chédiak–Higashi syndrome, Pelger–Huet anomaly, and juvenile periodontitis. A hallmark clinical feature of significantly abnormal chemotaxis is diminished neutrophil infiltration and decreased inflammation at sites of infection.

Functional testing of neutrophils has its greatest yield when evaluating patients with recurrent infections associated with a genetic neutrophil abnormality. Many patients with histories of recurrent cutaneous abscesses fail to demonstrate abnormalities in the above tests. This likely is related to the relative insensitivity of the available tests in discerning more subtle functional abnormalities.

EVALUATING THE COMPLEMENT SYSTEM

The clinical setting in which complement defects should be suspected varies depending on the type of defect. Abnormalities in the early components of the complement pathway may result in recurrent bacterial sinopulmonary infections but typically also have a history of autoimmunity. Defects in the later components of complement affecting the membrane attack complex (MAC, C5–C9) result in increased susceptibility to infections with *Neisseria* organisms usually presenting with meningitis and/or sepsis. There are rare defects in components of a second complement pathway, the alternative pathway, that may also present with recurrent infections (Table 84.4).

Table 84.4 Evaluation of suspected complement abnormality

Screening tests
CH50 assay
AP50 assay
Secondary tests
Component immunoassays
Component functional assays

The best screening test for the classical complement pathway is the total hemolytic complement activity (CH50) assay, which is often ordered together with the AP50 test used to screen for defects in the alternative complement pathway. Assuming correct handling of the serum sample (complement components are very labile), a markedly depressed or absent CH50 result strongly suggests a classical complement component deficiency. If the CH50 and AP50 are both abnormal, it suggests that the common components of both pathways (i.e., late components) are defective. Selected component immunoassays are available in larger laboratories, and component functional testing may be available in very specialized complement laboratories.

RECOMMENDATIONS

The clinical pattern of recurrent infections remains the single most useful clue in determining the likelihood of immune deficiency and identifying the best approach for evaluation. HIV infection has become the most likely cause of immune deficiency, and appropriate diagnostic testing for HIV is critical, particularly in the setting of recurrent opportunistic infection. When the history identifies repeated bacterial infections involving the sinopulmonary tract, abnormalities in antibody production, and very rarely complement component deficiency, should be considered. Opportunistic infections suggest T-cell dysfunction, while bacterial and fungal infections of the skin, lungs, and bone strongly suggest defective neutrophil function. The current area of intense investigation is focused on recurrent/chronic infections involving a more limited range of microorganisms with much of this focused on the innate immune system or the interface between the innate and adaptive immune systems. It is important to keep in mind

that the frequency of infections between individuals can vary significantly, and the line distinguishing normal from abnormal is not always clear. However, infections that are recurrent and difficult to treat or those that involve unusual organisms should definitely raise suspicion of an underlying immunodeficiency.

Laboratory studies are essential for evaluating the status of immune function. However, the prudent use of these tests requires that they be applied in an orderly fashion, starting with simpler screening tests selected according to the clinical clues provided from the patient history. The results of these tests are relatively easy to interpret when either clearly normal or absolutely abnormal. The difficulty arises in determining the actual degree of immune dysfunction when the results fall in an indeterminant region. To address this, combinations of tests often help to clarify the status of immune function or dysfunction, and involvement of a specialist with extensive knowledge of the clinical presentation and evaluation of immunodeficiencies can be crucial.

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85. Infections in the neutropenic patient

Eric Sachinwalla and Rafik Samuel

Patients receiving chemotherapy are at high risk for developing neutropenia and severe infections when their neutrophil count is depressed. Neutropenia is defined as an absolute neutrophil count (ANC) of $\leq$500 cells/mm^3. The term "profound neutropenia" is often used to describe an ANC <100 cells/mm^3. Fever in the neutropenic patient is defined as a single temperature of >38.3°C or a temperature of >38.0°C over at least 1 hour. Given the lack of inflammatory cells associated with neutropenia, signs of infection may be subtle. Skin and soft-tissue infections may lack the typical induration, erythema, and warmth often seen in patients with an intact immune system. A pulmonary infection may have only a subtle infiltrate on chest radiography and cerebrospinal fluid pleocytosis may be modest or absent despite ongoing meningitis. Some patients may not mount a fever at all and the presence of hypotension, tachycardia, or delirium may be the only presenting features of infection.

Several approaches have been developed to address the clinical entity of fever and neutropenia. Some research has looked at preventing neutropenia with the use of colony-stimulating factors. Other research has focused on preventing infection in the neutropenic patient; still others have looked at the empiric use of antimicrobials to treat infections when fever occurs. In this chapter, we focus on these three approaches as well as the main causes of infections in these severely immunocompromised individuals.

CAUSES OF INFECTION IN THE NEUTROPENIC PATIENT

Gram-negative organisms

Enteric gram-negative organisms play a significant role in the morbidity and mortality due to infection in neutropenic patients. These include *Escherichia coli*, *Klebsiella* spp., and *Enterobacter* spp. among others. These organisms gain entry into the bloodstream and lead to serious infections as a result of chemotherapy-induced mucositis leading to mucosal damage and the ability of these organisms to disseminate. Another important organism that can lead to significant disease is *Pseudomonas*, which colonizes patients and gains entry through skin damage or catheters. These organisms cause a variety of infectious processes ranging from primary bacteremia to infections of the gastrointestinal, genitourinary, and respiratory tracts. Appropriate coverage of *Pseudomonas* spp. is important when choosing empiric antibiotics because of high mortality rates associated with this infection.

One infection unique to neutropenic patients is neutropenic enterocolitis or "*typhlitis*," an inflammatory process of the cecum and ascending colon. While the exact etiology of this process is unclear, it is believed to be caused by mucosal injury from cytotoxic agents and impaired host defenses leading to invasion by microorganisms. This microbial invasion leads to necrosis of the bowel wall. Patients develop fever and right-sided abdominal pain and are at high risk for perforation. Computed tomography demonstrates right-sided colitis and in severe cases can show pneumatosis coli or evidence of bowel perforation. In cases where perforation has not occurred, broad-spectrum antibiotics that cover enteric gram-negative rods, anaerobes, and *Enterococcus* spp. such as β-lactam/β-lactamase inhibitors or carbapenems are recommended. Surgery is technically difficult in these patients and not usually needed, as studies have demonstrated that antibiotics alone are usually able to control the infection until the neutrophils recover.

Because infections due to gram-negative organisms, especially *Pseudomonas aeruginosa*, can be life threatening, patients with neutropenic fever should be started on an agent that targets these bacteria. There have been significant increases in

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the number of antibiotic-resistant gram-negative rods containing plasmid-mediated extended-spectrum β-lactamases in the Enterobacteriaceae family. These enzymes inactivate most penicillins, cephalosporins, and monobactams; therefore, knowledge of the local resistance patterns is crucial in choosing proper antibiotics. *Pseudomonas* resistance patterns are also important because carbapenemases and other resistance mechanisms can render *Pseudomonas* resistant to previously effective antibiotics. Because resistance patterns vary significantly between patients and over time, sensitivity testing from cultures is important to assure adequate therapy once the etiology of the infection is found. Even after empiric antibiotics are started, the origin of the infection should be ascertained so that appropriate interventions can be made (e.g., removal of indwelling catheter, incision and drainage of abscesses, etc.).

Gram-positive organisms

Among patients with neutropenia, there has been an increase in severity and numbers of gram-positive infections due to more indwelling catheters and damage to mucosal surfaces from chemotherapy. The bloodstream is the most common site of gram-positive infections. The three most common organisms causing bacteremia from indwelling catheters are coagulase-negative staphylococci, *Staphylococcus aureus*, and *Enterococcus* spp. When cellulitis occurs it is most commonly due to β-hemolytic streptococci and *S. aureus*. Infections due to viridans streptococci resulting in severe sepsis have been noted in patients with severe mucositis, ceftazidime use, or prophylaxis with ciprofloxacin or levofloxacin (Table 85.1).

In patients with possible gram-positive infections, vancomycin is effective initial treatment. It provides adequate coverage for the most common organisms such as staphylococci, streptococci, and most enterococci; however *Enterococcus faecium* can be resistant to vancomycin. The rates of this resistance vary from one institution to another, but may be as high as 90%. *Enterococcus faecalis* is much less likely to have vancomycin resistance. For patients with vancomycin-resistant organisms or vancomycin allergy, alternative agents include daptomycin or linezolid. Daptomycin is effective in staphylococcal bacteremia and serious skin and soft-tissue infection. Its main side effect is elevation of creatinine phosphokinase (CPK) and muscle damage; thus monitoring of CPK is warranted. Linezolid is approved for skin and soft-tissue infections but should not be used for bloodstream infections. Its major side effects of bone marrow suppression and optic neuritis limit its usefulness.

Table 85.1 Common gram-positive bacteria causing infection in the neutropenic patient

Bacteria	Form of infection	Antibiotic of choice
Staphylococcus aureus	Bacteremia, skin, and skin structure infection	Vancomycin
Coagulase-negative staphylococci	Bacteremia	Vancomycin
Enterococcus spp.	Bacteremia	Vancomycin[a]
β-hemolytic streptococci	Skin and skin structure infection	Penicillin
α-hemolytic streptococci	Bacteremia, endovascular infection	Ceftriaxone[b]
Streptococcus pneumoniae	Respiratory	Ceftriaxone[c]
Diphtheroids	Bacteremia	Vancomycin

[a] If vancomycin resistant, choices include daptomycin or linezolid.
[b] Variable resistance to penicillin, macrolides, and clindamycin.
[c] Penicillin resistance varies; local resistance rates should be reviewed.

Duration of treatment for gram-positive organisms varies based on the type of infection. In general these organisms do not result in the sepsis syndrome and early mortality but may lead to significant complications if not treated appropriately. Infections of the skin and soft tissue require at least 7 days of therapy with adequate debridement when indicated. Bacteremia due to *S. aureus* may require up to 4 weeks of therapy if the source is not located or if the bacteremia does not resolve quickly, whereas enterococcal and coagulase-negative staphylococcal infections can be treated for shorter durations, especially if infected catheters are removed. If gram-positive coverage was added empirically, it may be stopped after 2 days if no evidence of gram-positive infection is found.

Anaerobes

Anaerobes can cause infections in neutropenic patients as a result of mucosal damage. Anaerobic coverage is warranted in patients with significant abdominal complaints while awaiting cultures. This includes coverage for *Bacteroides* spp. and *Prevotella* spp. Acceptable antibiotics include a β-lactam/β-lactamase combination, carbapenem, tigecycline, or addition of metronidazole to other regimens.

Clostridium difficile colitis is always a concern in someone who develops diarrhea while on

antibiotics. In addition, some cancer chemotherapeutics have antimicrobial activity and *C. difficile* has been reported in patients who have not received an antibiotic. Any antibiotic can result in *C. difficile* diarrhea. What complicates the picture is that chemotherapeutic agents can lead to diarrhea because of mucositis. When a patient develops significant diarrhea and abdominal pain while receiving antibiotics, empiric metronidazole or oral vancomycin is warranted while awaiting the toxin assay results. An important part of *C. difficile* treatment includes stopping the agent that led to the diarrhea in the first place; unfortunately, that is not likely to be feasible in these patients because of the concern for other infections. Since the early 2000s there has been an increase in severe *C. difficile* diarrhea. There are epidemic strains of *C. difficile* that can lead to severe colitis resulting in colon perforation and emergent surgical intervention. This change in severity is believed to be due to overproduction of *C. difficile* toxin. Therapy still includes metronidazole or oral vancomycin; however, close monitoring for complications is necessary.

Fungi

Fungal infections are increasingly common among patients with neutropenia and especially those with acute leukemia or lymphoma as they can remain neutropenic for prolonged periods of time. Some reasons for the increased risk of infection include longer survival in patients with bacterial infections, chronic indwelling catheters, mucosal breakdown, parenteral nutrition, and prolonged antibiotic therapy (Table 85.2).

Candida spp. are the most common cause of fungal infections in these patients and one of the leading causes of catheter-associated bloodstream infections. *Candida* also cause disseminated disease involving organs such as the liver and spleen. Disseminated candidiasis may be difficult to diagnose by blood cultures alone because they are only 70% sensitive. In patients with prolonged neutropenia and fever, imaging of the abdomen, with attention to the liver and spleen, to look for disseminated fungal infection is necessary. Yeast and molds typically are not the cause of initial fever in neutropenic patients but rather present with persistent or recurrent fever in those already receiving antibiotics. Empiric antifungal therapy and investigation for fungal infection should be considered for patients who remain febrile after 4 to 7 days of appropriate antibacterial therapy or those who received antimicrobial prophylaxis.

Table 85.2 Common fungi causing infection in the neutropenic patient

Organism	Azole of choice	Echinocandin activity	Amphotericin activity
Candida albicans	Fluconazole	Yes	Yes
Candida tropicalis	Fluconazole	Yes	Yes
Candida parapsilosis	Fluconazole	Yes[a]	Yes
Candida glabrata	Voriconazole[b]	Yes	Yes
Candida krusei	Voriconazole	Yes	Yes
Cryptococcus neoformans	Fluconazole	No	Yes
Aspergillus spp.	Voriconazole	Yes	Yes
Zygomycetes	Posaconazole	No	Yes
Histoplasma capsulatum	Itraconazole	No	Yes
Coccidioides immitis	Fluconazole	No	Yes
Blastomyces dermatitidis	Itraconazole	No	Yes

[a] *C. parapsilosis* tends to have a higher minimal inhibitory concentration (MIC) to echinocandins, but is usually susceptible.
[b] *C. glabrata* tends to have a higher MIC to voriconazole, but is usually susceptible.

Therapy for *Candida* bloodstream infection includes removal of any indwelling catheter to help clear the organism from the bloodstream. In addition, ophthalmologic exam is necessary after therapy to make sure the patient did not develop endophthalmitis, a rare complication of candidemia. *Candida* spp. have variable resistance to available agents, and appropriate choice in antifungals is critical. Multiple agents are available for treatment of *Candida* and include the azoles, echinocandins, and polyenes. The traditional therapy with amphotericin B is uncommonly used because of adverse events such as infusion reactions and nephrotoxicity. The lipid formulations of amphotericin are also not used frequently for *Candida* infections because of cost and the availability of good alternative agents.

The triazole fluconazole has activity against most *Candida* spp., including *Candida albicans*, *Candida tropicalis*, and *Candida parapsilosis*. Fluconazole has variable activity against *Candida glabrata* and no activity against *Candida krusei* and should not be used to treat infections due to these organisms.

Another azole, voriconazole, has good activity against all the *Candida* spp.; however, interactions with other agents metabolized through the hepatic cytochrome P450 enzymes must be taken into account. Caution should be taken when considering voriconazole in patients who may have been previously on a different azole such as fluconazole because the *Candida* spp. isolated may have a higher minimal inhibitory concentration (MIC) and may not be susceptible to voriconazole. The newest medications in the antifungal armamentarium are the echinocandins. They target the β-1,3-synthase enzyme in the cell wall of *Candida* spp. These agents include caspofungin and micafungin. These agents are active against all *Candida* spp. and may be more active than azoles in the setting of prosthetic infections.

There is currently no consensus recommendation on the best choice of empiric antifungal. In patients who did not receive antifungal prophylaxis, candidemia is the greatest concern. For those that received fluconazole prophylaxis, infection with *C. glabrata, C. krusei*, or an invasive mold is more likely because fluconazole lacks coverage for these organisms. Amphotericin B deoxycholate has previously been used as the empiric antifungal of choice, but its potential for nephrotoxicity has limited its utility. Newer clinical trials have established roles for other antifungals including lipid formulations of amphotericin B, azoles with antimold activity (itraconazole or voriconazole), and the echinocandins.

In addition to yeasts, molds may cause significant disease in neutropenic patients that have underlying leukemia, lymphoma, myeloma, or myelodysplastic syndromes due to prolonged neutropenia. The most common pathogen in this setting is *Aspergillus*; however, other molds such as the zygomycetes have increased in frequency. *Aspergillus* spp. can cause a variety of different diseases; however, the most common infections include rhinosinusitis and pulmonary disease.

Any patient with neutropenia and fever who complains of sinus congestion, pain, or epistaxis should be evaluated for possible fungal sinusitis. Typical findings include mucosal thickening on radiography, necrosis or eschar on direct visualization. Definitive diagnosis is made by culture and histopathology of biopsy specimens. Immediate therapy with a lipid formulation of amphotericin B (until zygomycetes are excluded) should be administered along with rapid surgical debridement.

Pulmonary aspergillosis may present as nodular disease, pulmonary infiltrate, infarction, or cavity. In these settings a biopsy demonstrating the organism on pathology in addition to a positive culture makes the diagnosis. Because many filamentous fungi may resemble *Aspergillus* on stain, culture is important to distinguish it from the others. Once the cultures grow *Aspergillus*, therapy can be changed to voriconazole or can be continued with amphotericin B. Other agents with activity against *Aspergillus* include itraconazole and the echinocandins. Combination therapy with two of the three classes is occasionally used. Duration of therapy should be prolonged, with radiologic evaluation to demonstrate improvement or cure.

Reports of increased incidence of zygomycete infections in neutropenic patients are concerning. This trend has been noted since the early 2000s and may reflect increased use of agents such as voriconazole, which has no activity against zygomycetes but excellent activity against other invasive molds and may select for this infection. Other reasons include changes in immunosuppression regimens or variability in the epidemiology of the organism. These organisms can present similarly to *Aspergillus* and most commonly cause a locally invasive sinopulmonary infection. Surgical debridement is a necessary adjunct to antifungal chemotherapy for diagnostic and therapeutic purposes. While awaiting diagnostic test results, treatment with a lipid formulation of amphotericin B should be started. If rhinosinusitis or pulmonary disease consistent with fungal infection occurs while the patient is on voriconazole or an echinocandin, zygomycete infection should be considered. The only agents currently active against these organisms are amphotericin B and posaconazole. Posaconazole is available only as an oral agent and requires a fed state to be absorbed, resulting in variable absorption. Multiple studies looking at posaconazole in the salvage setting for treatment of zygomycete infections have demonstrated its efficacy. As with *Aspergillus*, prolonged therapy and evaluation with radiography to demonstrate improvement or cure is necessary.

Pneumocystis jirovecii (*carinii*) is seen in patients with leukemia or lymphoma – especially those who have been on long-term steroids. Pneumocystis pneumonia (PCP) may present insidiously with progressive dyspnea, dry cough, and fever. When this infection is suspected, bronchoscopy with appropriate staining for the organism can be diagnostic. The yield of bronchoscopy for the diagnosis of PCP is lower in cancer patients than human immunodeficiency virus (HIV)-1-infected patients

due to lower fungal burden. Therapy including high-dose trimethoprim–sulfamethoxazole (and steroids if significant hypoxia is present) should be adequate for a duration of up to 3 weeks. In certain patients known to be at high risk for PCP preventative antibiotics are useful.

Because the diagnosis of many fungal infections requires invasive procedures, two serum diagnostic tests can be used to help in the detection of common fungal infections. The β-(1–3)-D glucan test is used to detect a cell wall component of many pathogenic fungi, including *Candida, Aspergillus, Pneumocystis* and *Fusarium* spp. A 2011 meta-analysis found a pooled sensitivity of 77% and specificity of 85% but individual studies have sensitivities ranging from 55% to 95% and specificities from 77% to 96%. One significant limitation of the β-(1–3)-D glucan test is that it is not specific for any single fungal species. The galactomannan assay is more specific for *Aspergillus* spp. as it detects the galactomannan in the *Aspergillus* cell wall. A 2006 meta-analysis of patients with mostly hematologic malignancies found pooled sensitivity of 71% and pooled specificity of 89% for invasive aspergillosis. False-positive galactomannan results are possible with the use of β-lactam/β-lactamase inhibitor antibiotics. The β-(1–3)-D glucan test and the galactomannan test provide useful screening tools to help guide the need for further fungal testing and empiric treatment.

Other organisms

Other organisms such as viruses may cause fever in the neutropenic patient, but are not very common. Suspicion of viral infection requires understanding the epidemiologic setting and obtaining appropriate serology or cultures. Atypical bacteria such as *Legionella*, *Mycoplasma*, or *Chlamydia* can cause pneumonia similarly as in those without neutropenia. Other gram-negative rods or gram-positive bacteria not mentioned earlier can be identified by appropriate cultures and treated based on their susceptibilities. Mycobacterial infections are not very common in the neutropenic patient but adequate cultures with acid-fast stains can usually establish the diagnosis. Appropriate therapy is determined by the organism and the site of infection but is similar to what is given to the non-neutropenic patient. The endemic fungi such as *Histoplasma* or *Coccidioides* should be considered in the appropriate epidemiologic setting and treated similarly to the non-neutropenic patient. Finally, parasites should be considered where the epidemiology is appropriate and the symptoms are consistent with their diseases.

APPROACHES TO THE NEUTROPENIC PATIENT WITH FEVER

Prophylaxis

Granulocyte and granulocyte/monocyte colony-stimulating factors (CSFs) have been used in patients receiving chemotherapy to prevent neutropenia. The likelihood of developing neutropenia and subsequent fever is the driving factor for this approach. In controlled trials, human CSFs have been shown to decrease the risk of febrile neutropenia and infection associated with intensive chemotherapy. In one meta-analysis of patients who received chemotherapy for either solid tumors or lymphoma, the rate of developing fever in those who received granulocyte colony-stimulating factor (G-CSF) was significantly lower than placebo. The use of G-CSF resulted in half the infections. In addition, fewer patients required a decrease in chemotherapy or delay of treatment. The major complication of G-CSF was bone pain. In patients with established fever and neutropenia there is no evidence to suggest a survival benefit with the use of G-CSF and so it is not recommended.

The use of prophylactic antibiotics in neutropenic patients remains controversial. Studies involving fluoroquinolones have shown a decrease in the incidence of fever. A 2005 study looking at >1500 patients with solid tumors or lymphoma showed that the use of levofloxacin decreased the incidence of febrile neutropenia from 85% to 65%. It also demonstrated a decreased rate of infection in the levofloxacin group. There was no difference in mortality. A 2005 meta-analysis of fluoroquinolone prophylaxis trials demonstrated a reduction in all-cause and infection-related mortality. Routine, widespread use of fluoroquinolones is associated with an increased risk of bacterial resistance and *C. difficile* colitis. Therefore, prophylaxis should only be considered in patients with profound neutropenia who are expected to be neutropenic for a prolonged period of time.

Prophylaxis against *Candida* infections is recommended in patients with a high risk of invasive candidal infections, such as stem cell transplant recipients or patients with acute leukemia undergoing induction chemotherapy. Fluconazole has been studied and has been shown to be effective in reducing fungal infections in stem cell recipients; however, the data are not as clear for individuals

who have neutropenia due to cancer chemotherapy. Itraconazole has been shown to be more effective than fluconazole; however, poor bioavailability and tolerability issues limit its use. A recent study compared use of posaconazole to either itraconazole or fluconazole in leukemic patients with neutropenia. Posaconazole was shown to decrease infection with filamentous molds 10-fold and also decreased mortality. Side effects, mainly gastrointestinal, were greater in the posaconazole group. Fluconazole, itraconazole, voriconazole, posaconazole, micafungin, and caspofungin are all potential options. Antifungal prophylaxis should only be used in high-risk patients and is not recommended for patients with an anticipated duration of neutropenia <7 days.

Empiric therapy in the neutropenic patient with fever

Historically, patients with neutropenia and fever were treated similarly to non-neutropenic patients. Some of these patients developed sepsis and increased morbidity and mortality before an infection was identified. Therefore, early empiric therapy, especially for gram-negative infections, is recommended when neutropenic patients develop fever. However, over 50% of patients with neutropenia and fever have no identifiable cause. With better antibiotics and oral bioavailability, some neutropenic patients may be treated as outpatients and not require hospitalization; others need to be treated with intravenous antibiotics and monitored closely. Several risk prediction rules have been developed to identify low-risk patients. These are usually patients who have solid tumors receiving outpatient chemotherapy, those with no significant medical comorbidities, and expected neutropenia duration of less than 7 days. These patients may be treated with oral agents or outpatient parenteral antibiotics. In randomized studies comparing ciprofloxacin + amoxicillin/clavulanate to ceftriaxone + amikacin, the outcomes were similar. Similar results were seen in this population when compared to ceftazidime. Careful attention to susceptibility patterns in the local area should be made, especially community-acquired methicillin-resistant *S. aureus* (MRSA) and gram-negative rods resistant to fluoroquinolones. Persistent fever or signs and symptoms of worsening infection should prompt readmission to the hospital for these patients.

In patients who do not fit the criteria above, or have evidence of severe infection, hospital admission and empiric treatment with intravenous antibiotics is critical. Antibiotics should include broad gram-negative coverage, including *P. aeruginosa*. Acceptable empiric antibiotics are listed in Table 85.3.

Table 85.3 Antimicrobial agents for empiric therapy in the febrile neutropenic patient

Antibiotic[a,b]
Cefepime
Imipenem
Meropenem
Piperacillin/tazobactam

[a] If gram-positive infection is suspected, vancomycin can be added.
[b] If vancomycin allergic or suspect vancomycin-resistant enterococcus, alternative would be daptomycin or linezolid.

Table 85.4 Indications for addition of gram-positive coverage

Hemodynamic instability or severe sepsis
Radiographic evidence of pneumonia
Positive blood culture with gram-positive organism
Clinical suspicion of central line-associated infection
Skin or soft-tissue infection
Colonization with MRSA, vancomycin-resistant enterococci, or penicillin-resistant *Streptococcus pneumoniae*
Severe mucositis
Prior fluoroquinolone prophylaxis
Use of ceftazidime as empiric gram-negative coverage

The role of empiric gram-positive coverage has been well studied. Despite the preponderance of these organisms as a cause of bacteremia in patients with febrile neutropenia, routine addition of gram-positive coverage does not alter mortality in neutropenic patients and therefore is not required in all patients with neutropenic fever. Patients with significant risk for gram-positive infections should, however, receive vancomycin empirically when febrile (Table 85.4).

After patients have been started on empiric agents, reassessment of antibiotics at 2 to 5 days is necessary. By this time, results of initial cultures are available. If an infectious agent is identified, antibiotics can be tailored to that organism. If cultures are negative and the patient remains febrile, adjustment of antibiotics may be needed. Patients who are not on a glycopeptide could have vancomycin added. In those who are already on vancomycin, it can be stopped. In patients with continued fever at 4 days or in

high-risk patients, an antifungal agent can be added to prevent or treat an indolent fungal infection.

As stated above, there is no consensus recommendation on choice of empiric antifungal therapy. There have been studies comparing newer azoles and echinocandins with amphotericin or one of its lipid formulations. These studies had composite end points including tolerability, time to fever resolution, prevention of fungal infections, and death. The azoles fluconazole and itraconazole have indications for empiric antifungal therapy in the neutropenic patient with fever, whereas voriconazole does not. There are concerns with empiric use of fluconazole in this setting as it lacks activity against molds and some *Candida* spp. A study comparing voriconazole with liposomal amphotericin B demonstrated that voriconazole was inferior to liposomal amphotericin B when looking at the composite score; however, there were significantly more fungal infections emerging in the amphotericin arm (21 vs. 8). Many experts consider the balance of tolerability and efficacy to favor initiating voriconazole over amphotericin B. The echinocandin caspofungin was compared with liposomal amphotericin B with the results showing noninferiority of caspofungin.

Adjunctive agents

CSFs have been studied in febrile neutropenic patients. The results demonstrate decreased days of neutropenia in the patients who receive the CSFs, but CSFs have not been shown to decrease duration of fever, use of anti-infective agents, or cost. Importantly there has been no decrease in mortality. Therefore, the routine use of CSFs is not recommended in patients with neutropenic fever.

White blood cell (WBC) transfusions are not currently recommended as an adjunctive therapy for patients with neutropenic fever. Transfusions have significant risk and toxicity including transmission of viral infections such as cytomegalovirus, graft-versus-host reactions, and fever associated with transfusion reactions. Despite these risks, some centers give WBC transfusions to patients with refractory neutropenia and severe uncontrollable infections. At this point in time, this approach should be considered only experimental.

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86. Infections in patients with neoplastic disease

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Patients with neoplastic disease and suspected infection require the following main factors to be considered in their evaluation: (1) geographic predisposition for exposure to and to acquire infection including prior colonization with drug-resistant organisms and alteration in hosts' microbiota; (2) known and unrecognized immune defect or defects due to underlying malignancy or antineoplastic therapy, or both (Table 86.1); (3) breakthrough infections due to drug-resistant pathogens in patients receiving antimicrobial chemoprophylaxis, and (4) familial/genetic predisposition to certain infections in the immunocompromised host. The febrile cancer patient may also have fever from noninfectious conditions such as tumor fever or drug fever. After evaluation, the next question is whether to treat empirically.

EPIDEMIOLOGY

People may be exposed to a variety of organisms through travel, work, habits, or hobbies; in the home; or in other hospitals, outpatient clinics, and infusion centers. A person with children at home is likely to be exposed to a number of infectious agents such as influenza, parainfluenza, respiratory syncytial virus, varicella-zoster virus (VZV), human herpesvirus 6 (HHV-6), and cytomegalovirus (CMV). Hospitals are a rich source of antibiotic-resistant microorganisms, including multidrug-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant and/or vancomycin-tolerant *Enterococcus* species, multidrug-resistant *Pseudomonas* and *Stenotrophomonas*, and extended-spectrum β-lactamase-producing Enterobacteriaceae such as *Escherichia coli* and *Klebsiella* species. The recent global spread of carbapenem-resistant Enterobacteriaceae (CRE) has underscored the limitations of antibiotic regimens.

A recent review of 27 reports published since 2008 showed gram-negative bacteria continued to be the most prominent cause of bacteremia in cancer patients, especially patients not receiving broad-spectrum antimicrobial prophylaxis. Furthermore, high prevalence of invasive bacterial disease due to multidrug-resistant gram-negative bacteria has had substantial impact on prolonged hospitalization, higher morbidity, and death. It is important to know where an individual has been hospitalized and what resistance patterns are known to inhabit organisms in that hospital. Furthermore, as the spectrum of infection continues to change, it is imperative to follow these trends; just as community-acquired MRSA has recently surpassed hospitalization as a more common source of these resistant bacteria, other traditional risk factors for acquiring an infection may also change. In this regard, potentially life-threatening *Stenotrophomonas maltophilia* lung infections have been observed in cancer patients even in the absence of known risk factors for such infections including (1) severe, prolonged neutropenia, (2) prolonged hospitalization, and (3) stay in critical care units or mechanical ventilation.

Systemic infections due to multiple organisms have been largely underrecognized, probably reflecting underreporting due to the lack of well-established disease definition and guidelines. Polymicrobial infections, including bloodstream, pulmonary, gastrointestinal, and urinary tract, account for 15% to 20% of all infections in cancer patients. It is not uncommon to have gram-positive and gram-negative bacteremia along with *Candida* spp. bloodstream infection in severely immunosuppressed patients with orointestinal tract ulcers resulting from chemotherapy and/or radiation therapy.

With a thorough knowledge of the epidemiologic background of the patient the physician can direct investigation or start empiric antimicrobial therapy accordingly.

The next step is to consider the patient's underlying immune defect. The immune dysfunction may result from the underlying cancer, or

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Table 86.1 Infections causing pneumonia in cancer patients based on the underlying immune defect

Immune defect (associated neoplastic diseases)	Bacteria	Fungi	Parasites	Viruses
Granulocytopenia	*Staphylococcus aureus* *Streptococcus pneumoniae* *Streptococcus* spp. *Pseudomonas aeruginosa* Enterobacteriaceae *Escherichia coli* *Klebsiella* spp. *Stenotrophomonas maltophilia* *Acinetobacter* spp.	*Aspergillus fumigatus*; non-*fumigatus Aspergillus* Non-*Aspergillus* species hyalohyphomycosis such as *Pseudallescheria boydii*, *Fusarium solani* *Mucorales* (zygomycoses) Dematiaceous (Black) fungi such as *Alternaria*, *Bipolaris*, *Curvularia, Scedosporium apiospermum* *Scedosporium prolificans*		Herpes simplex virus I and II VZV
Cellular immune dysfunction	*Nocardia asteroides* complex *Salmonella typhimurium* *Salmonella enteritidis* *Rhodococcus equi* *Rhodococcus bronchialis* *Listeria monocytogenes* *Mycobacterium tuberculosis* Nontuberculous mycobacteria *Legionella* spp.	*Aspergillus* and non-*Aspergillus* filamentous molds *Pneumocystis jirovecii (P. carinii)* *Cryptococcus neoformans* Endemic mycoses due to *Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomyces dermatitidis*	*Toxoplasma gondii* *Microsporidium* spp. *Leishmania donovani* *Leishmania infantum* *Strongyloides stercoralis* Cryptosporidium *Cyclospora* spp.	Human cytomegalovirus Respiratory viruses Influenza A and influenza B Parainfluenza type-3 Respiratory syncytial virus Adenovirus VZV HHV-6 SARS-associated coronavirus? Parvovirus B19 Paramyxovirus? Hantavirus?
Humoral immune dysfunction and splenectomy	*S. pneumoniae* *Haemophilus influenzae* *Neisseria meningitidis* *Capnocytophaga canimorsus* *Campylobacter*	*P. jirovecii (P. carinii)?*	*Giardia lamblia* *Babesia microti*	VZV Echovirus Enterovirus
Mixed defects	*S. pneumoniae* *S. aureus* *H. influenzae* *Klebsiella pneumoniae* *P. aeruginosa* *Acinetobacter* spp. *Enterobacter* spp. *S. maltophilia* *Nocardia asteroides* complex *L. monocytogenes* *Legionella* spp.	*P. jirovecii (P. carinii)* *Aspergillus spp.* *Candida* spp. *C. neoformans* *Mucorales* (zygomycoses) Endemic mycoses (severe systemic dissemination)	*T. gondii* *S. stercoralis*	Respiratory viruses Influenza Parainfluenza Respiratory syncytial virus Adenovirus VZV

Abbreviation: HHV-6 = human herpesvirus 6; SARS = severe acute respiratory syndrome; VZV = varicella-zoster virus.

Note: Patients with mixed immune defects include recipients of allogeneic hematopoietic stem cell transplant; acute or chronic graft-versus-host disease; myelodysplastic syndrome; adult T-cell leukemia lymphoma. Antineoplastic agents such as cyclophosphamide, fludarabine, *L. donovani*, and *L. infantum* may lead to serious visceral leishmaniasis. *L. donovani* is seen in Africa and Asia, *L. infantum* is seen in Africa, Europe, Mediterranean, Central and South America. VZV is rarely associated with systemic dissemination in patients with humoral immune defects, or even those with mixed immune dysfunctions. *S. stercoralis* may lead to serious, life-threatening hyperinfection syndrome in patients with marked cellular immune defects.

antineoplastic therapy, including monoclonal antibodies. The organisms that must be considered in empiric therapy with reference to the host's immune dysfunction are listed in Table 86.1.

In hospitalized patients, the organisms may be specific to the hospital and, therefore, an empiric regimen appropriate for one hospital may not be appropriate for another. The infectious

complication also depends on the nature of the underlying neoplasm. In patients with a hematologic malignancy such as acute myelogenous leukemia, chronic lymphocytic leukemia, multiple myeloma, and lymphoma, the overall frequency of infections may be as high as 75% to 80%, whereas patients with solid tumors such as breast or colon cancer have lower frequency of infection (≤30%) during the course of their disease.

NEUTROPHIL DEFECTS

The most common neutrophil defect encountered in patients with malignancy is an absolute neutropenia following cytotoxic chemotherapy. Patients with acute myelogenous leukemia, aplastic anemia, or myelodysplastic syndrome may present with severe neutropenia (≤500 cells/mm^3) due to the underlying disease. It should be remembered that neutropenic patients do not make pus. Physical signs may be absent or altered, as may x-ray findings. After careful evaluation, if there is no obvious site of infection, such as cellulitis or pneumonia, the source of infection is often translocation of bacteria from the gastrointestinal tract, and empiric therapy should be directed against the organisms anticipated to be in that patient's intestinal microbiota at that time. The microbiota may vary according to the hospital the patient is in or has been in, previous courses of antibiotics, and other epidemiologic factors (see Chapter 85, Infections in the neutropenic patient). Recently, despite an overall increase in bloodstream infections due to gram-positive bacteria such as *Staphylococcus* spp., gram-negative bacteria including *E. coli* and *Pseudomonas* spp. have remained an important cause of serious systemic infection in patients with febrile neutropenia. Cather-related bacteremia is often a concern as most patients have indwelling intravascular access devices for chemotherapy and supportive care (see Chapter 107, Intravascular catheter-related infections).

Viridans streptococci can lead to rapidly fulminant sepsis, disseminated intravascular coagulation, multiorgan failure, and shock in neutropenic patients with treatment-induced disruption of orointestinal mucosa.

Patients with prolonged neutropenia (>2 to 3 weeks) are at increased risk of invasive fungal infections (IFI). With the frequent use of fluconazole prophylaxis in high-risk neutropenic patients, a decline in systemic candidiasis has been encouraging, although this has led to a rise in infections due to drug-resistant *Candida* spp. such as *Candida glabrata* and *Candida krusei*. During the past decade, introduction of echinocandin drugs such as caspofungin, micafungin, and anidulafungin has provided a safe and effective alternative for treatment of invasive candidiasis or empiric therapy in patients with persistent febrile neutropenia. In patients with profound neutropenia extending beyond 2 weeks, *Aspergillus* spp. account for most invasive mold disease. During the past two decades, a risk in non-amphotericin B-susceptible mold infections such as *Scedosporium* and *Pseudallescheria* spp. has been noted. Furthermore, increased use of *Aspergillus* active azole-based drugs such as voriconazole has resulted in a higher number of cases of sinopulmonary zygomycosis. Response to invasive mold disease continues to remain a challenge in patients with persistent neutropenia, those receiving high-dose systemic corticosteroids, and patients with graft-versus-host disease (GVHD) following hematopoietic stem cell transplantation (HSCT).

HELPER T-LYMPHOCYTE DEFECTS

$CD4^+$ lymphocyte–mononuclear phagocyte defects are seen regularly in patients with underlying lymphomas, such as Hodgkin's disease, peripheral T-cell lymphoma, cutaneous T-cell lymphoma/mycoses fungoides, and those with leukemia, such as acute lymphoblastic, hairy cell leukemia, human T-lymphotropic virus 1-associated adult T-cell leukemia/lymphoma, recipients of allogeneic HSCT, and patients receiving treatment for post-HSCT GVHD. Antineoplastic therapy that disrupts the adaptive cellular immune response includes high-dose systemic corticosteroids given for extended duration; irradiation therapy; treatment with fludarabine and other purine analogs; and cyclosporine, tacrolimus, and antithymocyte globulins used in the treatment of GVHD. The antineoplastic biologics such as antibodies that inhibit interleukin-2, tumor necrosis factor, and T-cell surface receptors such as CD52 can lead to prolonged and severe defects in the cellular immune function. These patients are prey to an entirely different group of opportunistic pathogens than are patients with neutrophil defects as shown in Table 86.1. Some of these, such as *Mycobacterium tuberculosis*, nontuberculous mycobacteriosis due to *Mycobacterium avium* complex, *Nocardia asteroides* complex, and CMV, produce subacute as well as acute disease, and immediate empiric therapy may not be necessary. In other instances, however,

optimal specimens should be collected and empiric therapy instituted for a subacute infection that can become acute and produce rapidly fatal disease in the severely immunosuppressed individual. Examples are tuberculosis, histoplasmosis, and pneumocystosis. If a patient with a severe T-cell defect does have fever and looks toxic without specific signs or symptoms and if there is any question about a B-lymphocyte defect, empiric therapy that covers pneumocystosis (even with negative chest radiographic findings), salmonellosis, and pneumococcus should be initiated. A reasonable regimen for this is ceftriaxone plus trimethoprim–sulfamethoxazole. *Listeria monocytogenes* can lead to serious systemic infection and due to neurotropism, empiric therapy in such patients with suspected bacterial meningitis should include coverage for listeriosis.

In patients with complex cellular immune defects such as those with GVHD receiving corticosteroids, infections due to filamentous fungi such as *Aspergillus* species and nonamphotericin B-susceptible *Pseudallescheria boydii*, *Scedosporium* species, and other black (dematiaceous) fungi may present with asymptomatic pulmonary, sinus, and/or skin lesions. If appropriate therapy with an effective antifungal agent such as voriconazole is delayed, the progressive invasive fungal disease may extend locally and disseminate to the brain. These infections at that stage are often refractory to therapy. However, immune enhancement strategies with recombinant growth factors such as granulocyte–macrophage colony-stimulating factor and a proinflammatory cytokine such as interferon-γ may be beneficial in select groups of cancer patients with difficult-to-treat invasive fungal infections. Because voriconazole is often preferred to amphotericin B as the drug of choice for the treatment of systemic aspergillosis, a rise in invasive zygomycosis is concerning. Patients who are at a higher risk include patients with refractory leukemia, prolonged neutropenia, corticosteroid therapy, diabetes mellitus, and involvement of paranasal sinuses. In these patients treatment should include lipid formulations of amphotericin B (AmBisome or Abelcet), although recent experience with posaconazole has led to favorable outcomes in select cancer and HSCT recipients with life-threatening zygomycosis. Because the outcome is so poor in these patients when treated with conventional therapy, other modalities have been tried, including combination antifungals (Abelcet plus caspofungin), hyperbaric oxygen therapy, granulocyte colony-stimulating factor–mobilized donor granulocyte transfusions, recombinant cytokine therapy, and prompt surgical debridement of the devitalized infected tissue.

SPLENIC AND B-CELL DEFECTS

Patients without a spleen may develop extraordinarily severe infections caused by *Streptococcus pneumoniae* (see Chapter 97, CT overwhelming postsplenectomy infection). They are also at risk for severe infections caused by *Haemophilus influenzae* and *Neisseria meningitidis*. The risk for severe disease due to *Babesia* species in such patients in the Northeastern United States has also been infrequently reported. With the emergence of penicillin-resistant pneumococci, an empiric regimen should contain ceftriaxone and vancomycin. Newer antipneumococcal agents such as linezolid may also be used. Infections with these same organisms are seen in patients with B-cell defects, especially those caused by multiple myeloma and chronic lymphocytic leukemia, in whom hypogammaglobulinemia may be severe and prolonged. In all of these patients, the disease resulting from these encapsulated organisms can be especially severe, with accompanying bacteremia, often with no obvious source. The defect may last for years, and, because of humoral immune dysfunction, these patients may respond poorly to conventional vaccines. Therefore, at present, antibiotic prophylaxis is recommended in cancer patients who are at increased risk of serious pneumococcal disease.

SUMMARY

Evaluation of infections in the patient with neoplastic disease depends on multiple factors, including (1) epidemiologic background, (2) immune defects, (3) resident organisms in a given hospital, and (4) clinical judgment. The first three can be estimated easily. The last requires considerable bedside experience, and, in general, it is prudent to err on the side of treatment rather than observation.

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87. Corticosteroids, cytotoxic agents, and infection

Babafemi O. Taiwo and Robert L. Murphy

Iatrogenic alteration of the immune system occurs with use of corticosteroids or noncorticosteroid immunosuppressants. Although there is overlap, noncorticosteroid immunosuppressants can be broadly divided into cytotoxic antineoplastic drugs and immunosuppressants used in transplantation. Because some of the cells or biologic pathways targeted by therapeutic immunosuppressive agents are essential for the body's defenses against pathogenic microorganisms, the use of immunosuppressants involves walking a fine line between therapy and iatrogenic harm.

The mechanism of action of the immunosuppressant, the dosage used, the length of therapy, and underlying disease(s) all affect the type and severity of subsequent infections. These factors also inform decisions on immunization, prophylaxis, or empirical therapy in high-risk patients.

CORTICOSTEROIDS

Mechanisms of immune suppression

Corticosteroids exert a broad suppressive effect on the immune system. They achieve this in part by inhibiting transcription factors involved in activating proinflammatory genes, and also inhibiting lymphocyte activation, proliferation, and migration. Further, corticosteroids impair cytotoxic T-cell response and delayed-type hypersensitivity reaction. By reducing the production of interleukin-2, interferon-γ, leukotrienes, and tumor necrosis factor corticosteroids dysreguate the cytokine response to antigens. Adhesion molecules on endothelial cells are reduced and the migration of granulocytes to sites of infection is inhibited. Indirectly, corticosteroids impair phagocytosis due to their effect on glucose homeostasis. Antibody formation and turnover are also affected especially at high corticosteroid dosages and with prolonged use, and there may be reversible lymphopenia and monocytopenia. Collectively, these effects blunt cellular immunity and antigen-specific responses. Thus, while corticosteroids can be beneficial to some patients, they increase susceptibility to pathogens, particularly those that are controlled by cellular immune responses. Corticosteroids can also induce anergy and block the normal febrile response to infection. There is essentially no bone marrow suppression.

Corticosteroids as therapeutic agents in infectious diseases

The immunologic and/or inflammatory response to a pathogen may be excessive and deleterious to the host. Because the inflammatory mediators of tissue damage such as tumor necrosis factor, interleukin-1, and interferon-γ can also cause significant injury at sites distant from the initiating infection, the systemic anti-inflammatory properties of corticosteroids may provide clinical benefit. The effectiveness of corticosteroid therapy in some infections such as herpes zoster is controversial, but its beneficial role is established for other infections such as severe *Pneumocystis jirovecii* (*carinii*) pneumonia (PCP). Table 87.1 outlines disease processes for which there is moderate to good evidence that corticosteroids confer clinical benefit.

Corticosteroids and risk of infection

Myriad pathogens are associated with impaired cellular immunity and corticosteroid use (Table 87.2). Most of the organisms listed rarely cause significant or life-threatening infections in the immunocompetent patient. Some, such as *P. jirovecii*, cause disease only in immunocompromised individuals.

Patients with severe opportunistic infections often have concurrent underlying impairment of cellular immunity separate from the iatrogenic impairment secondary to steroid use. Thus, the risk of infection varies by underlying disease process. For instance, patients with acquired

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Table 87.1 Infections/complications of infections with moderate to good evidence that adjuvant corticosteroid use has benefit

Infection	Corticosteroid therapy
Acute bacterial meningitis caused by *Haemophilus influenzae* type B in children or *Streptococcus pneumoniae* in adults	Dexamethasone 0.15 mg/kg q6h × 4 d
Pneumocystis jirovecii pneumonia, PO_2 ≤70 mm Hg in HIV-infected patients	Prednisone 40 mg BID × 5 d, then 40 mg qd × 5 d, then 20 mg qd for 11 d
Acute severe laryngotracheobronchitis (croup)	Dexamethasone >0.3 mg/kg qd × 3–4 d
Allergic bronchopulmonary aspergillosis	Prednisone 45–60 mg qd until infiltrate clears then taper
Typhoid fever, critically ill with mental status changes or shock	High-dose dexamethasone × 2–3 d
Tuberculous pericarditis and meningitis	Prednisone 60–80 mg qd for several weeks followed by taper

Abbreviations: HIV = human immunodeficiency virus.

Table 87.2 Pathogens associated with corticosteroid use or other causes of cellular immunodeficiency

Bacteria
Legionella pneumophilia
Listeria monocytogenes
Mycobacterium tuberculosis
Nocardia species
Salmonella species
Rhodococcus equi
Fungi
Blastomyces dermatitidis
Candida species
Coccidioides immitis
Histoplasma capsulatum
Cryptococcus neoformans
Aspergillus species
Helminths
Strongyloides stercoralis
Protozoa
Cryptosporidium parvum
Pneumocystis jirovecii
Toxoplasma gondii
Plasmodium species
Viruses
Cytomegalovirus
Epstein–Barr
Herpes simplex
Varicella-zoster
Influenza
Hepatitis B

immunodeficiency syndrome (AIDS) or childhood acute lymphocytic leukemia have higher rates of PCP than patients without these diseases but receiving chronic corticosteroid therapy. For patients requiring chronic corticosteroid therapy, the infection rate for many of the pathogens listed in Table 87.2 is actually quite low. Overall, the risk increases with the dose and duration of use and may be increased by concomitant administration of other immunosuppressants. Patients who require ≥15 mg of prednisone or an equivalent dose of other corticosteroids for more than 1 month should receive prophylaxis against PCP and other infections with trimethoprim–sulfamethoxazole. Alternative agents include dapsone, atovaquone, and inhaled pentamidine. Skin induration ≥5 mm after tuberculin skin test is indicative of latent tuberculosis in this population.

CYTOTOXIC ANTINEOPLASTIC AGENTS

Mechanisms of action

Cancer itself is associated with immune suppression such as neutropenia in acute leukemia or numerical/functional lymphocyte impairment in lymphoma patients. However, clinically significant infections in cancer patients are often related to the effects of cytotoxic antineoplastic agents.

The oldest class of cytotoxic drugs comprises alkylating agents, such as cyclophosphamide, busulfan, melphalan, and chlorambucil. The purine analogs fludarabine, pentostatin (2′-deoxycoformycin), and cladribine (2-chloro-2′-deoxyadenosine) constitute another important class. Although cytotoxic agents are primarily cancer chemotherapeutic drugs, they are also used in hematopoietic stem cell transplantation and severe autoimmune disorders. Clinicians must carefully consider the risks when cytotoxic agents are used in patients without cancer, recognizing that these agents, in general, inhibit DNA and/or RNA synthesis, and are bone marrow suppressive with effects on both B and T lymphocytes.

Cytotoxic antineoplastic agents and risk of infection

Inhibition of proliferative cell types by cytotoxic antineoplastic agents is important for their therapeutic effects. However, all replicating cells are affected. Mucositis occurs during cytotoxic chemotherapy due to the effects on proliferative cells of the gastrointestinal and genitourinary systems, as well as epithelial cells of the skin.

Accordingly, cytotoxic chemotherapy predisposes to translocation of normal microflora (e.g., viridans streptococci from the oropharynx and intestinal gram-negative bacteria and *Candida* species) into blood and other sterile spaces, provoking severe illness.

One of the most common infectious complications of cytotoxic antineoplastic agents is bacterial infection from neutropenia. Because neutrophils are terminally differentiated cells that are continuously replenished through hematopoiesis, the effect of cytotoxic agents is typically reversible within a few weeks of stopping cytotoxic therapy. Exceptions include patients with hematologic malignancies and bone marrow transplant recipients. Patients become at risk for fungal pathogens such as *Aspergillus* and *Mucorales* when neutropenia is prolonged.

Cytotoxic agents also alter T-cell-mediated immune competence. They cause variable numerical reduction in lymphocytes, changes in the ratio of B lymphocytes to T lymphocytes, or changes in ratio of CD4+ T lymphocytes to CD8+ T lymphocytes. In contrast to neutrophils, T-cell populations are heterogeneous, including quiescent long-lived cells and short-lived cells that are sustained by variable levels of antigen-mediated differentiation. Hence, restoration of T-cell populations and immunity after cytotoxic chemotherapy may be incomplete for prolonged periods, depending on the affected T-cell populations. These effects predispose patients to viral, fungal, and parasitic infections, some of which are listed in Table 87.2. The immunosuppressive effects of cytotoxic antineoplastic agents on T-cell mediated immune response are compounded in hematopoietic stem cell transplant recipients by the underlying disease and graft-versus-host disease.

Dysfunctional cellular immunity during cytotoxic chemotherapy is associated with reactivation of quiescent infections such as herpesviruses and hepatitis B virus (HBV). Reactivation hepatitis may be fulminant and fatal, but there is limited clinical trial evidence to guide HBV screening and treatment before and during cytotoxic chemotherapy. After considering available evidence and expert opinion in 2010, the American Society of Clinical Oncology recommended that clinicians should consider HBV screening (with hepatitis B surface antigen with or without hepatitis B core antibody) in patients from high epidemiologic risk groups. In addition, screening is recommended if highly immunosuppressive treatment such as hematopoietic transplantation or a regimen containing rituximab is planned. Corticosteroids may potentiate the effects of rituximab because corticosteroids binding to the glucocorticoid responsive element in the viral genome have been linked with HBV replication. HBV treatment before and during cytotoxic therapy should be considered in those with evidence of chronic HBV, but this should not delay initiation of chemotherapy. Some recommend continuation of pre-emptive HBV treatment for at least 12 months after cessation of rituximab-based chemotherapy.

Reactivation of latent tuberculosis can occur during cytotoxic chemotherapy and the risk varies between patient groups. For example, the risk of reactivation tuberculosis in foreign-born persons with hematologic malignancies was estimated to be 50 to 100 times that of US-born patients while the risk of tuberculosis in US-born individuals with solid tumors was estimated to be similar to the risk in US-born individuals without cancer. Skin induration $\geq$ 10 mm after tuberculin skin test is considered indicative of latent tuberculosis in patients with some hematologic malignancies or some solid tumors (e.g., carcinoma of the head and neck).

Importantly, antineoplastic agents are different in their propensity for immunosuppression. Illustratively, vincristine appears less likely to cause infectious complications compared to more toxic agents. The infectious complications of purine analogs deserve special mention because these agents cause profound lymphopenia plus selective suppression (delayed recovery) of CD4+ T lymphocytes that may last several years after administration. Thus, patients have infection risks not dissimilar to what occurs in patients with AIDS. Infections caused by cytomegalovirus, *P. jirovecii*, and *Listeria monocytogenes* are particular risks when corticosteroids are used concomitantly.

TRANSPLANT IMMUNOSUPPRESSANTS

Iatrogenic immune suppression is indispensable to prevent organ rejection post-transplantation. The degree of immune suppression is the net effect of underlying condition and treatments that the patient has received over time. This is because the immune suppressive effects of some drugs can be prolonged and become additive with subsequent treatment. The net immune suppression, hence risk of opportunistic infections, is particularly high in patients who have received multiple treatments for rejection or hematologic malignancies.

Table 87.3 Some of the pathogens encountered in patients with deficiencies in humoral immunity and/or granulocytopenia

Gram-negative bacilli
Escherichia coli
Klebsiella species
Pseudomonas aeruginosa
Enterobacter cloacae
Haemophilus influenzae
Serratia species
Proteus species
Salmonella species
Gram-positive cocci
Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pneumoniae
Streptococcus pyogenes
Enterococcus species
Anaerobes
Bacteroides species
Clostridium species
Fusobacterium species
Parasites
Giardia lamblia
Fungi
Candida species
Aspergillus species

TRANSPLANT IMMUNOSUPPRESSANTS AND RISK OF INFECTION (SEE CHAPTER 89, INFECTIONS IN TRANSPLANT PATIENTS)

The infectious disease complication is dictated by the induced immunosuppression. Because the immune defect usually involves T cells, intracellular pathogens (Table 87.2) are the primary culprits. Thus, cyclosporine, which blocks T-lymphocyte activation and inhibits cell-mediated immunity, is likely to predispose to infection with intracellular pathogens. Likewise, treatment with OKT3, antilymphocyte globulin (ALG), tacrolimus, methotrexate, and azathioprine are also likely to inhibit cell-mediated immunity and increase the risk of infection with intracellular pathogens. Special vigilance for *Mycobacterium tuberculosis*, endemic fungi, *Cryptococcus*, PCP, and Herpesviridae is warranted in patients receiving these drugs.

In situations where the main defect involves B lymphocytes and primary antibody responses, infections with extracellular bacteria (Table 87.3) are more likely. Other factors that are predictive of the infectious complication post-transplant include the time elapsed since transplantation, underlying disease, and the presence of active or latent infections in the transplant recipient or donor. In general, infections in the first month post-transplant are caused by bacteria or *Candida* and often are related to the hospitalization and the surgical procedure. With the exception of herpes simplex virus reactivation, opportunistic infections due to transplant immunosuppressants occur after 1 month post-transplant. Epstein–Barr virus is unique in that it can cause post-transplant lymphoproliferative disorder, typically after 6 months post-transplant. Appropriate prophylaxis or empiric therapy is necessary to minimize the infectious complications of transplant immunosuppression.

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88. Biologics

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INTRODUCTION

Biologic therapies have revolutionized nearly every discipline of medicine. As our understanding of the relevant immunologic pathways of cancer, rheumatologic disease, hematopoietic and solid organ transplantation has evolved, so has the discovery of new monoclonal antibodies for targeted therapy. Currently, over 100 monoclonal antibodies have been approved for clinical use. This chapter highlights two commonly used monoclonal antibodies and their associated infectious complications. We outline the immunologic mechanism of action and indications of use of these important biologic therapies. We also examine the commonly reported infectious complications and summarize the role for pre-implementation diagnostics, post-implementation surveillance, and antimicrobial prophylaxis.

LYMPHOCYTE-DEPLETING THERAPIES

Monoclonal antibodies that target surface proteins found on lymphocytes including alemtuzumab (humanized chimeric monoclonal antibody that recognizes CD52) and rituximab (chimeric murine/human monoclonal antibody directed against the CD20) have been used successfully in the management of lymphoproliferative disorders and autoimmune diseases. We focus on rituximab because of the propensity of available data. Rituximab is constructed with human IgG1 and kappa-chain constant regions and heavy and light chain variable regions from a murine antibody to the CD20 antigen, a hydrophobic transmembrane protein which is present on mature B lymphocytes but absent from the surface of normal plasma cells. Rituximab eliminates mature B cells. Although the CD20 antigen is absent from the surface of mature plasma cells, rituximab can be complicated by hypogammaglobulinemia; the precise mechanism is incompletely understood. Rituximab is currently approved for the treatment of non-Hodgkin's lymphoma (NHL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia (CLL), and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides. In addition, rituximab is approved as second-line therapy for rheumatoid arthritis (RA) not responsive to tumor necrosis factor (TNF)-blocking agents. This anti-CD20 monoclonal antibody has also been widely used off-label for lupus, autoimmune hematologic diseases (including primary idiopathic thrombocytopenic purpura and autoimmune hemolytic anemia), multiple sclerosis, bullous dermatologic disorders, immune-mediated glomerular disease, and cryoglobulinemia.

The B-cell immunomodulatory effects of rituximab can be long lasting. Rituximab persists in the serum for many months after the drug is initially administered and can cause sustained depletion of B cells for 6 to 9 months after completion of therapy. One year after completion of rituximab, even when the quantitative number of B cells has recovered, these populations of B cells are often functionally nonequivalent to pre-rituximab B cells, with decreased expression of CD27, suggesting a relative deficiency in memory B-cell populations. Additionally, late-onset neutropenia can complicate rituximab therapy, with the median time to onset of neutropenia around 102 days, often coinciding with B-lymphocyte depletion.

The nature and duration of these immunomodulatory effects of rituximab have implications for infectious complications. In a study evaluating the pre-emptive use of rituximab in treating Epstein–Barr virus (EBV)-related post-transplantation lymphoproliferative disorder (PTLD), individuals receiving rituximab had a significantly higher incidence of bacterial infections, predominantly from gram-negative bacilli (including *Pseudomonas* and *Haemophilus*), gram-positive cocci, and atypical mycobacteria, as compared to

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controls. Increased rates of post-rituximab viral infections have also been reported, with hepatitis B virus (HBV) reactivation, cytomegalovirus (CMV) infection, and varicella-zoster virus (VZV) all well documented, with the median time from initiation of rituximab treatment to diagnosis of viral infection approximately 5 months. HBV reactivation occurring in the context of rituximab therapy has been specifically associated with significant morbidity and mortality. The median duration of time from rituximab administration to HBV reactivation is approximately 3 months, with 29% of cases occurring greater than 6 months after the last dose of rituximab. While the control of HBV infection is mediated by HBV-specific cytotoxic T lymphocytes, the profound and durable depletion of circulating B lymphocytes prevents adequate antigen presentation and is thought to be a major contributing factor involved in HBV viral replication and reactivation complicating rituximab therapy. Although the risk of HBV reactivation is greatest in hepatitis B surface antigen positive (HBsAg (+)) individuals, HBV core antibody positive patients (HBcAb (+)) are also at risk for serious complications. Moreover, in a meta-analysis of patients with NHL treated with rituximab therapy where 387 individuals were found to have HBV reactivation, 304 were HBcAb (+)/HBsAg (−) individuals while only 83 individuals were HBsAg (+). Thus, early identification of patients at risk for HBV reactivation – before they receive rituximab therapy – is critical for avoiding morbidity and mortality from HBV-related disease. In patients who will receive rituximab therapy, screening for chronic HBV infection with HBsAg, HBcAb, HBsAb, and serum HBV DNA testing is indicated. HBsAg (+) individuals – regardless of whether HBV DNA is detectable in the serum – should be initiated on antiviral therapy immediately to block viral replication and disease progression prior to administration of rituximab. While there have been differing opinions as to whether HBcAb (+)/HBsAg (−) individuals should be monitored by serial HBV DNA and liver function tests (LFTs) versus immediately placed on pre-emptive antiviral therapy, more recent recommendations are to use prophylactic antiviral therapy in these individuals as well. While the nucleoside analog lamivudine has been most extensively studied for antiviral prophylaxis of chronic HBV, high rates of lamivudine resistance have been reported. Therefore, newer nucleoside analogs including entecavir and tenofovir – either alone or in combination – are the preferred prophylactic therapy for chronic HBV infection in the setting of rituximab administration. Current guidelines suggest initiation of anti-HBV viral therapy 1 to 2 weeks prior to rituximab therapy with continuation of antiviral therapy for a minimum of 6 months after this biologic therapy is discontinued, and recommend concomitant close monitoring of HBV DNA and LFTs during the course of rituximab therapy.

Progressive multifocal leukoencephalopathy (PML), a severe and fatal central nervous system (CNS) demyelinating disease caused by reactivation of the polyomavirus John Cunningham (JC) virus, has also been reported in individuals with lymphoproliferative disorders treated with rituximab. For example, HIV-negative individuals with CLL treated with fludarabine and rituximab have been described to have clinical syndromes compatible with PML with JC virus detectable by PCR in the cerebrospinal fluid; these patients survived only months after the diagnosis of PML was made. It is not clear if PML from reactivated JC virus was a direct result of mature B-lymphocyte depletion caused by rituximab or a consequence of concurrent T-cell depleting therapies. Many patients with lymphoproliferative disorders who developed PML received multiple other chemotherapeutic agents, including purine analogs, corticosteroids, and alkylating agents in addition to rituximab, thus making it difficult to ascribe the presentation of PML to rituximab-related immunomodulatory effects alone. Nevertheless, given PML has been described in individuals receiving rituximab therapy, it remains important for clinicians to remain vigilant about any neuropsychiatric decline that may be attributable to JC virus-related disease.

While no firm guidelines exist regarding prophylaxis against *Pneumocystis jirovecii* (*carinii*) pneumonia (PCP) in non-HIV infected patients who are immunosuppressed, there is evolving evidence that PCP prophylaxis is warranted in individuals who receive rituximab as either mono or combination therapy, particularly in the setting of use in individuals for hematologic malignancies or underlying renal disease.

It is important to ensure vaccinations against polio (inactivated), influenza (inactivated), *Haemophilus influenzae*, pneumococcus, tetanus, diphtheria, pertussis, hepatitis A and B, and meningococcus (when indicated) are up to date in individuals who may receive lymphocyte-depleting biologic therapies. Administration of live viral vaccines during the course of or in

the peri-administration period of rituximab is contraindicated. The United Kingdom Department of Health does provide some guidance on the timing of live vaccine administration in patients who receive biologic agents, suggesting that live vaccines should not be given 4 weeks before first administration of any biologic agent or 12 months after rituximab.

TUMOR NECROSIS FACTOR-α INHIBITING THERAPIES

Tumor necrosis factor-α (TNF-α) blocking therapy has revolutionized the care of individuals with rheumatologic disorders and inflammatory bowel disease (IBD). Four monoclonal antibodies to TNF-α – infliximab, adalimumab, golimumab, and certolizumab – are clinically used routinely. Infliximab is a chimeric monoclonal antibody comprising human immunoglobulin constant regions with murine variable regions, while adalimumab and golimumab have both human constant and variable immunoglobulin regions. These monoclonal antibodies against TNF-α are approved for the treatment of RA, psoriasis, psoriatic arthritis, and ankylosing spondylitis. Infliximab, adalimumab, and certolizumab (a pegylated humanized Fab fragment) are all approved for use in Crohn's disease. Infliximab is additionally approved for use in ulcerative colitis. Etanercept has a different mechanism of action from the anti-TNF-α monoclonal antibodies, and is a soluble TNF-α receptor that binds both TNF-α and lymphotoxin. Etanercept is used to treat RA, psoriatic arthritis, juvenile RA, and ankylosing spondylitis.

TNF-α is released by activated macrophages and is essential in the control and containment of intracellular pathogens. TNF-α production recruits inflammatory cells to an area of infection and stimulates the formation and maintenance of granulomas that physically contain infection. In addition, TNF-α directly activates macrophages, which phagocytose and kill mycobacteria and other pathogens. Thus, inhibition of TNF-α significantly increases the risk of infection. In a meta-analysis of nine randomized control trials to assess the harmful effects of infliximab and adalimumab versus methotrexate or other disease-modifying antirheumatic drugs (DMARDs), the odds ratio of risk of serious infection associated with anti-TNF-α therapy was 2.0. The rate of risk of serious infection in patients with rheumatologic diseases treated with anti-TNF-α agents ranged from 3 to 6 infections per 100 patient-year, with approximately 2.2 increase in relative risk of infection with use of these biologic agents. Anti-TNF-α therapy has also been shown to double the risk of opportunistic infections (OIs) in individuals with IBD.

The most common types of infection in RA patients treated with anti-TNF-α therapy are upper and lower respiratory tract infections, urinary tract infections, and skin infections. In the RATIO (Research Axed on Tolerance of bIOtherapies) registry where all cases of OI in patients receiving anti-TNF-α therapy for rheumatologic indications over a 3-year period were documented, multiple OIs were found in individuals receiving infliximab, adalimumab, or etanercept. The median time to occurrence of an OI from the initiation of anti-TNF-α therapy was found to be approximately 16 months. Twenty-six percent of infected individuals required hospitalization in an ICU and 10% ultimately died from OI-related complications. In almost all cases, infections were due to intracellular organisms. One-third of infections were bacterial (including *Listeria*, *Nocardia*, nontyphoidal *Salmonella*, *Legionella*, atypical mycobacterial spp.), 40% viral (primary and reactivation varicella, herpes simplex virus [HSV], CMV), 22% fungal (*Pneumocystis*, *Aspergillus* spp., cryptococcus), 4% *Mycobacterium tuberculosis*, and 4% parasitic (Leishmania). Listeriosis and legionella infections ultimately became black box warnings for anti-TNF-α therapies on US packing inserts. Interestingly, the anatomic sites of infection in anti-TNF-α therapies were often unusual – i.e., tuberculosis (TB) cases were predominantly extrapulmonary, and there were several cases of listeria and salmonella causing septic arthritis. At OI diagnosis, anti-TNF-α therapy was discontinued in all but one patient; anti-TNF-α therapy was resumed in 40% of patients after a median duration of 1.7 months of therapy for the OI. Postoperative *Staphylococcus aureus* infection has also been observed in individuals on anti-TNF-α therapy with increased wound dehiscence and postoperative bleeding noted in individuals who had continued anti-TNF-α therapy close to the perioperative time period.

In a meta-analysis of 22 randomized controlled trials of adults with either Crohn's disease or ulcerative colitis receiving biologic therapy, anti-TNF-α therapy was found to double the risk of OI. In IBD patients receiving anti-TNF-α therapy, infection with *Streptococcus pneumoniae*, *Legionella pneumophilia*, *Salmonella* species, *Listeria*

monocytogenes, Nocardia, and *Clostridium difficile* species have all been observed. Infection with *M. tuberculosis*, herpes simplex, primary varicella, herpes zoster, CMV, EBV, and oral/esophageal candidiasis was also reported.

Anti-TNF-α therapies are not equivalent in their risk of infectious complications; in fact, the infectious risks associated with infliximab and adalimumab therapies are higher than that associated with etanercept. This observation is particularly relevant for mycobacterial and fungal OIs, where compared to etanercept, infliximab has been associated with a 2- to 7-fold increased risk of coccidiomycosis, histoplasmosis, and TB, with a shorter time to TB onset (17 versus 48 weeks) and a higher proportion of TB cases with disseminated or extrapulmonary disease (25% versus 10%). Other studies demonstrate a 12-fold greater risk of latent TB infection (LTBI) reactivation with infliximab compared to etanercept. Interestingly, the risk of acquiring nontuberculous mycobacterial infections (including *M. avium*, *M. chelonae*, *M. abscessus*, *M. marinum*) appears to be equal whether TNF-α antibodies or soluble receptors are used for therapy. Although the exact immunologic differences portending the infectious risks associated with anti-TNF-α monoclonal antibodies and the soluble TNF-α receptor inhibitor are not known, multiple mechanisms have been postulated. Unlike etanercept, monoclonal antibodies to TNF-α may have the ability to cross-link transmembrane TNF-α and induce apoptosis of TNF-producing cells. The anti-TNF-α monoclonal antibodies also bind TNF-α with greater avidity and for longer duration than etanercept; the half-life of infliximab is approximately 11 days and its biologic effect can persist up to 2 months, whereas etanercept has a half-life of 3 days and its effect on TNF-α is much more short-lived. Etanercept binds strongly to soluble TNF-α alone, whereas infliximab binds TNF-α irreversibly and has high avidity for both soluble and transmembrane TNF-α, thus prolonging inhibition of TNF-α more than etanercept.

M. tuberculosis infection is a well-documented risk in the early phase of anti-TNF-α treatment, and often manifests as extrapulmonary and disseminated *M. tuberculosis* infection rather than isolated pulmonary infection. The majority of TB infection observed in the context of anti-TNF-α therapy is due to reactivation of LTBI rather than newly acquired TB infection. For these reasons, screening for LTBI is recommended prior to initiation of anti-TNF-α therapy and repeat screening is recommended for individuals who may have acquired TB since their first screening. Diagnostics options for evaluating for LTBI prior to or during anti-TNF-α therapy include regular tuberculin skin test (TST), boosted TST, and interferon-gamma release assay (IGRA) using *M. tuberculosis*-specific antigens. For individuals found to have LTBI, there are limited data on the time interval during which patients should be on LTBI therapy before initiation of anti-TNF-α therapy, though there is some evidence that suggests concurrent LTBI and anti-TNF-α therapy is acceptable. If active TB infection is diagnosed while an individual is on anti-TNF-α therapy, guidelines suggest discontinuation of anti-TNF-α therapy. However, there are reported cases of clinical worsening with discontinuation of anti-TNF-α therapy in the setting of disseminated or extrapulmonary TB. The hallmark of this clinical scenario – termed paradoxical reaction – is the presence of worsening inflammation despite evidence for microbiologic response and improvement. In this specific clinical situation, the optimal timing of reinitiation of anti-TNF-α therapy is not clear.

Endemic fungal infection is also a well-described complication in patients on anti-TNF-α therapy. Histoplasmosis, which can present as asymptomatic infection, severe pneumonitis, mediastinal lymphadenopathy, chronic pulmonary cavitary disease, pericarditis, and arthritis, is the most commonly reported invasive fungal infection in patients treated with TNF-α inhibitors and is actually reported more frequently in these immunocompromised hosts than TB. Even in the United States, individuals on anti-TNF-α therapy had significantly increased risk of histoplasmosis infection with mortality as high as 20%. Similar to *M. tuberculosis*, there is an increased risk of histoplasmosis with the anti-TNF monoclonal antibody therapies as compared to etanercept; the incidence of histoplasmosis is estimated at 18.8/100 000 persons treated with infliximab, compared to 2.7/100 000 persons treated with etanercept. Like histoplasmosis, blastomycosis infection (presenting as CNS involvement or severe pulmonary infection in the immunocompromised host) and coccidiomycosis infection (presenting as acute or subacute pneumonia) are typically acquired as a new infection rather than reactivation in individuals on anti-TNF-α therapy. In individuals who reside in endemic areas without prior history of fungal infection, a chest radiograph and *Coccidioides immitis* serology are recommended prior to initiation of anti-TNF-α therapy. Other fungal infections such as

invasive pulmonary aspergillosis, cryptococcal cavitating pneumonia, meningitis and disseminated disease, oral/genital candidal infection, and PCP have been less commonly described in the setting of anti-TNF-α therapies.

The impact of anti-TNF-α therapy on the incidence of viral infections is less clear. CMV infection is known to complicate therapy with TNF-α antagonists; while CMV reactivation is common, disseminated life-threatening end-organ disease is less common. Primary varicella and reactivation HSV and herpes zoster have been identified in individuals with IBD treated with anti-TNF-α therapy. While there is limited literature on hepatitis B reactivation in the setting of TNF-α blockade, animal models do suggests that TNF-α promotes clearance of HBV, and that TNF-α is secreted by HBV-specific cytotoxic T lymphocytes (CTL) and synergizes with interferons to suppress HBV viral activity. There have been case reports of individuals with chronic HBV who developed fulminant hepatitis after being treated with infliximab. For this reason, prophylactic anti-HBV therapy is recommended during the duration of anti-TNF-α therapy and for 3 to 6 months post completion of anti-TNF-α therapy in HBsAg (+) individuals, and can be considered in HBcAb (+) individuals. Hepatitis C infection does not appear to progress in the setting of TNF-α blockade. The limited data on HIV infection in the setting of anti-TNF-α therapy suggest that HIV infection does not progress in individuals where anti-TNF-α therapy is used. However, there are limited data on HIV outcomes and risk for OI in the setting of anti-TNF-α therapy, and consequently, HIV infection is still considered a relative contraindication to initiation of anti-TNF-α therapy. Human papillomavirus (HPV) infection is not a contraindication for use of anti-TNF-α therapy, though individuals with extensive cutaneous and/or anogenital HPV-related disease are at high risk for progressive skin disease. Individual case-reports of EBV-related PTLD in the setting of anti-TNF therapy have also been reported. PML from JC-virus reactivation is not a common complication of anti-TNF-α therapy.

In addition to identifying epidemiologic risk factors that place an individual on anti-TNF-α therapy at risk for reactivation LTBI, endemic fungal infection, and/or reactivation of latent herpesvirus or chronic HBV infection, ensuring that vaccinations are up to date prior to initiation of anti-TNF-α therapy is critical in preventative care. All patients receiving anti-TNF-α therapy should be vaccinated against pneumococcus and should receive inactivated influenza vaccination annually. Hepatitis B vaccination is also prudent. Other non-live vaccines can be given according to established Centers for Disease Control and Prevention (CDC) guidelines/schedules. Live attenuated vaccines including intranasal influenza, oral polio, measles/mumps/rubella, yellow fever, and zoster should not be administered in individuals who have been recently treated with anti-TNF-α therapy, and guidelines suggest waiting a minimum of 6 months after infliximab and 4 weeks after etanercept is completed before any live vaccine is considered for administration.

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89. Infections in transplant recipients

Raymund R. Razonable

INTRODUCTION

Infections are the most common complication of organ and tissue transplantation. While the focus of antimicrobial prevention after transplantation has been on reducing the incidence of opportunistic infections, transplant recipients remain at risk of virtually any bacterial, fungal, viral, and parasitic pathogen. These pathogens cause clinical disease with increased severity in a transplant recipient. Several factors inherent to the transplant recipient or related to the donor, the environment, and the circumstances surrounding the transplant procedure (such as surgical techniques and immunosuppressive drugs) increase the risk of infectious complications. Generally, the overall infection risk after transplantation is determined by (1) epidemiologic exposures of the donor and the recipient and (2) the overall net state of immunosuppression.

RISK FACTORS OF INFECTION AFTER TRANSPLANTATION

Epidemiologic exposures

The major sources of pathogens are (1) the transplant recipient who may harbor latent, active, or subclinical infection prior to transplantation; (2) the donor who may harbor latent, active, or subclinical infection that could be transmitted through the allograft (donor-derived infections); and (3) the environment (hospital and community). Table 89.1 lists some risk factors for acquiring infection after solid organ transplantation.

THE TRANSPLANT RECIPIENT

The epidemiologic exposures of potential transplant recipients should be assessed to determine the risk of infection and guide preventive measures. Table 89.2 lists the recommended screening tests in the evaluation of potential recipients (and their donors) prior to transplantation. Some candidates will be found to have active infection; these infections do not generally preclude transplantation, but they should be adequately controlled and treated prior to and after the transplant procedure.

THE TRANSPLANT DONOR

The epidemiologic exposures of transplant donors should be determined so that the potential for donor-derived infections is reduced. Screening for cytomegalovirus (CMV), Epstein–Barr virus (EBV), *Toxoplasma gondii* (for heart transplant recipients), hepatitis B and C viruses, and human immunodeficiency virus (HIV) are routinely performed in transplant donors (Table 89.2). Transplant donors often have prolonged stay in the hospital prior to organ harvest, and they may have acquired nosocomial infections (Table 89.3) which could be transmitted to the transplant recipient through transplantation. Occurrence of donor-derived infections should be reported to the national database.

THE ENVIRONMENT

The healthcare environment is a major source of pathogens that cause infectious disease in transplant recipients, including invasive procedures, such as the insertion of indwelling urinary catheters, intravascular catheters, and endotracheal tubes; administration of blood products; and surgical procedures.

Many infections are acquired by the transplant recipients from the community, where natural transmission of pathogens continually occurs. Table 89.3 lists the epidemiologic exposures and the pathogens associated with the specific exposure.

Net state of immunosuppression

The two major factors that influence the overall net state of immunosuppression are: (1) the intensity of pharmacologic immunosuppression and (2) the reactivation of immunomodulating

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Table 89.1 Some of the risk factors for acquiring infection following solid organ transplantation

Preoperative period	Intraoperative period	Postoperative period
Lack of pathogen-specific immunity	Presence of pathogens in the transplant allograft (donor-derived infections)	Prolonged hospitalization
Severity of underlying clinical illnesses and comorbidity	Prolonged operative time	Prolonged duration of stay in intensive care unit
Fulminant hepatic failure	Complicated surgical procedure	Prolonged antibiotic use (fungal infections and *Clostridium difficile*)
Renal insufficiency	Profound blood loss and infusion of large volume of blood products	Renal insufficiency
Anemia	Choleduchojejunostomy (liver recipients)	Gastrointestinal and biliary complications
Prior fungal infection (i.e., endemic mycoses and aspergillosis)		Vascular complications
		Anastomotic leaks
		Wound dehiscence
		Lymphocyte-depleting drugs, high-dose steroid use, and treatment of allograft rejection
		Immunosuppresive drugs
		CMV and HHV-6 reactivation
		Reoperation within 1 month post-transplantation
		Retransplantation

Abbreviations: HHV = human herpesvirus; CMV = cytomegalovirus.

Table 89.2 Recommended infectious disease screening tools in the evaluation of donors and recipients prior to transplantation

Human immunodeficiency virus (HIV) antibody
Herpes simplex virus (HSV) 1 and 2 antibody
Cytomegalovirus (CMV-IgG) antibody
Epstein–Barr virus (EBV) antibody panel
Varicella-zoster virus (VZV) antibody
Toxoplasma antibody (in heart recipients)
Rapid plasma reagin test and treponemal tests for syphilis
Human T-cell lymphotropic virus (HTLV) I and II antibody (selected cases only)
Hepatitis C virus (anti-HCV) antibody
Hepatitis B virus (HBV) surface antigen
HBV surface antibody
HBV core immunoglobulin (IgM) and IgG antibody
PPD skin testing or interferon-gamma release assay (e.g., QuantiFERON TB test)
Strongyloides stercoralis serology (with stool ova and parasites for candidates from endemic areas)
Coccidioides immitis serology (for candidates from endemic areas)
Trypanosoma cruzi serology (for donors and recipients from endemic areas)
West Nile virus (nucleic acid testing for living donors)

Table 89.3 Epidemiologic exposures and various examples of associated pathogens in the evaluation of transplant patients with infectious syndromes

Community-acquired infections	
Residence in endemic areas	*Mycobacterium tuberculosis, Strongyloides stercoralis, Blastomyces dermatitidis, Histoplasma capsulatum, Coccidioides immitis, Trypanosoma cruzi*, human herpesvirus 8, *Plasmodium* species, dengue virus
Exposure to index cases	*Mycobacterium tuberculosis*, respiratory viruses (influenza, parainfluenza, respiratory syncytial virus, adenoviruses, SARS)
Ingestion of contaminated water and food	*Salmonella* species, *Campylobacter jejuni, Listeria monocytogenes, Giardia lamblia, Cryptosporidium parvum*
Environmental source	*Aspergillus fumigatus, Nocardia asteroides, Sporothrix schenkii*, norovirus
Vector-borne	West Nile virus, tick-borne diseases, *Plasmodium* species
Nosocomial infections	
Contaminated air	*Aspergillus fumigatus*
Contaminated water	*Legionella pneumophila*
Hand contact	Methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, drug-resistant gram-negative bacilli, influenza virus

Abbreviation: SARS = Severe acute respiratory syndrome.

viruses. There is increasing evidence that inherent defects in innate and adaptive immunity may augment the net state of immune deficiency, further increasing the risk of infectious complications after transplantation. The use of immunosuppressive drugs is essential to maintain allograft survival (by preventing acute and chronic graft rejection among solid organ transplant [SOT] recipients) and to prevent graft-versus-host disease (in allogeneic hematopoietic stem cell transplant [HSCT] recipients). The degree of drug-induced immunosuppression is particularly intense during the first 3 months after transplantation, and is characterized by severe impairment of cellular

and humoral immunity. Although defect in cell-mediated immunity is a well-recognized effect of the immunosuppressive drugs, impairment in humoral immunity, as indicated by severe hypogammaglobulinemia, may also occur. As a result, the use of immunosuppressive drugs (e.g., mycophenolate mofetil [MMF], prednisone, tacrolimus, cyclosporine, alemtuzumab, among others) places the patients at very high risk of infectious complications. For example, lymphocyte-depleting agents such as OKT3 monoclonal antibody and antithymocyte globulin increase the risk of CMV disease and other opportunistic infections such as human herpesvirus 6 (HHV-6), *Aspergillus* spp., and *Pneumocystis jirovecii* (*carinii*). These drugs could accelerate the clinical course of post-transplant hepatitis C virus (HCV) infection. Severe hypogammaglobulinemia after transplantation may increase the risk of infections with encapsulated organisms such as *Streptococcus pneumonia*. The reactivation of viruses with immunomodulating properties, such as CMV and HHV-6, during periods of intense drug-induced immunosuppression may paradoxically further enhance the overall state of immunosuppression. CMV and HHV-6 have been associated with an increased risk of bacterial and fungal opportunistic infections. The negative effect of CMV and HHV-6 on the course of post-transplant HCV infection is also well described.

TIME COURSE OF INFECTIONS AFTER TRANSPLANTATION

Infections after transplantation follow a stereotyped temporal pattern. Figures 89.1 and 89.2 depict the timing of infections after SOT (Figure 89.1) and allogeneic HSCT (Figure 89.2). However, the natural history of these infections is evolving, as influenced by various factors, most notably the use of antimicrobial prophylaxis. For example, CMV disease traditionally occurs during the first 3 months after transplantation, but this has been delayed among high-risk CMV donor-positive/recipient-negative patients to the first 3 months after completion of antiviral prophylaxis. In addition, use of antimicrobial prophylaxis has modified the drug susceptibilities of various pathogens, as exemplified by the emergence of fluconazole-resistant *Candida* spp. infections in centers utilizing fluconazole prophylaxis. There is also increasing incidence of drug resistance among bacterial pathogens, which could complicate antimicrobial prophylaxis and treatment approaches.

Timetable of infections after solid organ transplantation

Infections after SOT follow a characteristic time frame that reflects the net state of immunosuppression. These time frames are important to

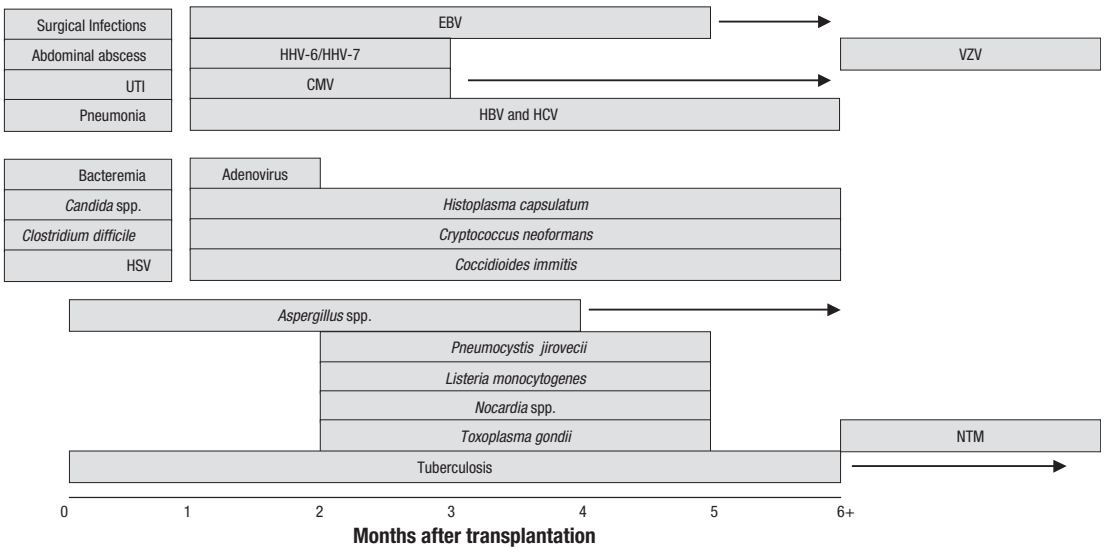

Figure 89.1 Natural history timeline of infections following solid organ transplantation in the absence of antimicrobial prophylaxis. Abbreviations: HSV = herpes simplex virus; CMV = cytomegalovirus; EBV = Epstein–Barr virus; HHV = human herpesvirus; VZV = varicella-zoster virus; HBV = hepatitis B virus; HCV = hepatitis C virus; UTI = urinary tract infection; NTM = nontuberculous mycobacteria.

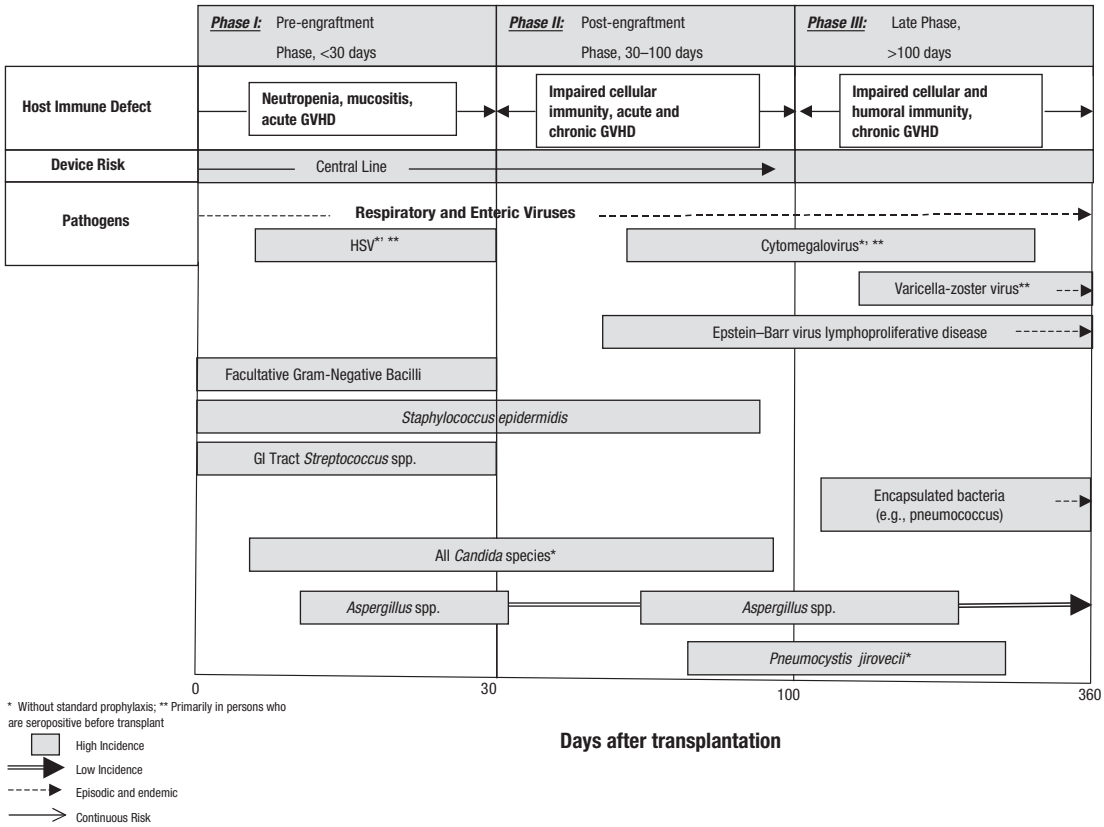

Figure 89.2 Natural history timeline of infections following allogeneic hematopoietic stem cell transplantation in the absence of antimicrobial prophylaxis. HSV = herpes simplex virus; GVHD = graft-versus-host disease; GI = gastrointestinal.

remember during the clinical evaluation of patients presenting with various clinical syndromes after transplantation. In this regard, clinical syndromes such as pneumonia and cellulitis may occur at any time, but the offending pathogen may vary depending on its onset after transplantation.

THE FIRST MONTH AFTER SOT

The three major sources of infections during this period are (1) infection that is present in the recipient prior to transplantation (i.e., bacterial peritonitis in liver recipients, catheter-related bloodstream infection in kidney recipients, bacterial pneumonia in lung recipients, and infected cardiac device in heart transplant recipients); (2) infection transmitted in the allograft (e.g., unrecognized or undiagnosed bacterial, viral, and fungal infection prior to organ harvest); and (3) infections related to surgery and hospitalization.

The majority of infections that occur during this period are related to surgical procedures and hospitalization (Figure 89.1): surgical site infections due to *Staphylococcus* spp. and *Streptococcus* spp. or other nosocomially acquired pathogens; catheter-associated urinary tract infections with gram-negative bacteria such as *Escherichia coli*, gram-positive bacteria such as enterococcus, and fungi such as *Candida albicans*; nosocomial and ventilator-associated pneumonia due to drug-resistant *Pseudomonas aeruginosa, Acinetobacter* spp., *Staphylococcus aureus*, and others; and catheter-associated bloodstream infection with gram-positive bacteria such as *S. aureus*, enterococcus, and coagulase-negative staphylococcus are seen. Intra-abdominal infections are especially common among liver recipients who require abdominal re-exploration (for hepatic artery thrombosis, bleeding, biliary leakage, or retransplantation). Prolonged hospitalization further increases the risk of nosocomial pneumonia, urinary infections, and antibiotic-related *Clostridium difficile* diarrhea. The widespread use of antibacterial agents for prophylaxis and treatment

of defined infections has led to the rising incidence of *C. difficile* infection during this period.

During this time period, herpes simplex virus (HSV) types 1 and 2 commonly reactivate and may cause localized ulcerative or disseminated disease in the HSV-seropositive SOT recipients; antiviral prophylaxis with acyclovir (or valganciclovir for CMV) has significantly decreased its incidence. Donor-derived infections such as an unrecognized fungal infection (due to *Histoplasma capsulatum* or *Cryptococcus neoformans*) and other unusual infections such as West Nile virus (WNV), rabies virus, or lymphocytic choriomeningitis virus may be manifested clinically during this period. One clue to the possible donor-derived infection is the occurrence of similar illness among recipients of organs from the same organ donor.

SECOND TO THE SIXTH MONTH AFTER SOT

This is the period when most opportunistic infections classically occur. During this period, infections due to CMV, EBV, and HHV-6 occur as a result of the severe impairment in cell-mediated immunity. Opportunistic infections with *Listeria monocytogenes, Aspergillus fumigatus*, and *Pneumocystis jirovecii* are also a clinical reflection of a severely impaired immune function. In the absence of antiviral prophylaxis, the β-herpesviruses (CMV and HHV-6) reactivate and cause fever and tissue-invasive clinical disease during this period. Invasive aspergillosis, most commonly due to *A. fumigatus*, may occur during this time, especially among patients transplanted for fulminant hepatic failure and those with epidemiologic exposure (i.e., renal insufficiency, exposure to areas of construction, or previous colonization among lung transplant recipients) and profound immunosuppression. Pneumonia is the most common clinical presentation of aspergillosis, but the clinical illness may disseminate to any body organ system, possibly due to the vasculotropic nature of *Aspergillus* spp., and cause abscesses in many organs, including the liver and the brain. Infections with endemic fungi (e.g., *H. capsulatum* and *Coccidioides immitis*) and *C. neoformans* may occur during this period. *P. jirovecii* pneumonia traditionally occurs during this period but prophylaxis with trimethoprim–sulfamethoxazole has made this infection, and those due to *Nocardia* spp., uncommon during this period.

BEYOND THE SIXTH MONTH AFTER SOT

There are generally two types of patients with varying risk of infection during this period: (1) those with good allograft function and minimal immunosuppression, and (2) those with poor allograft function as a result of recurrent rejection or chronic allograft dysfunction. In addition, liver transplant recipients with underlying chronic viral hepatitis (due to hepatitis B or C) may develop an accelerated clinical course characterized by graft failure and the need for retransplantation. These patients may benefit from prophylaxis with hepatitis B immunoglobulin and nucleoside or nucleotide analogs (for hepatitis B patients), or targeted therapy (for hepatitis C patients).

The vast majority of transplant patients will have good allograft function, and their level of immunosuppression has already been reduced to minimal levels. These patients are primarily at risk of infections similar to those observed in non-immunocompromised populations. However, a small group of SOT patients will have poor graft function as a result of recurrent rejection or chronic dysfunction; these patients are generally considered to be over-immunosuppressed and remain at high risk of opportunistic infections, including those due to *P. jirovecii, L. monocytogenes, C. neoformans, Nocardia asteroides*, CMV, and *Aspergillus* spp. infections. Patients with a persistent hypogammaglobulinemia are particularly at risk of pneumonia and bacteremia due to encapsulated organisms.

Infection with endemic mycoses such as *H. capsulatum* and *C. immitis* may occur in patients residing in certain geographic regions. One of the most common opportunistic infections during this time is the reactivation of varicella-zoster virus (VZV) causing dermatomal zoster, which has the potential for dissemination. In endemic areas, HHV-8 may reactivate to cause Kaposi's sarcoma (KS); in these endemic regions, KS is one of the most common malignancies in transplant recipients. EBV infection may occur at any time after SOT, and primary infection may result in a post-transplant lymphoproliferative disorder. CMV disease is increasingly observed during the late period (i.e., beyond the sixth month after SOT, especially among high-risk CMV D+/R− SOT recipients who receive 6 months of antiviral prophylaxis). Late-onset CMV disease may also sporadically occur years after transplantation, and these may present with atypical clinical presentations. Infections due to respiratory pathogens such as *Streptococcus pneumoniae*, and seasonal viruses such as influenza virus and respiratory syncytial virus, may occur with increased severity during this period.

Timetable of infections after hematopoietic stem cell transplantation

Infections after HSCT follow a traditional pattern (Figure 89.2) that reflects the severity of immune dysfunction and the different phases of immune recovery after transplantation.

PHASE 1: THE PRE-ENGRAFTMENT PERIOD (0 TO 30 DAYS AFTER HSCT)

The two major factors that influence the risk of infection during this period are (1) severity and duration of neutropenia and (2) disruption of mucocutaneous barrier, such as mucositis and use of vascular access catheters. *Candida* species is traditionally the most prevalent fungal infection during this period, and, hence, antifungal prophylaxis with fluconazole is commonly used for prevention. As the duration of neutropenia is prolonged, the risk for *Aspergillus* spp. is increased; and in these high-risk patients, prophylaxis with posaconazole or voriconazole is preferred. HSV reactivation commonly occurs, causing mucosal ulcerations that could complicate chemotherapy-induced mucositis. Breaks in mucocutaneous barrier, such as severe mucositis, may cause translocation of oral and gastrointestinal flora. For example, this condition predisposes to severe systemic infection and septic shock due to viridans group streptococcus. Gram-positive bacteria such as *S. aureus* and coagulase-negative staphylococci, gram-negative bacteria such as *E. coli* and *P. aeruginosa*, and fungi such as *C. albicans* may gain entry into the bloodstream through indwelling vascular catheters. HSCT patients are commonly febrile during this period, especially during periods of severe neutropenia, and receive empiric broad-spectrum antimicrobial therapy. However, this predisposes them to develop *C. difficile* diarrhea.

PHASE 2: POST-ENGRAFTMENT PERIOD (DAYS 30–100 AFTER HSCT)

This period is characterized by an impaired cell-mediated immunity, and the occurrence of classic opportunistic infections. Following engraftment, the risk of acute and chronic graft-versus-host disease is increased and immunosuppressive drugs are given to prevent this complication, thereby increasing the risk of opportunistic infections. This period is classically associated with the occurrence of CMV disease, which could manifest as severe and potentially fatal pneumonia. Allogeneic HSCT recipients undergo serial (at least once weekly) CMV surveillance using pp65 antigenemia or CMV nucleic acid testing so that CMV reactivation is detected early and treated promptly. Alternatively, patients may receive anti-CMV prophylaxis, but this may only delay the onset of CMV disease to beyond 100 days after HSCT. HHV-6 and adenovirus infections may occur during this period and cause febrile illness, rash, and hepatitis. Other pathogens that cause disease during this period include *Aspergillus* species, *Fusarium* species, *Mucor* and *Rhizopus* species, and *P. jirovecii*.

PHASE 3: LATE PHASE (BEYOND 100 DAYS AFTER HSCT)

In some HSCT patients, such as those with chronic graft-versus-host disease, the period beyond 100 days after transplantation is characterized by persistent impairment in cell-mediated and humoral immunity. In these patients, infections with CMV, VZV, EBV, *Aspergillus* species, and *P. jirovecii* may continue to occur. These patients may therefore continue to benefit from prolonged administration of antimicrobial prophylaxis.

The majority of HSCT patients will have adequate immune reconstitution during this period, and the risk of infections will be lower, although still at a relatively higher rate compared to healthy hosts. Infections with community-acquired respiratory viruses such as influenza, parainfluenza, and respiratory syncytial viruses may occur and so do infections with encapsulated bacteria such as *S. pneumoniae* and *Haemophilus influenzae*. These infections with encapsulated bacteria are particularly more common among patients with persistent low levels of immunoglobulins.

SELECTED PATHOGENS AND SYNDROMES

Bacterial infections

Any bacterial pathogen can cause clinical disease, oftentimes with increased severity, in transplant patients. Bloodstream infection due to gram-positive and gram-negative bacteria may occur among HSCT recipients, especially during the period of mucositis and neutropenia. In many of these cases, bloodstream infection is related to indwelling vascular catheters. One of the causes of septic shock in HSCT recipients with severe mucositis is bloodstream infection due to viridans group streptococci. Kidney transplant recipients are particularly at high risk of developing urinary tract infection, most often due to *E. coli* and other members of the Enterobacteriaceae, especially during the first year after transplantation.

Table 89.4 Suggested prophylactic strategies in transplantation

Indication	Prophylaxis	Dose and duration	Comments
Perioperative prophylaxis	Cefotaxime	1–2 g q8h IV for 24 h	Should be adjusted based on resistance patterns; alternative agents (vancomycin plus quinolone) may be used if resistance risk is high
Perioperative prophylaxis	Cefazolin	1–2 g q8h IV for 24 h	Should be adjusted based on resistance patterns; alternative agents (vancomycin plus quinolone) may be used if resistance risk is high
Pneumocystis jirovecii	Trimethoprim–sulfamethoxazole	80 or 160 mg of trimethoprim component PO once daily	Trimethoprim–sulfamethoxazole may protect against *Nocardia* spp., *Listeria* spp., and other bacteria Alternatives: pentamidine, atovaquone, dapsone
Herpes simplex virus	Acyclovir	200 mg PO TID for 28 d	Should be withheld when ganciclovir or valganciclovir is used; valacyclovir may be used if available
Cytomegalovirus	Valganciclovir	900 mg 1× daily; duration variable	Used as prophylaxis; dose should be increased to 900 mg twice daily for pre-emptive therapy; may protect against HHV-6, HSV, VZV
Cytomegalovirus	Ganciclovir	1 g PO TID; duration variable	Used as prophylaxis; may protect against HHV-6, HSV, VZV
Candida spp.	Fluconazole	200–400 mg PO daily for 28 d	Targeted to patients with risk factors such as complicated and prolonged surgery or profound blood loss
Gram-negative bacilli and fungi	OBDS	Variable	Benefit is debated. Selective pressure favoring anaerobic environment, with goal of decreasing risk of fungal and bacterial infection
Hepatitis B virus	Hepatitis B immunoglobulin with nucleotide/nucleoside analogs	10 000 IU daily for first week then every 4 wk (the dose of nucleotide and nucleoside analog varies depending on the drug)	Maintain serum HBIg level >100 IU; may be used in combination with nucleotide analogs such as lamivudine and entecavir
Aspergillus spp.	Amphotericin B Voriconazole Posaconazole Echinocandin	Variable depending on the drug	Administered to patients with risk factors such as prolonged neutropenia, and fulminant hepatic failure

Abbreviations: HBIg = hepatitis B immunoglobulin; PO = orally; IV = intravenous; tid = 3 times daily; HHV = human herpesvirus; ; HSV = herpes simplex virus; VZV = varicella-zoster virus; OBDS = oral bowel decontamination solution.

Bacterial pneumonia and tracheobronchitis may occur among lung recipients, potentially due to impaired mucociliary clearance. Intra-abdominal bacterial infections, such as cholangitis, peritonitis, and abscesses, may occur during the early period after liver transplantation; many of these intra-abdominal abscesses are polymicrobial in etiology. Table 89.4 lists the most common strategies for the prevention of bacterial and other infections after transplantation.

In HSCT patients, it is standard practice to provide antibacterial prophylaxis during the high-risk period of neutropenia. Some have also advocated the use of intravenous immunoglobulins (IVIG) to prevent bacterial infections, such as sinopulmonary infections with *S. pneumoniae*, in patients with severe hypogammaglobulinemia. Antibacterial prophylaxis, often with penicillin and fluoroquinolones, is often given to reduce the incidence of bacterial infections during periods of severe mucositis and neutropenia. However, fluoroquinolone use may increase the risk of sepsis due to viridans group streptococci. Empiric treatment of HSCT patients with fever during the period of neutropenia may include intravenous vancomycin and broad-spectrum cephalosporins or carbapenems.

MYCOBACTERIUM SPECIES

Transplant candidates should be screened for latent tuberculosis by tuberculin skin testing or interferon-gamma release assay, and treated preferably prior to transplantation. Some cases of donor-derived tuberculosis have been reported, and hence, all living donors are also screened for the infection. Pulmonary disease is the most

common clinical presentation, although dissemination may occur. *M. tuberculosis* has a higher propensity for dissemination and a lower response rate to treatment in transplant patients compared with the general population. The diagnosis is confirmed by mycobacterial culture, acid-fast smear, and molecular testing such as polymerase chain reaction (PCR) assays.

In the transplant patient, atypical mycobacteria, such as *Mycobacterium avium* complex may be a cause of pulmonary infection after lung transplantation. *Mycobacterium abscessus*, *M. chelonae*, *M. fortuitum*, and *M. marinum*, among others, should be considered as potential causes of skin lesions, tenosynovitis, or joint infection.

NOCARDIA SPECIES

Nocardia spp. typically cause pneumonia but can disseminate to involve the joints, skin, and especially the brain. Risk factors for nocardiosis include the degree of immunosuppression, as influenced by immunosuppressive drugs, graft rejection, and neutropenia. The routine use of trimethoprim–sulfamethoxazole prophylaxis during the first 3 to 6 months after transplantation, although intended to prevent *P. jirovecii* pneumonia, has lowered the incidence of nocardia (as well as listeria and other bacterial infections). However, breakthrough nocardia infections have been observed in patients receiving low-dose trimethoprim–sulfamethoxazole prophylaxis. The diagnosis is often established using a modified acid-fast stain and culture. Antimicrobial resistance has been reported, hence susceptibility testing of the isolate is recommended.

Viral infections

CYTOMEGALOVIRUS

CMV is the most common infection that causes significant morbidity and preventable mortality after transplantation. CMV infection occurs traditionally (in patients not receiving antiviral prophylaxis) during the first 3 months after transplantation. The onset of CMV reactivation is expected during the first 3 months after transplantation among allogeneic HSCT recipients who are undergoing CMV prevention using surveillance and pre-emptive therapy. In CMV D+/R− SOT recipients who receive antiviral prophylaxis, the onset of CMV infection and disease has been delayed to the first 3 to 6 months after completion of antiviral prophylaxis.

CMV causes direct and indirect effects that negatively affect the outcome of transplantation. The direct effects, otherwise known as CMV disease, can be manifested as CMV syndrome (febrile illness, flu-like illness, myalgias, and bone marrow suppression) or tissue-invasive disease (CMV pneumonitis, gastrointestinal disease, hepatitis, retinitis, encephalitis, allograft infection, and others). The indirect effects of CMV infection include its association with increased risk of acute and chronic allograft rejection, higher risk of other opportunistic infections such as invasive fungal disease and EBV-post-transplant lymphoproliferative disorder, and higher rate of chronic allograft dysfunction such as accelerated vasculopathy in heart recipients, bronchiolitis obliterans in lung recipients, and tubulointerstitial fibrosis in kidney transplant recipients. Risk factors for CMV disease include a CMV mismatch status; a CMV-seronegative SOT patient who receives solid organ allograft from a CMV-seropositive donor (CMV D+/R−) is at highest risk of CMV infection and disease after SOT. In contrast, a CMV-seropositive HSCT patient who receives hematopoietic stem cells from a CMV-seronegative donor (CMV D−/R+) represents a high risk after allogeneic HSCT. Immunosuppressive regimens such as OKT3 monoclonal antibody, antithymocyte globulins, anti-lymphocyte globulins, alemtuzumab, and mycophenolate mofetil increase the risk of CMV. The diagnostic tests for CMV after transplantation include viral culture (highly specific but with poor to modest sensitivity), histopathology (to diagnose tissue-invasive CMV disease), pp65 antigenemia (which detects pp65 expressed in neutrophils during active CMV infection), and molecular tests such as PCR to detect CMV nucleic acid (currently considered as the most sensitive assay for CMV detection). Serology is not useful for diagnosis of acute CMV disease after transplantation because transplant patients have delayed and impaired ability to develop antibodies during infection.

Prevention of CMV disease is an integral component in the management of transplant recipients. There are two major methods of prevention: (1) antiviral prophylaxis, the administration of antiviral drugs, most commonly with valganciclovir, to all patients at risk of CMV disease; and (2) pre-emptive therapy, the administration of antiviral drugs, most commonly with IV ganciclovir or oral valganciclovir, to transplant patients with asymptomatic CMV infection as indicated by a positive pp65 antigenemia or CMV PCR test. Treatment of CMV disease is with IV ganciclovir or oral valganciclovir. Oral

valganciclovir has been used for treatment of mild to moderate CMV disease, while IV ganciclovir is preferred for severe disease. Because of adverse effects such as nephrotoxicity and electrolyte imbalances, cidofovir and foscarnet are reserved only for the treatment of ganciclovir-resistant CMV disease. CMV viral load monitoring to detect the response to antiviral treatment is recommended; antiviral treatment is continued until clearance of the virus is demonstrated.

HERPES SIMPLEX VIRUS

The vast majority of HSV infections after transplantation represent reactivation of endogenous latent virus. Most commonly, the clinical presentation is orolabial and genital ulcers, although disseminated disease may occur in the form of hepatitis, pneumonitis, and esophageal disease. Most of the HSV infections occur during the first month after transplantation, but antiviral prophylaxis with acyclovir (or ganciclovir, which is intended primarily against CMV) has remarkably reduced its incidence. The diagnosis of mucocutaneous HSV disease is based mainly on clinical findings of typical herpetic lesions. PCR testing to demonstrate the viral DNA may confirm the diagnosis. Treatment is with oral acyclovir, valacyclovir, and famciclovir, for a duration that is guided by clinical response.

VARICELLA-ZOSTER VIRUS

Because over 90% of the adult population have antibodies against VZV, almost all cases of VZV disease after SOT and HSCT represent reactivation disease. Most commonly, this is in the form of mono- or multidermatomal zoster. Disseminated VZV disease may occur in severely immunocompromised transplant recipients. The incidence of VZV disease is approximately 10% of transplant patients. The median onset of disease is around 9 to 12 months after transplantation. The diagnosis is based mainly on clinical grounds with typical vesicular lesions in a dermatomal distribution (for typical localized disease) or in a widespread distribution (for disseminated disease). Treatment is with intravenous acyclovir for serious disease and with oral acyclovir, famciclovir, or valacyclovir for limited disease. Duration of treatment should be guided by clinical response.

EPSTEIN–BARR VIRUS AND POST-TRANSPLANT LYMPHOPROLIFERATIVE DISEASE

EBV–post-transplant lymphoproliferative disease (PTLD) consists of all clinical syndromes associated with EBV-driven lymphoproliferation, whether this is nodal or extranodal, symptomatic or subclinical, localized or disseminated, monoclonal or polyclonal, benign hyperplasia or true malignancies containing chromosomal malignancies. Primary EBV infection is the most significant risk factor for developing EBV–PTLD; the presence of CMV disease and the use of lymphocye-depleting drugs further enhance the risk. The incidence varies among organ transplant types; it is highest in small bowel and lowest in kidney transplant recipients. The diagnosis of EBV–PTLD is confirmed by histopathology of specimens obtained by excisional biopsy. Surveillance measures such as PCR assays to quantitate EBV viral load are commonly utilized, in order to assess the risk of PTLD in high-risk EBV D+/R− patients. Detection of EBV by PCR in high-risk patients should trigger evaluation for PTLD and reduction in the degree of immunosuppression. The clinical utility of EBV PCR for diagnosis of PTLD is debatable. Although low or absent EBV viral load has a very good negative predictive value, the specificity of higher EBV load is only modest. The first-line treatment of EBV–PTLD is reduction in immunosuppression. Since it is predominantly B-cell proliferation, rituximab has become the main drug for the treatment of EBV-related PTLD. Antiviral prophylaxis with acyclovir and ganciclovir is of theoretical value but has not been proven to be effective for prevention. Antiviral therapy has no role in the treatment of established PTLD.

HUMAN HERPESVIRUSES 6 AND 7

HHV-6 (variants A and B) and HHV-7 infect >95% of humans. Primary infection with HHV-6 and HHV-7 is uncommon in transplant recipients. In adult transplant recipients, most of the cases of HHV-6 and HHV-7 infection are due to reactivation of latent virus. The clinical impact of HHV-6 and HHV-7 infection can be classified as direct and indirect effects. HHV-6 can cause febrile illness, bone marrow suppression, hepatitis, pneumonitis, and encephalitis. The indirect effects of HHV-6 and HHV-7 appear to relate to their interaction with CMV and through their immune-modulating properties. The most common diagnostic test for HHV-6 and HHV-7 is nucleic acid amplification by PCR. Serology is rarely helpful since the majority of individuals are seropositive. Viral culture is not readily available due to its labor-intensive nature, and slow turnaround time. Histopathology and immunohistochemistry may be used to confirm the diagnosis of tissue-invasive disease. There are

no solid clinical data to guide antiviral treatment of HHV-6 and HHV-7, although HHV-6 appears to be susceptible to ganciclovir, cidofovir, and foscarnet, whereas HHV-7 may be resistant to ganciclovir.

HUMAN HERPESVIRUS 8

Infections with HHV-8 may occur after transplantation to cause KS, Castleman's disease, primary effusion lymphoma, and nonmalignant myelosuppressive disease. HHV-8 may occur as primary infection or reactivation of latent virus. The incidence of post-transplant KS parallels the geographic seroprevalence of HHV-8, so that it occurs at a range of <1% in the United States to as high as 5% in endemic regions such as Saudi Arabia and South Africa. KS is considered as the most common malignancy in kidney transplant recipients in some parts of the Middle East. The median time to onset of KS is 22 months after transplantation. Skin involvement is the most common manifestation, and visceral lesions such as gastrointestinal and pulmonary KS may also be observed. Reduction (or withdrawal) of immunosuppression is the mainstay of treatment. Surgery and chemotherapy with doxorubicin, vincristine, and bleomycin has been used for treatment.

POLYOMAVIRUSES BK AND JC

Infection with the BK polyomavirus is mainly reported in kidney transplant recipients, where it causes tubulointerstitial nephritis; this is often manifested clinically as an unexplained rise in serum creatinine and impairment in renal function. Ureteral stenosis and strictures may also be observed. In HSCT recipients, BK virus may manifest as hemorrhagic cystitis. The definitive diagnosis of BK virus-associated nephropathy is made by histopathologic examination of kidney biopsy specimens. Screening for BK virus infection is often performed, and high BK viral load in the plasma has been correlated with BK virus-associated nephropathy. In HSCT recipients, the role of BK virus in hemorrhagic cystitis is indicated by very high BK viral load in the urine. Infection with the JC virus causes fatal progressive multifocal leukoencephalopathy. Diagnosis of progressive multifocal leukoencephalopathy (PML) is suggested by typical MRI findings and the demonstration of JC virus in the cerebrospinal fluid by PCR. Reduction in immunosuppression is the mainstay of treatment for both BK virus infection and PML. Cidofovir and leflunomide are used as experimental therapies but are of no proven benefit. Surveillance testing, with the use of PCR or decoy cell testing, is used to identify BK infection early, which is treated pre-emptively with reduction in immunosuppression, in efforts to prevent progression into allograft failure.

PARVOVIRUS B19

Parvovirus B19 primarily infects and lyses erythroid cells and clinically manifests mainly as recurrent and refractory anemia. Almost all transplant patients with parvovirus B19 infection have anemia, and some also have low platelet count and leukocyte counts. It should be considered as a potential cause of failure of engraftment in HSCT recipients. Organ-invasive manifestations may occur in the form of pneumonitis, hepatitis, and myocarditis, although these are not common. The diagnosis is based on serology (although this may be falsely negative in some patients due to delayed and impaired ability of transplant patients to mount an antibody response), bone marrow examination to demonstrate pure red cell aplasia and giant pronormoblasts, and PCR tests to demonstrate the presence of parvovirus B19 DNA in clinical specimens. PCR is considered as the most sensitive method for diagnosis, while bone marrow examination is highly specific for the disease. The treatment is with IVIG, although the dose and duration remain undefined. Reduction in the degree of immunosuppression should be considered, and blood transfusion should be given for symptomatic patients and those with severe anemia.

HEPATITIS C VIRUS

Chronic hepatitis C is the leading indication for liver transplantation. With immunosuppression after liver transplantation, the clinical course of HCV may be accelerated. There is currently no optimal strategy for preventing HCV recurrence following liver transplantation. The use of interferon-α and ribavirin has been shown to reduce HCV replication following liver transplantation, but current practice avoids anti-HCV therapy unless histologic recurrence is demonstrated, because of intolerance and high failure rates. Protease inhibitors, such as telaprevir and boceprevir, have become available as part of anti-HCV combination treatment, although they have not been investigated in the setting of organ transplantation. The positive impact of novel anti-HCV drugs after liver transplantation is anticipated.

Fungal infections

Colonization with yeasts and fungi is common in transplant recipients. It is essential to differentiate whether the isolation of fungi represents colonization or true infection. Factors that could indicate true infection include (1) the presence of compatible clinical symptoms and (2) radiographic signs. Confirmation of true invasive fungal infection is made by the demonstration of the pathogen on biopsy specimens. Diagnosis may be considered as probable or definitive based on the strength of evidence. The use of PCR assays to demonstrate fungal nucleic acid, and the detection of antigens such as galactomannan and β-D-glucan in clinical samples offer non- or less-invasive methods for diagnosis.

The most common fungal infections in transplant patients are *Candida* spp., *Aspergillus* spp., and *C. neoformans*. The majority of invasive fungal infections during the early post-transplant period are due to *Candida* spp., and these are often related to surgical procedures, indwelling urinary and intravascular catheters, and prolonged antibiotic use. *Aspergillus* spp. may also occur during the early period after transplantation, especially among patients with prior colonization, fulminant hepatitis, prolonged neutropenia, and severe immunocompromise. *C. neoformans*, endemic mycoses, zygomycosis, dermatophytes, hyalohyphomycoses, and phaeohyphomycosis may also occur over the post-transplant period. Zygomycosis due to *Mucor* species, *Rhizopus* species, and others is one of the most fatal invasive fungal diseases, partly due to limited therapeutic options.

Liver transplant patients are at especially high risk of fungal infection with *Candida* spp. and *Aspergillus* spp. Antifungal prophylaxis, usually with low-dose amphotericin B, azoles, or an echinocandin, is often given to liver transplant patients with certain risk factors, such as fulminant hepatitis, those who require renal replacement therapy, those who undergo abdominal re-exploration, those who have high blood transfusion requirement, and those who require retransplantation. Lung transplant recipients with certain identifiable risk factors (hyperacute rejection, ischemic bronchial segments, *Aspergillus* spp. colonization, CMV disease, anastomotic dehiscence, and retransplantation) are also at higher risk of developing invasive fungal disease, especially with *Aspergillus* spp. Heart transplant patients may infrequently develop invasive fungal infection. Kidney transplant patients have a risk of fungal infection, most commonly presenting as candida urinary tract infection. Pancreas transplant patients are also at high risk of invasive *Candida* spp. infections, often as part of a polymicrobial intra-abdominal abscess.

Treatment of opportunistic invasive fungal diseases entails reduction in immunosuppression, surgery (in some cases), and antifungal drug therapy. There are three different antifungal strategies: (1) therapeutic, which is the the treatment of established infection; (2) pre-emptive, which is the administration of antifungal drug to transplant patients at high risk of invasive fungal disease as suggested by clinical and laboratory features; and (3) prophylactic, which is the administration of antifungal drug to all at-risk patients to prevent infection.

PNEUMOCYSTIS JIROVECII

Pneumocystis jirovecii is an important pathogen that causes pneumonia in SOT and HSCT patients. The clinical presentation is often subacute with low-grade fever, progressive dyspnea, hypoxemia, and nonproductive cough. This is accompanied by typical radiographic finding of diffuse pulmonary infiltrates. Extrapulmonary disease may occur rarely. Coinfection with CMV and *Aspergillus* spp. is not uncommon. The overall incidence has decreased with the use of prophylaxis, either trimethoprim–sulfamethoxazole, dapsone, or aerosolized pentamidine. The current guidelines recommend the use of *P. jirovecii* prophylaxis during the periods of immunocompromise in all allogeneic HSCT and SOT recipients. The duration of prophylaxis is often at least 6 months after transplantation; the duration should be prolonged in patients who remain highly immune compromised from use of drugs to treat recurrent rejection or graft-versus-host disease. The diagnosis of *P. jirovecii* pneumonia requires the demonstration of the organism in lung tissue and respiratory secretions, with the use of calcofluor staining or methenamine silver stain. Nucleic acid amplification by PCR has emerged as a sensitive method for diagnosis. The treatment of choice is with trimethoprim–sulfamethoxazole with or without corticosteroids in patients with significant hypoxemia. Alternative therapies include pentamidine, atovaquone–dapsone–trimethoprim, primaquine–clindamycin, and pyrimethamine–sulfadiazine.

Parasitic infections

Parasitic infections are becoming more common after transplantation, as a result of international travel and immigration. In the transplant recipient, parasitic infections may occur as a result of primary infection, reactivation of latent endogenous infection, or "activation" of an active but subclinical infection. Allograft-transmitted disease may also occur, as illustrated by the occurrence of donor-derived primary toxoplasma infection after heart transplantation.

TOXOPLASMA GONDII

Toxoplasma gondii infection after transplantation may manifest with fever and lymphadenopathy and could progress to cause tissue-invasive infection, including pneumonia, heart failure, and neurologic manifestations. Parasitism is often extensive in the brain, heart, lungs, and lymphoid organs. Infection is especially more common in heart transplant recipients since the parasite may be harbored in cardiac muscles, and thus could be transmitted through the heart allograft. The diagnosis may be demonstrated by serology, and the demonstration of the organism in biopsy specimens. Molecular testing with the use of PCR may also be utilized. The prevention of toxoplasmosis is recommended mainly in heart transplant recipients, especially when there is a *Toxoplasma* D+/R− serologic mismatch. In this regard, the suggested prophylaxis is pyrimethamine and sulfadiazine or trimethoprim–sulfamethoxazole prophylaxis. Most centers provide lifelong trimethoprim–sulfamethoxazole prophylaxis for heart transplant recipients at high risk of toxoplasmosis. Alternative regimens include dapsone with pyrimethamine, and atovaquone. The treatment of established toxoplasmosis after transplantation includes the synergistic combination of pyrimethamine and sulfonamide or clindamycin.

TRYPANOSOMA CRUZI

Trypanosoma cruzi may cause Chagas disease (or American trypanosomiasis) and may be manifested as heart failure and brain abscesses in transplant recipients. Infection may occur in patients residing in endemic regions such as Latin America. Donor-derived infection has been observed in transplant recipients of organs from donors from endemic regions. Treatment of Chagas disease is with benznidazole, reduction of the immunosuppression, and long-term administration of nifurtimox. Treatment often fails to eradicate the parasite.

STRONGYLOIDES STERCORALIS

Strongyloides stercoralis is a nematode whose larval stage has the tendency to disseminate in the setting of immune compromise, with larval accumulation in the lungs causing Loeffler's syndrome or eosinophilic pneumonia. Peripheral eosinophilia is often present. The gut penetration by the larva may also cause the translocation of bacteria and fungi and leads to systemic bacterial and fungal hyperinfections. This hyperinfection syndrome may be associated with pneumonitis, abdominal crisis, eosinophilic meningitis, and septic shock. Polymicrobial bloodstream infection, including *Candida* spp., gram-negative organisms such as *E. coli*, and other gut-derived bacteria, may occur and clue in for the diagnosis. Death is often due to gram-negative bacterial septic shock. The treatment options for *S. stercoralis* infection are thiabendazole, ivermectin, and albendazole. Treatment of the other superimposed infections should complement parasite-directed therapy.

CONCLUSIONS

Infections cause significant morbidity and preventable mortality after transplantation. Infections in transplant recipients are generally more severe and at times, the classic clinical manifestations of these infections may not be clearly evident. Hence, a high degree of suspicion is necessary for prompt and proper diagnosis of these infections.

Infections portend a worse outcome after transplantation. Hence, the major goal is prevention, prompt diagnosis, and aggressive treatment. To the extent possible, reduction of the degree of pharmacologic immunosuppression should complement antimicrobial therapy.

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90. Diabetes and infection

Stefan Bughi and Sylvia J. Shaw

Diabetes mellitus affects more than 25.8 million people in the United States; 79 million are known to have prediabetes. Worldwide the prevalence of diabetes will increase to 366 million by 2030. More than 90% of diabetic patients have type 2 diabetes. Diabetes is not only a metabolic but also a vascular disease; both microvascular and macrovascular complications are related to blood glucose control and disease duration and are more commonly seen in the elderly.

Diabetic patients have increased risk for infections (Table 90.1) and approximately 50% of diabetic patients will have at least one hospital admission or outpatient visit for infection. Respiratory and foot infections are over-represented in the diabetic population and have increased risk of infection-related mortality.

Table 90.1 Common infections associated with diabetes mellitus

Organ system	Type of infections
Respiratory	Pneumonia Aspiration pneumonia Pulmonary TB
Head and neck	Mucormycosis Invasive otitis externa
Gastrointestinal	Periodontal infections Candida esophagitis Emphysematous cholecystitis
Genitourinary	Upper and lower urinary tract infections Emphysematous cystitis Emphysematous pyelonephritis Papillary necrosis Perinephric abscess Fungal UTI
Skin and soft tissue	Superficial infections Superficial necrotizing infections Deep necrotizing infections Diabetic foot infections (mild/moderate/severe)
Nosocomial	Soft tissue UTI Respiratory tract infections

Abbreviations: TB = tuberculosis; UTI = urinary tract infection.

PREDISPOSING FACTORS TO INFECTION

Uncontrolled diabetes alters host immune response and has been implicated in disorders of immune function by alteration of polymorphonuclear leukocyte (PML) chemotaxis, phagocytosis, and decreased intracellular bactericidal activities. The effect of hyperglycemia on phagocytic activity is associated with an increase in cytosolic calcium and is reversible with the improvement of blood glucose level. There are other metabolic imbalances, which impair the immune system, such as presence of acidemia. In addition, presence of chronic inflammatory changes may contribute to the metabolic imbalances. Tumor necrosis factor-α, interleukin-1β, interleukin-6, and interleukin-18, are known to activate the stress hormones, creating hyperglycemia and insulin resistance.

Hyperglycemia was reported to impair complement receptor-3- and Fcy receptor-mediated phagocytosis. Defective cellular immunity includes decreased opsonization, decreased response to phytohemagglutinins, and poor skin test reactivity. Diabetics also have poor granuloma formation. All these changes are aggravated by microcirculatory failure, which alters the diffusion of both cellular and humoral factors to the affected site. The risk of infection also is enhanced by presence of peripheral and autonomic neuropathy and presence of peripheral arterial disease (PAD). Obesity is also a risk factor for moderate or severe infection-related morbidity.

RESPIRATORY INFECTIONS

Respiratory infections in the diabetic population are associated with increased mortality. Diabetic patients are four times more likely to die from pneumonia or influenza compared to nondiabetics.

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The risk of developing staphylococcal pneumonia is increased since 30% of diabetics are nasal carriers of *Staphylococcus aureus*. Patients with diabetes have a higher risk of developing pneumonitis and pneumonia (*Klebsiella, Legionella*) following influenza, and for this reason immunization against pneumococcus and influenza is recommended. The incidence of acute bronchitis, pneumonia, or exacerbation of chronic pulmonary obstructive disease (COPD) is similar in type 1 and type 2 diabetics. Diabetic patients are also prone to aspiration pneumonia, especially in the presence of gastroparesis (occurs in 40% to 60% of patients with diabetes). The risk of aspiration also increases with impairment of consciousness (i.e., hypoglycemia, hyperosmolar state).

The incidence of tuberculosis is 16 times higher in the diabetic population than in the nondiabetic population, and atypical locations are common. For this reason, the presence of a positive purified protein derivative (PPD) skin test, even with a normal chest radiograph, requires isoniazid (INH) prophylaxis for a minimum of 6 months, regardless of age. Diabetes also predisposes to cavitary lung disease with coccidioidomycosis considered to be a more severe form of infection. Pulmonary mucormycosis is complicated with fungal vascular invasion and high mortality. These infections require cultures, serology, and biopsy for positive diagnosis. Antifungal agents (i.e., itraconazole, voriconazole, posaconazole, or amphotericin B) should be initiated early pending the laboratory results.

MUCORMYCOSIS

More than three-fourths of cases of rhinocerebral mucormycosis occur in diabetics, particularly in the presence of diabetic ketoacidosis. Mucormycosis is caused by a group of fungi known as *Mucorales*, the most common genera being *Rhizopus, Absidia*, and *Rhizomucor*. These fungi invade nasal and paranasal membranes, as well as blood vessels, resulting in thrombosis and tissue infarction. Local spread of infection results in ophthalmoplegia, blindness, cavernous sinus thrombosis, meningoencephalitis, and brain abscesses, leading to rapid death in untreated cases. Patients with mucormycosis may present with facial or ocular pain, nasal stuffiness, generalized malaise, and fever. Periorbital edema, chemosis, and nasal black eschars or necrotic turbinates are common presentations. Diagnosis is made by biopsy of the necrotic eschars and demonstration of nonseptate thick-walled hyphae with special staining. Computed tomography (CT) scan or magnetic resonance imaging (MRI) can be helpful in assessing the extent of disease and can aid the surgeon in debridement. Treatment with intravenous amphotericin B, 1 mg/kg/day, or liposomal amphotericin B, 5 mg/kg/day, should be started as soon as possible. Posaconazole (800 mg in divided doses) is the only oral agent that is useful in zygomycosis and can be effective in 60% to 70% of patients. Hyperbaric oxygen therapy was reported to be also beneficial, since it inhibits fungus growth and improves wound healing. Those who survive may require reconstructive surgery and long-term psychological counseling due to facial disfiguration. Even with early diagnosis and treatment, mortality with mucormycosis can be as high 50%, but is 100% if untreated.

INVASIVE OTITIS EXTERNA

Invasive otitis externa is an aggressive infection usually caused by *Pseudomonas aeruginosa*. Rarely, the etiologic agent is *Aspergillus, Klebsiella pneumoniae*, or other organisms. More than 90% of patients have diabetes, often with poor metabolic control. Characteristically, the disease begins with periauricular cellulitis and granulation tissue at the junction of the cartilaginous and osseous portions of the external auditory canal. When infection spreads it may result in parotitis, mastoiditis, septic thrombophlebitis, cranial nerve palsy, and meningitis. Osteomyelitis of the temporomandibular joint, skull base, and cervical vertebrae can also occur. Facial nerve VII palsy occurs in 30% to 40% of cases and does not necessarily carry a poor prognosis. However, development of palsies of cranial nerves IX and XII implies deep infection. This can be complicated by sinus thrombosis and central nervous system (CNS) infection, which results in death in 30% of patients. The use of MRI or CT scan can help to assess the extent of infection and needed debridement.

Four weeks of parenteral antipseudomonal antibiotic therapy is generally recommended. Combination therapy of β-lactam agents (piperacillin, ceftazidime, cefipime, imipenem, or aztreonam) with an aminoglycoside can be used. If oral quinolones are used, longer therapy (3 months) is recommended by some authorities. If aspergillus is the causative organism, liposomal amphotericin B needs to be used for at least 12 weeks. Hyperbaric oxygen therapy may have an adjuvant effect.

GASTROINTESTINAL INFECTIONS

Since 1993, *periodontal* infections are considered the sixth most common complication of diabetes; these affect 17.3% of the diabetic population and 9% of the general public. The risk factors for periodontal disease are: increased salivary glucose, decreased salivary pH, small vessel disease, changes in collagen metabolism, and immune changes (i.e., inflammatory cytokines). *Porphyromonas gingivalis* is the most common pathogen. Professional cleaning and local treatment of periodontal infections may be adequate. However, antibiotic treatment is needed if patients develop fever or lymphadenopathy.

Candida esophagitis has been reported to occur with increased frequency in diabetic patients and more often in those who receive broad-spectrum antibiotics. The most common presentation is retrosternal pain or dysphagia after the ingestion of cold or hot drinks. Oral thrush can be absent. Endoscopic examination and biopsy are the preferred diagnostic procedures. Treatment with oral fluconazole (400 mg initial dose, followed by 200 mg/day) is necessary for a minimum of 3 weeks or at least for 2 weeks after resolution of symptoms. An alternative therapy is itraconazole, 100 mg swished in the mouth daily for 3 weeks. Oropharyngeal infection can be treated with itraconazole, 200 mg swished in the mouth daily for 1 to 2 weeks. Infections with *Candida* species also respond to voriconazole intravenously or orally or caspofungin intravenously. Success of treatment may depend on normalization of blood sugar.

Emphysematous cholecystitis, characterized by gas production in or around the gallbladder, is a surgical emergency. The infection is highly virulent and often induced by multiple pathogens; among the most common are *Clostridium* (50% to 70%) and gram-negative bacilli such as *Escherichia coli* and *Klebsiella*. Other common organisms reported are *Salmonella enteritidis*, *Campylobacter*, and *Bacteroides fragilis*. This infection is predominantly seen in diabetic male patients (70%) and is associated with gallbladder gangrene (74%) and perforation (21%). Gallstones are present in half of these patients. Diagnosis requires serial x-ray examinations or CT scan. Treatment requires high-dose parenteral broad-spectrum antibiotics aimed at both anaerobic and gram-negative bacteria (imipenem or piperacillin–tazobactam), together with prompt surgical intervention. There is high mortality even with early diagnosis (15% to 25%).

URINARY TRACT INFECTIONS

Diabetic female patients have a 2-fold to 4-fold higher incidence of bacteriuria. Diabetic women are at risk to develop recurrent asymptomatic bacteriuria, which in general is benign and seldom permanently eradicable. Treatment of asymptomatic bacteriuria is not beneficial, since the long-term outcome does not change. Diabetic patients have a higher prevalence of developing nosocomial urinary tract infection (UTI) and a higher risk of developing pyelonephritis. Predisposing factors are the presence of neurogenic bladder, uncontrolled diabetes and glycosuria, recurrent vaginitis, renal disease, and urologic instrumentation. Neurogenic bladder makes single-dose or a 3-day course of antibiotic treatment less effective. Cystitis may require a longer course of therapy (i.e., 7 to 14 days).

Emphysematous cystitis is often the result of infection with *E. coli* or other Enterobacteriaceae. More than 80% of diabetic patients present with pneumaturia. Gas in the urinary bladder wall and the collection system may be seen on either plain x-ray or CT scan studies. The disease usually responds to antibiotics targeting the Enterobacteriaceae.

Emphysematous pyelonephritis is a life-threatening suppurative infection of the renal and perirenal tissue. It occurs predominantly in diabetic patients (70% to 90%), more often in women. The disease is usually unilateral, more often affecting the left kidney. More than 40% of cases have underlying urinary tract obstruction; *E. coli* is the predominant isolated organism (70%). Patients present with fever, chills, flank pain, confusion, and often sepsis. Thrombocytopenia, cognitive changes, and proteinuria are independent risk factors for poor outcome. Patients present with fever of unknown origin and the diagnosis is made by demonstration of gas on plain x-ray film or CT scan of the abdomen. Treatment usually requires a combination of surgical intervention, removal of urologic obstruction when present, and frequently unilateral nephrectomy and antibiotic therapy. Survival rate is more than 90% in patients who have both surgical and antibiotic treatment versus 25% in cases treated with antibiotics alone. Rarely the emphysematous cystitis can coexist with emphysematous pyelonephritis, having a mortality rate as high as 50%.

Papillary necrosis can occur as a complication of emphysematous pyelonephritis or as an isolated entity. More than 50% of cases are described

in diabetic patients. Other cases are seen in patients with analgesic abuse, sickle cell disease, and urinary tract obstruction. Many patients present acutely with fever, ureteral colic, microscopic or macroscopic hematuria, and pyuria, with renal failure developing in 50% of cases. Some patients have an indolent presentation and may pass sloughed papillary tissue in the urine. Diagnosis can be made by renal ultrasound. However, the test of choice is retrograde pyelography. For patients who present with obstruction and do not pass the detached papilla spontaneously, surgical removal is indicated through cystoscopy with ureteral instrumentation. Antibiotic therapy for a minimum of 2 weeks may be required.

Perinephric abscess should be suspected in patients who present with "pyelonephritis" but who have a poor response to 4 or 5 days of intravenous antibiotic therapy. One-third of cases are described in diabetic patients who present with pyuria, moderate fever, and a mass over the affected kidney (50% of cases). Among the gram-negative organisms, *E. coli* is the most common isolate, and ascending infection is the usual route of spread. The diagnosis requires use of renal ultrasound, CT, or MRI studies, which also can help exclude ureteral obstruction. Surgical drainage is mandatory (open surgery or percutaneous catheter placement) in combination with 4 weeks of cephalosporins, piperacillin–tazobactam, or ticarcillin–clavulanate.

Fungal UTIs occur with increased frequency in the diabetic population, especially after long-term broad-spectrum antibiotics or Foley catheter placement. Most of the patients have asymptomatic candiduria and are afebrile. However, severe infections complicated with fungus ball formation, obstruction, and sepsis have been reported. For this reason, all asymptomatic (presumably colonized) patients should be carefully observed for any signs of deterioration. Development of fever or azotemia must be investigated for possible ureteral obstruction, renal involvement, or disseminated fungal disease. Quantitative colony counts of only 10 000/mL of yeast in the urine may be sufficient to cause disease. Among the most common isolates are *Candida albicans, Candida tropicalis*, and *Candida glabrata*. Fluconazole is the drug of choice (50 to 200 mg/day) with a dose of 400 mg/day for systemic infection. Alternatively, amphotericin B can be used intravenously if there is renal involvement or as bladder irrigations in patients with cystitis. Patients who have evidence of obstruction will require surgical intervention.

SKIN AND SOFT-TISSUE INFECTIONS

Superficial infections are often caused by *S. aureus*, which commonly colonizes the nasal mucosa and the skin of diabetic patients. The most common soft-tissue infections reported in the diabetic population are: impetigo, carbuncles, cellulitis, folliculitis furuncles, necrotizing fasciitis, septic bursitis, and subcutaneous abscesses. Elimination of *S. aureus* carrier state requires application of mupirocin ointment to the nares and oral administration of rifampin, bactrim, or minocycline (two drugs in combination for 10 to 14 days). Recurrent abscesses require drainage and antibiotic therapy.

SUPERFICIAL NECROTIZING INFECTIONS

Crepitant (anaerobic) cellulitis is a superficial process produced by multiple organisms, most often anaerobes. Infection is seen more frequently in diabetic patients with chronic, nonhealing lower-extremity ulcers. Crepitus is present on palpation because of subdermal and subcutaneous gas dissection. Treatment of this infection requires appropriate parenteral antibiotics and surgical debridement. Necrotizing fasciitis occurs when infection spreads along the superficial fascial planes without muscle involvement. This is a mixed infection (type I variant) that in 90% of cases is caused by aerobes and anaerobes (e.g., *Bacteriodes* species, *Enterococcus* species, *Peptostreptococcus, E. coli, Proteus*). Group A streptococci either alone or in combination with *S. aureus* (type II variant) are present in 10% of cases. Group B streptococci-induced necrotizing fasciitis has also been reported. This potentially lethal infection frequently presents with cutaneous necrosis, suppurative fasciitis, vascular thrombosis, and extreme systemic toxicity. In the later stages of the infection, destruction of the small nerve fibers results in patchy area of skin anesthesia. Necrotizing fasciitis early in its evolution is clinically indistinguishable from other soft-tissue infection. The most commonly affected sites are upper and lower extremities, perineum, groin, and thorax. Mortality rate is 30% to 70% if diagnosis is delayed. Management requires thorough debridement and drainage, using the "filleting procedure," and broad-spectrum antibiotics (i.e., piperacillin–tazobactam, imipenem). The subcutaneous tissue is left open, and irrigation with normal saline or Ringer's lactate solution is performed. Many patients require repeated debridement followed later by reconstructive surgery. Infection

produced by *Streptococcus pyogenes* is often complicated by toxic shock syndrome.

DEEP NECROTIZING INFECTIONS

Necrotizing cellulitis (nonclostridial myonecrosis) is produced by the same bacteria responsible for necrotizing fasciitis. This form of infection occurs most commonly in diabetic patients (75%) and involves the muscle, skin, fat, and fascia. Necrotizing fasciitis of the male genitalia (Fournier's gangrene) is associated with diabetes in 40% to 60% of cases. Infection can also affect the abdominal wall or perineum, especially after surgery, penetrating trauma, or instrumentation. Treatment requires coverage of both aerobic and anaerobic pathogens and should cover *S. aureus*, gram-negative enteric organisms, *E. coli, Proteus, Bacteroides fragilis*, and *Enterococcus* species. All patients need to have aggressive debridement, resection of the necrotic muscle, hyperbaric oxygen, and supportive therapy.

Clostridial myonecrosis, if present requires aggressive surgical debridement and appropriate antimicrobial therapy.

Diabetic foot infections are responsible for 20% of hospital admissions and a frequent precursor of amputations. Predisposing factors are: peripheral neuropathy, PAD, immunopathy, and history of a previous ulcer. The severity of diabetic foot infection can vary from mild and superficial (often monobacterial, caused by *S. aureus* or *Staphylococcus epidermidis*) to severe deep infection. Tissue gangrene is usually induced by polymicrobial (mixed aerobic and anaerobic) infections. An MRI study is used to make the diagnosis of bone involvement and also to delineate the extent of bone resection necessary to treat osteomyelitis. Clinically a probe to bone can be suggestive of osteomyelitis. If any patient has diminished or absent peripheral pulses arterial Doppler (with both pressure and waveform studies) and/or transcutaneous oxygen tension ($TcPO_2$) are needed. Ankle brachial index of <0.80 mm Hg or $TcPO_2$ of <40 mm requires vascular consultation.

Mild infections without systemic symptoms can be treated with oral antibiotics (amoxicillin–clavulanate, quinolones, or first-generation cephalosporins) and require close follow-up at 48 to 72 hours. If parenteral therapy is considered, cefazolin or cefuroxime may be used for presumed monobacterial infection. Moderate non-limb-threatening infections require local debridement and parenteral antibiotic therapy with a broader coverage. The empiric therapy can be altered based on culture results of biopsy, ulcer curettage, or aspiration (Table 90.2). No systemic treatment should be carried out, unless wound is infected. For soft-tissue infection, duration of therapy should be 10 to 14 days based on the clinical outcome. Limb-threatening infections (extensive

Table 90.2 Suggested empirical antibiotic regimens, based on clinical severity, for diabetic foot infections

Route and agent(s)	Mild	Moderate	Severe
Advised route	Oral for most	Oral or parenteral, based on clinical situation and agent(s) selected	Intravenous, at least initially
Dicloxacillin	Yes	–	–
Clindamycin	Yes	–	–
Cephalexin	Yes	–	–
Trimethoprim–sulfamethoxazole	Yes	Yes	–
Amoxicillin/clavulanate	Yes	Yes	–
Levofloxacin	Yes	Yes	–
Cefoxitin	–	Yes	–
Ceftriaxone	–	Yes	–
Ampicillin/sulbactam	–	Yes	–
Linezolid[a] (with or without aztreonam)	–	Yes	–
Daptomycin[a] (with or without aztreonam)	–	Yes	–
Ertapenem	–	Yes	–
Cefuroxime with or without metronidazole	–	Yes	–
Ticarcillin/clavulanate	–	Yes	–
Piperacillin/tazobactam	–	Yes	Yes
Levofloxacin or ciprofloxacin with clindamycin	–	Yes	Yes
Imipenem–cilastatin	–	–	Yes
Vancomycin[a] and ceftazidime (with or without metronidazole)	–	–	Yes

Note: Definitive regimens should consider results of culture and susceptibility tests, as well as the clinical response to the empirical regimen. Similar agents of the same drug class may be substituted. Some of these regimens may not have U.S. Food and Drug Administration approval for complicated skin and skin-structure infections, and only linezolid is currently specifically approved for diabetic foot infections.

[a] For patients in whom methicillin-resistant *Staphylococcus aureus* infection is proven or likely.

From Lipsky BA, Berendt AR, Deery HG, *et al.* Diagnosis and treatment of diabetic foot infections. *Plastic Reconstruct Surg.* 2006;117:212S–238S. Reprinted with permission.

cellulitis, deep ulcer, plus lymphangitis and/or osteomyelitis) may require broad coverage (piperacillin–tazobactam, imipenem, or meropenem). Surgical debridement should be done promptly. Bone infection may require extirpation of the affected bone or amputation. Preservation of the ambulatory capacity should be considered. The intraoperative culture should be used to guide the choice of antibiotic therapy. Following surgery duration of treatment should be 2 to 4 weeks for residual soft-tissue infection, 4 to 6 weeks for residual (viable) bone, or more than 3 months if surgery for osteomyelitis is declined. Indefinite oral suppressive therapy may be considered for patients with complicating factors (i.e., extensive osteomyelitis, poor vascular supply, not surgical candidates).

Nosocomial infections affecting skin/soft tissue, urinary tract, and respiratory system are common in the diabetic population. Therefore, 50% of isolates from diabetic foot ulcers are methicillin-resistant *S. aureus* (MRSA). Vancomycin-resistant enterococci (VRE), diphtheroids (group JK), and *Pseudomonas* are also common pathogens. Management of these infections requires use of newer antibiotics such as linezolid (MRSA, VRE), quinupristin/dalfoprisitin (VRE), tigecycline (MRSA, VRE), daptomycin (MRSA, VRE), and others.

Overall, because patients with diabetes mellitus have a high incidence of chronic kidney disease, adjustment of the antibiotic dose based on renal function is imperative. Drug interactions and toxicity should always be considered prior to therapy, since these patients are frequently on multiple medications.

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91. Infectious complications in the injection and non-injection drug user

Carlo Contoreggi

Drug abuse is a widespread public health problem because many of its medical complications are infectious due to the transmission of bloodborne, environmental, and respiratory infectious agents. Availability of highly active antiretroviral therapy (HAART) in human immunodeficiency virus (HIV)-infected substance abusers has reduced the severity and frequency of opportunistic infections seen in the intravenous drug users (IVDUs) and other drug users (DUs). That said DUs/IDUs remain the groups least likely to access care and to maintain adherence for optimal benefit. Recent studies find social and access factors related to criminalization are major barriers to care including HAART for these individuals. Increasing treatment options and societal acceptance of harm reduction efforts have been demonstrated to improve outcomes in countries that have undertaken them.

ENDOCARDITIS

Endocarditis, a life-threatening infection of the heart valves and/or endocardium, is associated with septic parenteral injections. Right-sided valvular infections are very frequent in IDUs because of septic inoculations. Intravenous injection with low-pressure venous return increases the susceptibility of right-sided valvular and other structures to infection. Concurrent pulmonary hypertension from drug adulterants, such as talc, may also predispose to right-sided disease.

Despite the high prevalence of endocarditis, the offending pathogens are not specific to injectors. *Staphylococcus aureus*, often methicillin-resistant *S. aureus* (MRSA), is the most commonly identified organism, but other pathogens are seen. These include *Pseudomonas*, *Serratia*, enterococci, *Streptococcus* groups A and B, and *Streptococcus viridans*. Increasingly, fungal pathogens are seen with and without immunodeficiency.

Clinical diagnosis of endocarditis in the drug abuser can be difficult. The hallmark symptom is fever. Other constitutional symptoms such as chills, sweats, and arthralgia are less specific, but they are commonly observed in opiate withdrawal. The physical signs associated with left-sided endocarditis are seldom present. Coexistent HIV-1 immunodeficiency appears to predispose to more severe systemic infections.

Because clinical diagnosis alone presents challenges, echocardiographic findings have developed into the primary method to diagnose and treat endocarditis. Blood cultures and other routine tests should be used to identify the offending pathogen and antimicrobial sensitivities.

Transthoracic (TTE) and transesophageal echocardiography (TEE) are used to evaluate suspected endocarditis (e.g., high clinical suspicion but negative blood cultures). Detection of valvular vegetations, valve disease with hemodynamic compromise, associated shunts or abscesses, or patients with persistent fever, continued bacteremia, or clinical deterioration may mandate serial testing.

Therapy should be multidisciplinary as patients may be unwilling to comply with adequate treatment regimens especially if long-term hospital stays and serial testing are required. Combination short course IV followed by oral therapy may be considered. Left-sided disease, large vegetations, or presence of cardiovascular compromise mandates more intensive therapy. Medication selection is an evolving science and isolation of pathogen and drug sensitivities are critical in this respect. Mortality with right-sided disease is low; the presence of left-sided valvular and/or chordae tendineae involvement, fungal pathogens, congestive heart failure, other cardiovascular compromise, vegetation size > 20 mm, and HIV with immune compromise all greatly increase risk. Inflammatory myocarditis can be seen independently and with endocarditis; it is multifactorial in substance abusers with cocaine or HIV-1 infection, and inflammatory responses from adulterants in drugs are common causes.

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PULMONARY INFECTIONS

Complications due to intravenous drug use include pneumonia, aspiration pneumonitis, lung abscess, and septic pulmonary emboli. Talc contamination of the injected drugs enters the bloodstream and lodges in the pulmonary capillary bed, causing foreign-body granulomatosis that results in pulmonary fibrosis and acute inflammatory pneumonitis. Septic pulmonary emboli may result in clinically evident ventilatory and perfusion mismatch on scintigraphic imaging.

Chronic inhalation of drugs and their adulterants will accelerate alveolar destruction and result in early-onset chronic obstructive pulmonary disease (COPD) and emphysema. Chronic immunosuppression from HIV increases likelihood of pneumonitis, and community and immune-compromised respiratory disorders. Chronic opiate and cocaine addiction is often associated with COPD, from smoking the drug. Smoking (nicotine/marijuana) may result in decreased vital capacity and a decrease in diffusion capacity and small airway disease. IDUs also have a 10-fold increased risk of community-acquired pneumonia compared to the general population, due to failure to vaccinate, the destructive action of marijuana/tobacco abuse, and increased susceptibility to viral and bacterial exposures.

BONE AND JOINT INFECTIONS

Septic arthritis and osteomyelitis from disseminated cutaneous infection as well as direct injection at or near the affected area has been described in the IDU. Gram-positive organisms and *Pseudomonas aeruginosa* are the most commonly implicated organisms. Osteomyelitis most commonly affects the fibrocartilaginous joints such as the vertebral, sternoarticular, and sacroiliac joints. In addition to bacterial infections, fungal infections are increasingly described in both immunocompetent and immunodeficient hosts, i.e., diabetics, end-stage renal disease, HIV, and neoplastic disease. Treatment protocols do not differ from other immunosuppressed hosts; bone or joint cultures are necessary for accurate diagnosis. Compliance with long-term therapies poses additional problems with adherence in the DUs/IDUs.

SKIN AND SOFT-TISSUE INFECTIONS

Septic parenteral injections frequently lead to skin and soft-tissue infections. Infectious and chemical thrombophlebitis, abscesses, and cellulitis are common venous insults. Life-threatening cutaneous infections include fasciitis, myonecrosis, and gangrene. Tissue crepitance, extensive cellulitis, evidence of systemic toxicity, severe pain, and sepsis suggest serious and life-threatening infections. Plain radiographs may be helpful though MRI would be optimal to determine the extent of soft tissue, bone, and marrow involvement.

Injected drugs and their adulterants are often damaging to veins. Progressive sclerosis of the veins is common. With loss of peripheral access, deeper and more dangerous sites, i.e., femoral, axillary, jugular, penile, and mammary veins may be used. More serious infections, thrombosis, and gangrene may result from injections at these sites.

Once easy intravenous access is not available, many substance abusers will administer drugs subcutaneously. Staphylococci and streptococci are frequent pathogens. However, with immunosuppression, other bacterial pathogens are encountered. *Escherichia coli, Klebsiella, Bacteroides*, *Clostridia*, and mixed flora consisting of both aerobic and anaerobic organisms as well as fungal organisms such as *Candida* may be encountered.

Small localized infections can usually be treated locally with or without systemic antibiotics. Severe infections should be managed with surgical debridement and inpatient antibiotic therapy.

VIRAL HEPATITIS

The epidemiology of hepatitis A has changed dramatically in the past decade, with drug abuse being recognized as a significant risk for its transmission. Hepatitis A is associated with fecal–oral transmission. Contaminated marijuana has been reported as a transmission agent for hepatitis A.

Hepatitis B, C, and D (HBV, HCV, and HDV, respectively) are associated with parenteral transmission. The incidence of HBV and HCV in IDU populations is very high worldwide, with a significant proportion infected with both HBV and HCV.

Chronic HBV infection is associated with persistent hepatitis B surface antigen (HBsAg) and hepatitis Be antigen (HBeAg), although hepatic inflammation varies widely. HBeAg is associated with increased infectivity, more severe disease, and eventual cirrhosis. The HBV virion is not cytotoxic but mediates a host cytotoxic T-cell response that causes hepatocellular inflammation and necrosis. Coinfection with HIV-1 with its

associated cellular immune deficiency reduces the severity of the host cytopathic response. Progressive HIV-1-associated cellular immunodeficiency manifests with reduced hepatic inflammation and lower serum transaminase concentrations. Other serologic measures of HBV infection in HIV-1 are not diminished.

HDV, or delta particle infection, is common in IDUs. This infection, which requires coinfection with HBV, imparts a more severe course than HBV alone. Coinfection with HBV and HDV is associated with increased incidence of fulminant hepatic failure. Vaccination with HBV vaccine will also prevent HDV infection.

Though less well characterized than HBV, HCV appears to be heterogeneous, with significant genetic and immunologic variability. Parenteral transmission is better established than other routes of HCV transmission (i.e., familial, sexual, or maternal–fetal). Most cases are traced to parenteral exposures, either through blood or blood-product transfusion or injection drug use.

In IDU populations there is evidence that HBV and HCV coinfection increases the severity of clinical hepatitis and the persistence of transaminase elevation. The development of progressive hepatitis and end-stage liver failure in the IDU population is likely to increase as this population ages. Effective therapy for chronic HBV and HCV remains limited, but initial studies have shown efficacy of interferon-α treatment.

Despite improvements in therapy of patients with hepatitis C, substance abuse, alcohol abuse, and comorbid psychiatric disorders are major barriers to achieving improvement and disease remission. Treatment with interferon requires considerable compliance and medication adherence and is challenging in non-substance-abusing patients. Patients who continue to abuse drugs and alcohol have limited economic and social support and often experience suboptimal outcomes. Individuals stabilized with opiate substitution therapy, i.e., methadone or buprenorphine, show sustained virologic responses comparable to non-drug-abusing populations. Discontinuation of injection use also removes these individuals from the HCV dissemination pool.

Interferon therapy is associated with neuropsychiatric complications and side effects, and data suggest patients with existing comorbid psychiatric disorders prior to institution of immune therapy fare worse overall. Many providers recommend prophylactic treatment with antidepressant medication prior to interferon therapy and this strategy should be considered in these patients. In DUs, overall poorer outcomes from HCV and long-term liver failure are most likely due to limited treatment adherence, making critical the importance of therapeutic interventions for their substance abuse. As with most other medical conditions that affect the DUs/IDUs, integration of medical treatment with effective substance abuse and psychiatric care improves efficacy while improving the overall quality of life.

There remains considerable debate on the ethics of performing liver transplants in patients with alcohol and drug abuse. When organ recipients significantly outnumber available organs, many transplant groups routinely disqualify patients with substance abuse from consideration. The principal reasons for disqualification are history of abuse relapse, poor social support, and noncompliance with medical management. The availability of adequate alcohol and substance abuse treatment with patient compliance appears to contribute to better long-term outcomes.

HUMAN T-CELL LEUKEMIA/LYMPHOMA VIRUS

The incidence of non-HIV retroviral infections is lower than that of HBV, HCV, or HDV among IDUs in Europe, North America, and Australia. Human T-cell leukemia/lymphoma virus (HTLV)-2 infection is more frequently reported than HTLV-1 in IDUs. Viral transmission occurs primarily parenterally and sexually, and maternal–fetal transmission is less frequent than with HIV. Injection drug use remains the principal route of transmission. Endemic pockets of HTLV-2 infection exist in South America, the Caribbean basin, and Africa. Monitoring IDU populations over the last 20 years has found a significant decrease in HTLV-2 seroconversions. With decreasing injection drug use and current epidemiologic data we expect the prevalence of HTLV-2 infection to continue to decrease.

The long-term sequelae of HIV/HTLV-2 coinfection seem to point to a low level protective effect from HTLV-2. The number of long-term non-progressors was significantly higher in the coinfected compared with HIV infection alone. The reason for this is not clear but HTLV-2 induction of cytokine/chemokines may provide an inflammatory milieu less conducive to HIV replication though the specific molecular actions are not understood. Cohort studies have been performed in IDUs and it is not certain that these findings are applicable to other HIV-infected groups.

HTLV-2 infection alone causes subtle immune dysfunction that is mild compared with that of HIV-1 infection. The clinical sequelae of HTLV-2 infection alone are less well defined and the incidence of disease from HTLV-2 infection alone is low. About 0.5% of solitary HTLV-2 infection causes T-cell leukemia and lymphoma in both immunocompetent and immunodeficient patients. Tropical spastic paraparesis has also been associated with HTLV-2 infection.

IMMUNOLOGIC ABNORMALITIES

IDUs have subtle abnormalities in immune function independent of HIV and other retroviral infections. Effects of opiates have been widely studied; in vivo, measures of cellular immunity show diminished cellular defensive actions, while in vitro studies point to decreased cytokine and cellular signaling actions. Cannabinoids and cocaine show immune-suppressive effects though subtle differences in cellular signaling are seen.

Abnormalities in circulating immune factors include elevated plasma immunoglobulins, especially the immunoglobulins IgM and IgG; false-positive rheumatoid factor and syphilis serology; and febrile agglutinins and complement fixation tests. Cellular immunity is abnormal in the DU/IDU with the IDU most affected. HIV-1 antibody-negative parenteral opiate abusers may have elevated total T-lymphocyte counts as well as increases in both T-helper and T-suppressor cells. Injection behaviors increase HIV susceptibility. Measures of cellular immunity show diminished function. Natural killer (NK) cell function and cytotoxic T-cell (CTL) function are impaired.

Cellular immune functions are essential for host recognition of pathogens and for immune stimulants such as those in vaccines. It is likely that without intact cellular immunity, future HIV-1 vaccine effectiveness may be compromised in the active DU/IDU.

Effective substance abuse treatment with discontinuation of septic injections may restore immunocompetence. Immune studies of patients maintained on methadone show some reversal of immune dysfunction after discontinuation of intravenous injecting.

TUBERCULOSIS

Mycobacterium tuberculosis (TB) remains endemic in vulnerable and marginalized populations, i.e., IDUs, HIV infected, prisoners, the homeless, and alcoholics. TB is a highly virulent pathogen that infects both immunocompetent and immunodeficient individuals. Coinfection of TB and HIV-1 is present in a significant number of new TB cases. In those infected with HIV-1, TB primarily shows pulmonary involvement early, whereas with progressive immunosuppression, disseminated extrapulmonary TB is not uncommon.

IDUs risk latent TB from immunosuppression from both frequent parenteral injections and from drugs with known immunosuppressive effects such as opiates.

All HIV-1-infected IDU patients should be tested for TB as early in the course of their disease as possible as the first several years post seroconversion show peak infection rates. Patients should be tested for TB every 6 months or if clinical symptoms dictate. Previously untreated individuals with past exposure to TB as evidenced by positive tuberculin skin test (TST) with positive purified protein derivative (PPD) are at high risk for recurrence of latent infection with progressive immunodeficiency. Positive results for the TST in immunocompetent individuals is induration of at least 15 mm, 10 mm for the IDU, and 5 mm for HIV+. Anergic responses are common in these populations, though there is no clear consensus for additional testing. Immunocompromised hosts that are TST positive and recently exposed to TB should receive prophylaxis, as should anergic individuals with known environmental exposure or patients who are at high risk. If compliance with TST readings is poor, chest radiography of high-risk individuals has been demonstrated to decrease disease incidence.

PNEUMOCYSTIS JIROVECII (CARINII) PNEUMONIA

Pneumocystis jirovecii is a ubiquitous environmental organism that colonizes the respiratory tract early in life and becomes a pathogen in the setting of moderate to severe immunodeficiency. Prior to HAART *P. jirovecii* pneumonia (PCP) occurred in nearly 90% of New York City's HIV IDU population and was the most frequent AIDS-defining diagnosis.

TOXOPLASMOSIS

Toxoplasma gondii, a ubiquitous protozoal parasite found in soil, may be ingested in raw meat. Activation of infection, often in the central nervous

system, usually occurs with severe immunosuppression, with CD4 counts in the 100/mm^3 range. With the advent of HAART the incidence of toxoplasmosis has decreased markedly. In those at risk serologic testing early in the course of HIV-1 infection to determine exposure is indicated, with prophylaxis necessary only for seropositive patients with CD4 counts below 100/mm^3.

FUNGAL INFECTIONS

These pathogens infect in the setting of moderate to severe immunosuppression, with CD4 counts in the 250/mm^3 to 100/mm^3 range. Invasive *Candida* infections are commonly seen as vaginitis in mild to moderate immunosuppression; oropharyngeal and invasive esophageal candidiasis is seen in moderate disease. Systemic colonization and central nervous system infection is seen with profound immunodeficiency. Fungal endocarditis requires more intensive pharmacotherapy and carries higher morbidity and mortality in the IDU.

OPPORTUNISTIC VIRAL INFECTIONS

Herpes simplex virus, varicella-zoster virus, cytomegalovirus, and Epstein–Barr virus are common viral pathogens seen with immunosuppression. Varicella-zoster vaccination should be considered especially in patients in their sixth decade and beyond.

COMMENTS

The integration of substance abuse treatment with primary and specialized care for immunodeficiency and other medical conditions is most effective for both clinical outcome and cost of care. It is essential for healthcare providers to realize that addiction is a brain disease with neurochemical underpinnings causing a chronically disrupted reward system. This leads to maladaptive behaviors fundamental to cognition, emotional control, motivation, drug abuse, sexual drive, and impulsivity. The nature of the disease often results in limited adherence with therapy. A provider's view and acceptance of these patients is critical for successful management; many providers have difficulty with these patients thus a team approach may be most effective for care delivery.

Therapeutic constraints can influence treatment options, such as prescribing oral instead of intravenous antibiotics, diagnostic testing, and duration of therapy. Access to social workers and specialized providers who can coordinate complex services will greatly aid in management.

Societal realization and acceptance of harm reduction have made additional treatment options more accessible to many substance abusers. Buprenorphine, a mixed agonist/antagonist opiate, is a more acceptable alternative to methadone for many and is widely available. It can be administered in more convenient settings (i.e., doctors' offices), has increased financial coverage through social services, and has increased the availability of treatment. This has aided treatment compliance, though this population remains challenging and medical nonadherence and continued illicit drug use is common.

The realities of demographics are evident in current and former DUs/IDUs. Populations are aging, with average ages of many inner city treatment patients now mid-50s and higher. Injection heroin use is increasingly replaced with prescription opiate abuse in younger addicts. With age, chronic medical conditions along with infectious diseases, HCV and HIV account for increasing morbidity and associated mortality. The challenges for treating this population are changing but are no less important for overall public health. Integrating treatment and care with a changing and aging population offers new challenges. Addiction specialists can learn from these individuals how to better tailor care and treatment to future substance abusers.

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92. Infections in the alcoholic

Laurel C. Preheim and Mir Akbar Ali

Alcoholic patients have an increased susceptibility to bacterial infections such as pneumonia, tuberculosis, peritonitis, and bacteremia. They are also more likely to develop viral hepatitis and human immunodeficiency virus (HIV) disease. Acute and chronic alcohol ingestion exerts direct and indirect effects on host defenses against infection (Table 92.1). Studies suggest that the immunotoxic effects of ethanol are due to direct cytotoxicity and to a shift in the balance of cytokines produced from the proinflammatory to more immunoinhibitory products. However, the adverse effects of ethanol itself may be indistinguishable from those due to concomitant alcoholic liver disease and other conditions related to alcoholism including malnutrition, poor hygiene, adverse living conditions, and abuse of tobacco and other drugs. This discussion includes infections associated with increased frequency or severity in these patients (Table 92.2). Antibiotic suggestions are made according to current treatment guidelines, but therapeutic decisions should always be made with the knowledge that alcoholic liver disease can interfere with the metabolism and excretion of certain agents and that some antimicrobials can cause or exacerbate hepatic dysfunction.

Table 92.1 Immunodefects and alcoholism

Mechanical defects
Diminished cough reflex
Impaired glottal closure
Lung atelectasis due to ascites
Decreased ciliary function
Humoral immunity
Increased serum immunoglobulins
Decreased alveolar IgG subclasses
Decreased complement activity
Decreased serum bactericidal activity
Cell-mediated immunity
Decreased skin test reactions
Decreased numbers of T lymphocytes
Alterations in T-lymphocyte subsets
Altered cytokine production
Decreased suppressor cell activity
Decreased lymphocyte mitogenic response
Decreased natural killer cell function
Altered antigen presentation by macrophages and dendritic cells
Phagocytes
Granulocytopenia (rare)
Decreased granulocyte chemotaxis
Decreased granulocyte bactericidal activity
Decreased macrophage phagocytosis
Decreased macrophage bactericidal activity

Abbreviation: IgG = immunoglobulin G.

PNEUMONIA

Bacterial pneumonia usually follows aspiration of oropharyngeal flora into the lungs. Severe intoxication is associated with altered consciousness and a diminished cough reflex. Elevated ethanol levels can interfere with cilial function on the surface of respiratory epithelial cells. Most alcoholics also smoke cigarettes, which further impairs mucociliary defenses against infection of the respiratory tract. The most frequent bacterial causes of pneumonia in alcoholics include *Streptococcus pneumoniae*, anaerobes, aerobic gram-negative bacilli, and *Haemophilus influenzae*.

Standard diagnostic approaches are used to evaluate alcoholic patients who exhibit signs or symptoms of pneumonia. Organisms seen on sputum Gram stain often can help guide empiric antibiotic therapy. In addition to obtaining sputum and blood cultures, any significant pleural fluid visible on chest radiographs should be sampled for appropriate stains and cultured for aerobic and anaerobic organisms.

Because the severity of bacterial pneumonia is increased in alcoholics, hospitalization for parenteral antibiotic therapy is usually indicated. The length of hospital stay and the need for intensive care units are likely to be higher, and the expected mortality rate is greater than twice that for nonalcoholics.

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Table 92.2 Infections in alcoholics

Bacterial pneumonia
Streptococcus pneumoniae
Anaerobes
Klebsiella pneumoniae
Haemophilus influenzae
Tuberculosis
Spontaneous bacterial peritonitis
Escherichia coli
K. pneumoniae
S. pneumoniae
Bacteremia
Escherichia coli
S. pneumoniae
Group A streptococcus
Clostridium perfringens
Non-01 *Vibrio cholerae*
Vibrio vulnificus
Salmonella
Bartonella quintana
Endocarditis
Gram-negative bacilli
S. pneumoniae
Diphtheria
Pancreatic abscess
Hepatitis B and C
HIV infection and AIDS

Abbreviations: HIV = human immunodeficiency virus; AIDS = acquired immunodeficiency syndrome.

Pneumococcal pneumonia

Streptococcus pneumoniae, or pneumococcus, remains the most common cause of both community-acquired bacterial pneumonia and bacterial meningitis in adults. Outbreaks of pneumococcal pneumonia have occurred among residents of shelters and prisons, where close proximity enhances the risk of transmission. Alcoholics have the usual signs and symptoms of pneumococcal pneumonia, including a sudden onset, often with a single shaking chill, fever, and subsequent productive cough. Secondary complications, including acute respiratory distress syndrome, empyema, and bacteremia, are common in alcoholics, particularly those with liver disease. Despite appropriate therapy, the reported overall mortality for adult bacteremic pneumococcal pneumonia increases from approximately 20% to >50% in patients with cirrhosis. The Advisory Committee on Immunization Practices recommends pneumococcal polysaccharide vaccine for all alcoholics. However, the antibody responses may be blunted, and the efficacy of the vaccine has been questioned in this high-risk population.

Current guidelines on the management of community-acquired pneumonia in alcoholic adults recommend either the empiric use of a respiratory fluoroquinolone such as moxifloxacin or levofloxacin, or the combination of a β-lactam agent such as ceftriaxone or ampicillin–sulbactam with a macrolide such as azithromycin. For less severe cases not requiring inpatient treatment, oral β-lactam agents available for outpatient use include high-dose amoxicillin and amoxicillin–clavulanate.

Anaerobic pneumonia

Anaerobic oropharyngeal bacteria, including peptostreptococci, *Fusobacterium* spp., and *Prevotella melaninogenica*, are commonly involved in aspiration pneumonia and can cause lung abscess and empyema. Intoxication interferes with several host defenses against aspiration of oropharyngeal contents. Elevated circulating ethanol levels can disrupt the coordinated beating of cilia on respiratory epithelium and thus impair mucociliary clearance of inhaled or aspirated organisms. Inebriation also can be associated with diminished gag and cough reflexes. Alcoholics frequently have severe periodontal disease, which can increase the number of anaerobic organisms in the aspirated inoculum. Clinical signs and symptoms of anaerobic pneumonia commonly progress slowly over weeks or months before patients present with malaise, low-grade fever, cough producing foul-smelling sputum, and/or weight loss. Recommended therapy includes a β-lactam/β-lactamase inhibitor such as piperacillin–tazobactam, ampicillin–sulbactam, or amoxicillin–clavulanate. Alternatively, a carbapenem may be used such as ertapenem or meropenem. Clindamycin is indicated for anaerobic pleuropulmonary infections in patients who are allergic to penicillin.

Gram-negative pneumonia

Gram-negative bacilli such as *Klebsiella pneumoniae* and *Enterobacter* spp. are more likely to colonize the oropharynx and cause pneumonia in alcoholics than in nonalcoholics. The combination of bloody sputum and an upper lobe infiltrate with a bulging fissure that has been classically associated with *Klebsiella* pneumonia is rarely seen today. Mortality with gram-negative bacillary pneumonia exceeds that of pneumococcal

pneumonia and increases further if neutropenia is also present. For pneumonia due to Enterobacteriaceae, recommendations include either a third-generation cephalosporin such as ceftriaxone, a fourth-generation cephalosporin such as cefepime, or a carbapenem such as ertapenem or meropenem. If the pathogen is an extended-spectrum β-lactamase producer, a carbapenem should be used. Alternative antimicrobials include β-lactam/β-lactamase inhibitor combinations or a fluoroquinolone.

When *Pseudomonas* is suspected or identified as the causative agent, an antipseudomonal β-lactam such as piperacillin, ceftazidime, cefepime, aztreonam, imipenem, or meropenem should be used in combination with either an antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or an aminoglycoside such as gentamicin. An alternative regimen would be an aminoglycoside plus the antipseudomonal fluoroquinolone.

The coccobacillus *H. influenzae* frequently causes pneumonia in alcoholics. Resistance to antibiotics other than penicillin and ampicillin is rare. Recommendations include either a third-generation cephalosporin such as ceftriaxone, a β-lactam/β-lactamase inhibitor, a carbapenem, or a fluoroquinolone.

TUBERCULOSIS

Tuberculosis has historically been associated with ethanol abuse, and alcoholics have 15 to 200 times the tuberculosis incidence rates of nonalcoholics. Homelessness and immunocompromising conditions such as human immunodeficiency virus (HIV) disease have also been linked to an increased incidence of tuberculosis. Most cases occur in urban areas, where outbreaks of tuberculosis have occurred among indigent alcoholics housed in shelters.

After decades of steady decline, the number of new cases of tuberculosis in the United States started to rise in the late 1980s and continued to climb into the early 1990s. Due to renewed control efforts, the number of new cases has again declined annually since 1992.

Most individuals remain asymptomatic early in the disease. They may note a gradual onset of malaise, fatigue, anorexia, weight loss, afternoon fevers, or night sweats. Cough is frequent, generally producing mucopurulent sputum that may be blood tinged. The most common abnormality on chest radiographs is multinodular cavitary infiltrates in the apical or subapical posterior areas of the upper lobes or in the superior segment of a lower lobe. Pleural effusions may be present. Findings of tuberculosis are confined to the lower lung fields in up to 18% of patients.

Hospitalized patients suspected of having active pulmonary tuberculosis should be placed under airborne infection precautions. The diagnosis of tuberculosis depends on isolation of *Mycobacterium tuberculosis* from clinical specimens. For evaluation of active pulmonary tuberculosis, sputum samples are helpful, but yield is increased by more direct collection methods such as via bronchoalveolar lavage. Susceptibility testing should be performed on *M. tuberculosis* isolates from any clinical specimen.

Several tests are available for the evaluation of clinical specimens in the diagnosis of active tuberculosis. Culture, the gold standard for isolating *M. tuberculosis*, provides organisms for speciation, strain identification, and susceptibility testing but may require up to 2 months. Acid-fast stains should be performed on clinical samples the day of collection. They are helpful in ruling out mycobacterial disease but are less sensitive than culture. Positive acid-fast stains do not distinguish between *M. tuberculosis* and other mycobacteria.

Newer assays employ nucleic acid amplification directly on clinical samples. They offer same day results, more sensitivity than acid-fast stains, and the ability to detect members of the *M. tuberculosis* complex. Nucleic acid probes on culture isolates are even more sensitive. These nucleic acid probes complement other tests and are helpful in initiating therapy. However, cultures are still needed for species identification within the *M. tuberculosis* complex and for susceptibility testing.

Although there is no convincing evidence that alcohol abuse is associated with increased risks of extrapulmonary tuberculosis infection, miliary tuberculosis should remain in the differential diagnosis of fever of unknown origin in an alcoholic patient.

Alcoholic patients are less likely than nonalcoholics to be compliant with therapy for tuberculosis and thus are more likely to relapse. Current treatment guidelines with special emphasis on directly observed therapy should be followed to reduce risks of both therapeutic failure and emergence of drug-resistant strains (see Chapter 157, Tuberculosis).

PERITONITIS

Up to 30% of patients with alcoholic liver disease and ascites develop spontaneous bacterial peritonitis (SBP). In this condition bacterial cultures

of ascitic fluid are positive, the fluid contains more than 250 neutrophils/mm^3, and there is no evident intra-abdominal source of infection. Aerobic gram-negative bacilli, especially *Escherichia coli*, cause approximately 75% of SBP infections. Aerobic gram-positive cocci, including *S. pneumoniae, Enterococcus faecalis*, other streptococci, and *Staphylococcus aureus*, are responsible for most other SBP cases. Anaerobes cause only 6% of SBP cases, presumably because of the relatively high pO_2 of ascitic fluid.

Because enteric bacteria predominate in SBP, it is thought that the gut is the major source of organisms for this infection. Several mechanisms have been proposed to explain the movement of organisms from the intestinal lumen to the systemic circulation. Cirrhosis-induced depression of the hepatic reticuloendothelial system impairs the liver's filtering function, allowing bacteria to pass from the bowel lumen to the bloodstream via the portal vein. Cirrhosis also is associated with a relative increase in aerobic gram-negative bacilli in the jejunum. A decrease in mucosal blood flow due to acute hypovolemia or drug-induced splanchnic vasoconstriction may compromise the intestinal barrier to enteric flora, thereby increasing the risk of bacteremia. Finally, bacterial translocation may occur with movement of enteric organisms from the gut lumen through the mucosa to the intestinal lymphatics. From there bacteria can travel through the lymphatic system and enter the bloodstream via the thoracic duct. It is assumed that SBP caused by nonenteric organisms is also due to bacteremia secondary to another site of infection with subsequent seeding of the peritoneum and ascitic fluid.

Patients with severe acute or chronic liver disease have decreased serum complement levels, diminished serum bactericidal activity, and reduced bacterial clearance by macrophages of the reticuloendothelial system. Because the ability of ascitic fluid to opsonize bacteria and thus facilitate phagocytosis correlates closely with total protein concentration, patients with low ascitic fluid protein levels are at particular risk for SBP. Other risk factors have been associated with SBP, including gastrointestinal bleeding, fulminant hepatic failure, and invasive procedures such as the placement of peritoneovenous shunts for the treatment of ascites. An elevated bilirubin level is also correlated with a high risk of peritonitis in patients with cirrhosis.

Many patients exhibit other findings of end-stage liver disease such as hepatorenal syndrome, encephalopathy, and variceal bleeding. Other clinical features include fever, vomiting, abdominal pain, and physical signs of peritonitis. However, signs or symptoms of infection are absent in approximately one-third of patients with SBP, so diagnostic paracentesis is indicated for all alcoholic patients with ascites. Fluid should be submitted to the laboratory for chemistry tests, cell count and differential, and microbiologic stains and cultures. Centrifugation of ascitic fluid and Gram stain of the sediment will reveal organisms in 25% to 68% of patients with SBP. Some authorities recommend that a portion of ascitic fluid be inoculated directly into blood culture bottles at the bedside. Peripheral blood cultures should be performed if SBP is suspected.

Empiric therapy should be directed against the most likely gram-negative and gram-positive pathogens discussed above. Recommended choices include either a third-generation cephalosporin, β-lactam/β-lactamase inhibitor combination, or a carbapenem (see Chapter 57, Peritonitis).

Tuberculous peritonitis can occur in patients with alcoholic liver disease. Clinical findings resemble those of bacterial peritonitis, and acid-fast stains of ascitic fluid are usually negative. The diagnosis is best made with stains and cultures of peritoneal tissue, especially when obtained by peritoneoscope-directed biopsy. The treatment regimen is the same as for pulmonary tuberculosis.

BACTEREMIA AND SEPSIS

The liver plays a major role in clearing bacteria from the bloodstream. Alcoholic cirrhosis adversely affects hepatic reticuloendothelial system function. Both intrahepatic and extrahepatic arteriovenous shunts divert blood from macrophages that line liver capillary beds. In addition, both acute intoxication and cirrhosis interfere with bactericidal activity of these tissue phagocytes. Complications of liver cirrhosis including hypocomplementemia, neutropenia, and reduced serum bactericidal activity may also contribute to bacteremia in these patients.

Escherichia coli is the most common cause of spontaneous bacteremia in alcoholic and cirrhotic patients. Additional organisms causing bacteremia or sepsis include other gram-negative bacilli, *S. pneumoniae*, group A streptococci, and *Clostridium perfringens*.

Alcoholics with cirrhosis are particularly susceptible to sepsis caused by non-01 *Vibrio cholerae* and *Vibrio vulnificus*, an opportunistic pathogen found in marine waters. Bacteremia can follow

ingestion of contaminated shellfish, or exposure to seawater can result in a cutaneous infection. The latter may progress from erythematous or ecchymotic patches to bullae formation, subcutaneous necrosis, and bacteremia. *Vibrio vulnificus* infections are associated with high mortality rates. The recommended antibiotic therapy includes doxycycline with ceftazidime. Alternative regimens include cefotaxime or ciprofloxacin.

Nontyphoidal salmonella septicemia, especially due to *Salmonella typhimurium* and *Salmonella choleraesuis*, has been associated with alcoholic liver disease. Homeless people and alcoholics are also at increased risk for bacteremia due to *Bartonella quintana*, and the seroprevalance for this organism is high among homeless people in both the United States and Europe.

Bacteremia with or without sepsis syndrome is associated with increased mortality among alcoholics. A multicenter study conducted in four US urban university hospitals confirmed that a history of chronic alcohol abuse substantially increases the risk of acute respiratory distress syndrome for critically ill patients with septic shock. These patients also experienced greater frequency and severity of nonpulmonary organ dysfunction and, for survivors, an increased length of hospital stay.

Chronic alcoholic patients also have a 3-fold or greater increased risk for developing a severe infection or septic shock after surgery. A German study evaluated patients with and without a history of chronic ethanol abuse who developed severe sepsis. At the onset of infection and during early septic shock, chronic alcoholic patients had lower plasma levels of proinflammatory cytokines, including interleukin (IL)-1β, IL-6, and IL-8. The authors concluded that ethanol abuse altered proinflammatory cytokine production and thus the host's immune defenses to infection.

ENDOCARDITIS

Alcoholism is one of the strongest risk factors for pneumococcal endocarditis, and reports link cirrhosis with increased frequency and severity of endocarditis due to other bacteria. It is a less common but significant complication of cirrhosis, seen in up to 14% of cirrhotic patients. The aortic valve is most likely to be involved, and many patients have no demonstrable underlying cardiac valvular abnormalities. Compared with that in nonalcoholics, endocarditis in cirrhotic patients is also more likely to involve gram-negative bacilli such as *E. coli* and less likely to be caused by α-hemolytic streptococci.

OTHER INFECTIONS

Diphtheria

The lifestyle and poor hygiene of many alcoholics can predispose them to infections due to *Corynebacterium diphtheriae*. Cutaneous rather than pharyngeal diphtheria was reported among most cases from three outbreaks from the Skid Row district of Seattle. Many skin lesions were secondarily infected with group A streptococci. For diphtheria, a macrolide such as azithromycin or clarithromycin remains the treatment of choice. The Tdap (tetanus, diptheria, and pertussis) vaccine is recommended for all patients 19 years of age and older.

Pancreatitis and pancreatic abscess

Alcohol abuse is a common cause of acute and chronic pancreatitis, and infectious complications including development of a pancreatic abscess are potentially catastrophic. Primary abscesses characteristically evolve rapidly and culminate in severe sepsis. Secondary abscesses, which may present weeks after the acute inflammation, commonly involve infection of a pancreatic pseudocyst.

The cardinal signs of a pancreatic abscess are high fever, septicemia, a rapidly enlarging abdominal mass, and multisystem organ failure in severe cases. Early surgical drainage is important. Initial empiric antibiotic therapy should be aimed at the most common pathogens, including *E. coli*, other enteric aerobes, and anaerobic gram-negative bacilli. Recommended choices include a β-lactam/β-lactamase inhibitor combination or a carbapenem.

Viral hepatitis

Hepatitis viruses and alcohol abuse are the two main causes of liver cirrhosis. In patients with chronic infection due to hepatitis B virus (HBV), the prevalence of e antigen tends to be higher, and levels decrease more slowly in alcoholics versus nonalcoholics. Current evidence suggests that alcohol use may adversely affect cellular immune responses to the virus, and is associated with increased risks of cirrhosis and hepatocellular carcinoma in chronic HBV infection. In

addition, alcoholics have a lower rate of responsiveness to the hepatitis B vaccine.

Hepatitis C virus (HCV) is found at a high incidence in alcoholic patients, and 20% to 30% of patients infected with hepatitis C will progress to cirrhosis. Some studies suggest that even moderate alcohol consumption may accelerate liver damage and hasten the clinical progression of hepatitis C infection. Abstinence from alcohol also has been shown to result in a reduction of viremia. The effect of alcohol on the interaction between HCV viral proteins and the immune system is poorly understood. Indirect evidence suggests that alcohol contributes to suppression of T-cell function, which may lead to persistence of HCV infection after exposure to the virus. Alcohol abuse is considered a relative contraindication to interferon-based therapy of hepatitis C due to concerns regarding patient compliance. Response rates to interferon therapy are diminished by alcohol use, and the effectiveness is further reduced if alcohol consumption is increased.

Human immunodeficiency virus infection

Individuals with HIV infection have significantly higher rates of alcohol use than the general population. Studies have reported the prevalence of alcohol abuse or dependence to range from 20% to 40% among HIV-infected patients.

It is unclear whether alcohol abuse predisposes to HIV infection at the time of exposure, although intoxication does have a disinhibiting effect on risk-taking behavior. It also is not certain whether alcohol consumption increases the rate of HIV replication within the host, although ethanol intake has been shown in some studies to increase HIV replication in isolated human blood mononuclear cells. It is likely that the well-described adverse effects of ethanol on cell-mediated immune function may reduce host defenses against HIV infection.

Aside from the direct effects of acute alcohol ingestion, the concomitant malnutrition and liver disease seen with chronic alcoholism may amplify the immunosuppressive effects of ethanol and hasten the progression from asymptomatic HIV infection to manifestations of AIDS.

The effect of ethanol ingestion on progression from asymptomatic HIV infection to AIDS-defining opportunistic infections has not been clearly established, but there are recent studies showing associations between heavy alcohol consumption with declines of CD4 cell counts and decreased ability to suppress HIV viral load. Heavy alcohol users receiving antiretroviral therapy are twice as likely to have CD4 counts <500 than light or nondrinkers, and antiretroviral-treated heavy alcohol users are four times less likely to achieve a positive virologic response. Further, there is evidence that any alcohol use among HIV-infected patients is associated with diminished compliance with antiretroviral therapy.

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93. Infections in the elderly

Kent Crossley

Although virtually all significant infections are discussed throughout this book, certain aspects of infectious diseases in older individuals need to be emphasized. This chapter stresses the unique aspects of infection in the elderly (defined here as older than 65 years of age). Infections that occur in long-term care institutions are briefly discussed.

Infections in the aged are an important area of concern for medicine. The number of individuals who are older than 65 is increasing dramatically and is expected to double in the United States between 2010 and 2040. Although representing only 13% of the US population at present, the elderly consume 25% of all prescription medications and a similarly disproportionate amount of other healthcare services. With few exceptions (some viral infections and venereal diseases), most common infections occur more often in older individuals.

Although mortality associated with many infections is increased in the elderly, age alone is now seen as a relatively unimportant risk factor for infection-related death or serious morbidity. Rather, it is the variety of comorbid conditions that are increasingly common with advancing age that appears to be closely associated with greater morbidity and mortality from infection.

Since the early 1990s it has become clear that there is a general hyporesponsiveness of the immune system in elderly individuals. This is the most likely explanation for the muted symptoms and signs that are a common denominator of infections in the aged. In a number infectious illnesses maximum temperatures, white blood cell count elevations, and the overtness of clinical signs and symptoms are all less pronounced in older individuals. In clinical terms, this means that an elderly patient may have a serious bacteremic infection without chills, fever, or leukocytosis.

PRINCIPLES OF ANTIBIOTIC USE

Table 93.1 summarizes recommendations for treatment of common infections in the elderly. Important points include the following:

1. Aminoglycoside antibiotics are best avoided in older individuals because of their toxicity. Although probably appropriate in neutropenic, immunocompromised elderly or in the presence of documented *Pseudomonas* infection, try to use other agents when possible. With careful monitoring, once-daily administration of these drugs for at least 10 days does not appear to be associated with more side effects in the elderly.
2. Because most antibiotics (quinolones, aminoglycosides, and most penicillins are examples) are excreted by renal routes and because of the decline in renal function with increasing age, higher dosages may be potentially more toxic in the elderly.
3. Broad-spectrum therapy is appropriate initially in the treatment of serious infection if the cause is unclear. Older individuals lack the physiologic reserve of younger adults and usually have one or more comorbid diseases. In the presence of a serious infection, the elderly can rapidly deteriorate. Using drugs that are active against most of the likely causes of the infection (with the least possible toxicity) is the best approach.

URINARY TRACT INFECTION

Urinary tract infection (UTI) is increasingly common with increasing age. This reflects obstruction from prostatic enlargement in men and a variety of changes in the defense mechanisms of the female urinary system. The risk of instrumentation and catheterization, procedures often associated with development of infection, also increases in the elderly population.

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Table 93.1 Antibiotics recommended for initial (empiric) therapy for the elderly

Infection	Antibiotics	Comments
Acute fever, unidentified source	Ertapenem, 1 g q24h IV, or imipenem, 0.5 g q6h IV, or meropenem, 1.0 g q8h IV plus vancomycin 15 mg/kg q12h IV	Broad spectrum, limited toxicity
Urinary tract infection	*Gram-negative organisms*: Third-generation cephalosporin (e.g., ceftazidime, 2.0 g q8–12h), or broad-spectrum penicillin with β-lactamase inhibitor (e.g., piperacillin–tazobactam, 3.375 g IV q6h), or imipenem, or meropenem, or quinolone (e.g., ciprofloxacin, 400 mg IV q12h) *Gram-positive organisms*: Vancomycin, 10–15 mg/kg q12h IV	Consider imipenem or meropenem if in LTCF or a recurrent infection; use in combination with low-dose aminoglycoside (e.g., gentamicin, 40–60 mg/d) if resistant organisms are probable Oral quinolone (e.g., ciprofloxacin, 250 mg BID) appropriate if not seriously ill Active against enterococci, staphylococci, and streptococci
Pneumonia	Third-generation cephalosporin (ceftriaxone, 1 g IV q12h) or ertapenem, 1 g IV q24h plus a macrolide (e.g., azithromycin, 0.5 g/24h IV)	Consider using ceftazidime or imipenem for nosocomial pneumonia Macrolide (preferably azithromycin, 500 mg on day 1, then 250 mg on days 2–4), or quinolone with antipneumococcal activity (e.g., levofloxacin, 500 mg/d) for oral therapy in less seriously ill patients
Pressure sores	Broad-spectrum β-lactam agent with β-lactamase inhibitor (e.g., piperacillin–tazobactam), ertapenem or imipenem (doses as above)	Other treatment regimens active against *Bacteroides*, and enteric gram-negative organisms, may be used. Add vancomycin if gram-positives present in wound
Infective endocarditis	Vancomycin, 15 mg/kg IV q12h with gentamicin 1 mg/kg IV or IM q8h	Modify as appropriate after results of cultures and antibiotic susceptibility testing are available
Infectious (bacterial) diarrhea	Ciprofloxacin (500 mg PO BID) or other quinolone for 1–3 days.	
Meningitis	Third-generation cephalosporin (e.g., ceftriaxone, 2 g IV q12h) plus ampicillin, 2 g IV q4h plus vancomycin 10–15 mg/kg IV q6h	*Listeria monocytogenes* is not susceptible to cephalosporins
Septic arthritis	Vancomycin 10–15 mg/kg IV q6h plus ceftazidime 1–2 g IV q8–12h	

Abbreviation: LTCF = long-term care facility.

Note: Therapy should be modified as appropriate after results of Gram stain, culture, and antibiotic susceptibility testing are available. Renal function in patients receiving vancomycin and gentamicin therapy must be carefully monitored.

Asymptomatic bacteriuria is more common in both elderly men and women than in younger subjects. Multiple studies have demonstrated that treatment of bacteriuria is without value, primarily because it usually recurs after therapy.

Escherichia coli accounts for the bulk of UTIs in young women. In older individuals, the bacteriology is more complex. Infecting organisms are usually from other genera (e.g., *Serratia* and *Pseudomonas*) and are often resistant to multiple antibiotics. For this reason, urine culture and sensitivity should always be done before initiating therapy in an elderly individual.

Recent studies indicate treatment of lower UTI in elderly women may be safely done with 3-day therapy. In men, a 2013 study examining 40 000 episodes of UTI showed that shorter course therapy (<7 days) was as effective as longer periods of treatment. While trimethoprim–sulfamethoxazole (TMP–SMX) or a quinolone is a good initial choice for treatment of a lower UTI, resistance to these drugs is increasing in frequency and nitrofurantoin or fosfomycin may be required.

For patients with upper tract infection and for those who are seriously ill, therapy should be initially parenterally. Selection should be guided by Gram stain of the urine. If gram-negative organisms are present, a broad-spectrum β-lactam agent with activity against *Pseudomonas aeruginosa* (e.g., piperacillin–tazobactam) or a quinolone would be an appropriate initial choice. If a gram-positive organism is present in the Gram stain (nearly always representing staphylococci or enterococci), vancomycin would be the most appropriate antibiotic to start, pending culture and susceptibility results. Multiply-resistant gram-negative organisms may cause infection in patients with previous UTIs, those who have recently taken antibiotics, nursing home residents, and immunosuppressed patients. In these

situations (and in documented *Pseudomonas* infections), an agent such as imipenem, meropenem, or another broad-spectrum β-lactam should be given with an aminoglycoside.

Infections in individuals with chronic indwelling urinary catheters should be treated only when symptomatic. Virtually all catheterized patients will have asymptomatic bacteriuria. Treatment of catheterized patients with symptomatic infection should be based on culture and sensitivity. Although there is not good evidence that catheter removal is important, it is often done before initial therapy for these infections.

PNEUMONIA

Pneumonia is an increasingly common problem with increasing age. *Streptococcus pneumoniae* is the single most common cause in the elderly. The effectiveness of administering pneumococcal polysaccharide vaccine in the elderly is a topic of continuing controversy. Gram-negative organisms (e.g., *Haemophilus influenzae, Moraxella*, and, less often, enteric organisms such as *E. coli*) are also causal. Nonbacterial organisms such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* are also recognized as important causes of pneumonia in older adults. *Mycoplasma pneumoniae* and *C. pneumoniae* may each account for up to 10% of episodes of acute pneumonia in the elderly. Respiratory syncytial virus (RSV) is recently recognized as a significant cause of pneumonia in the aged. Although RSV-associated illness is similar to clinical influenza, bronchospasm is more common. Rhinoviruses also occasionally cause pneumonia in older individuals.

Because of the variety of agents that may cause pneumonia in the elderly, attempts to document the etiology of the infection by sputum cultures (and blood cultures if the patient is seriously ill) are important. Sputum cultures after initiation of treatment are usually of no value; appropriate cultures need to be obtained before starting therapy.

In an otherwise healthy elderly adult living in the community, initial therapy for pneumonia could be with either a macrolide or a quinolone. The newer quinolones (e.g., levofloxacin) have activity against many gram-negative organisms, atypical agents such as *Mycoplasma* and *S. pneumoniae*. Because of their broad spectrum and once-daily dosing, these agents have become increasingly popular in the outpatient therapy of pneumonia in elderly individuals.

For patients with community-acquired pneumonia who are hospitalized, empiric treatment should be broad spectrum and effective against gram-positive and gram-negative bacteria as well as atypical agents. Broad-spectrum parenteral β-lactams such as a third-generation cephalosporin (e.g., ceftriaxone) or a penicillin/β-lactamase inhibitor combination (e.g., piperacillin–tazobactam) in conjunction with a parenteral macrolide (e.g., azithromycin) represents optimal therapy. Although limited data are available, in a patient with a functioning gastrointestinal tract, oral therapy with a newer quinolone (such as levofloxacin) may be a possible option. Although parenteral therapy is most often appropriate in patients who are ill enough to be hospitalized, the nearly complete absorption of the quinolones after oral dosing and their broad spectrum suggest this may become a convenient and cost-effective approach.

TUBERCULOSIS

About one-quarter of tuberculosis cases in the United States occur in individuals older than 65. This is a special problem for nursing homes because the incidence in long-term care is about four times that in the community. Older individuals with a positive tuberculin skin test who have one of a number of additional risk factors (e.g., gastrectomy or steroid therapy) or who have recently converted their skin test need to be treated with isoniazid, 300 mg/day for 6 or 9 months, or rifampin for 4 months. Managing clinical tuberculosis in an elderly individual is similar to that in a younger patient. Monitoring for hepatic toxicity is advisable.

PRESSURE ULCERS

Efforts to attempt to prevent pressure-associated ischemia are extremely important. Once an ulcer develops, infection often follows. Topical antimicrobials are ineffective in the management of these lesions. Systemic antimicrobials should be used if clinical cellulitis is evident at the margin of a pressure ulcer or if there is evidence of deep infection or osteomyelitis. Therapy needs to be effective against anaerobic bacteria and both gram-negative and gram-positive organisms. Oral therapy might include a combination of an oral cephalosporin and metronidazole or amoxicillin–clavulanate. Appropriate parenteral therapies include imipenem, piperacillin–tazobactam, or one of the broader-spectrum cephalosporins (e.g., ceftriaxone and cefotaxime)

or a quinolone combined with metronidazole or clindamycin for anaerobic coverage. If material can be obtained for culture (usually best done by needle aspiration), therapy can be modified when results are available.

Most other skin and soft-tissue infections in the aged, as in younger individuals, are caused by group A β-hemolytic streptococci or *Staphylococcus aureus*. Treatment of these infections is not significantly different in older individuals. Community-acquired methicillin-resistant *S. aureus* (MRSA) is of concern in all patients with skin and soft-tissue infection. For seriously ill patients, vancomycin is appropriate. In outpatient treatment, TMP–SMX should be used.

BACTEREMIA

In one recent study, nearly 15% of the cases of community-acquired bacteremia were in individuals older than 84 years. Usual primary sites of infection include the urinary tract, intra-abdominal sites, the lower respiratory tract, and skin and soft tissue. Evaluation should rule out abscess or obstruction of an airway or hollow viscus.

MENINGITIS

Streptococcus pneumoniae remains the most common cause of meningitis in older adults. The second most common cause is *Listeria monocytogenes*. This is important to know when selecting therapy because *Listeria* is not killed by cephalosporin, and initial therapy of meningitis of unknown cause in an elderly individual must include ampicillin, which is active against *L. monocytogenes*.

INFECTIONS IN RESIDENTS OF LONG-TERM CARE FACILITIES

All the infections that occur in older individuals may develop in residents of long-term care facilities (LTCFs). MRSA and, in some areas of the United States, vancomycin-resistant enterococci (VRE) have a strong association with LTCF residency. Residents are also especially prone to epidemic respiratory or gastrointestinal diseases, particularly in winter months. Selecting antibiotic therapy for patients who reside in LTCFs requires an awareness that resistant gram-negative organisms, MRSA, and VRE are all potential pathogens.

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94. Neonatal infection

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BACTERIAL INFECTIONS

Epidemiology

Neonatal infections are usually classified according to time and mode of onset in three categories: (1) prenatal, (2) perinatal (early onset), and (3) nursery-acquired (late onset). The division in time between early and late onset is usually 2 to 7 days of age (Table 94.1). Different investigators have divided early-onset from late-onset infections at different days of life but most early-onset infections are evident during the first day of life. Infections that begin within the first month of life are considered neonatal, but many intensive care units for neonates provide continuing care for infants several months of age with complex problems that are the result of prematurity and complications of neonatal disorders. Therefore, neonatal nursery-associated infections may occur in infants up to a year or more of age. Bacterial infections due to rapidly dividing high-grade pathogens that set in substantially before birth usually result in a stillbirth. Often it is difficult to distinguish infections acquired shortly prior to birth from those acquired as a result of contact with maternal vaginal, fecal, or skin flora during delivery.

Neonatal sepsis occurs in approximately 2 to 4 per 1000 live births in the United States. Worldwide reports vary from <2 to 50 per 1000 live births. The rates of early-onset sepsis have fallen to <1.0/1000 in the United States and Western Europe. Risk factors noted in Table 94.1 have a very strong predictive influence on infection rates. Full-term infants born without incident have a very low incidence of infection, lower than any other population of hospitalized patients. Infants susceptible to early-onset postnatal infections are primarily those born prematurely. Those premature infants born to mothers with an infection or whose membranes rupture more than 18 hours before delivery may have an infection rate of 20% or more. In extremely premature infants extra vigilance is required for early recognition and treatment of infection. Premature infants are much more likely to develop sepsis as a consequence of the amnionitis caused by ascending infection than are full-term infants. Similarly, premature infants are at a greater risk for developing an invasive infection if born to a mother with peripartum infection than are full-term infants. The practice of treating parturient women suspected of having amnionitis with antibiotics is probably an important factor in the decrease in early-onset sepsis observed in the United States.

Hospital-acquired infection in the nursery is an important and growing problem, and now represents most of the infections seen in neonatal units. As the technology for treating very premature and very sick infants has increased, so too has the population of surviving immunocompromised infants who require therapy with ventilators, intravascular catheters, total parenteral nutrition, and various surgical interventions, each of which carries a substantial risk of infection (see Table 94.1). The liberal use of broad-spectrum antibiotics in neonatal care units increases the risk of acquisition of pathogens by interfering with the development of normal flora in these infants. Recent data suggest that antibiotic treatment early in life increases the risk of developing neonatal necrotizing enterocolitis. In contrast, the risk of acquiring hospital-acquired viral infections appears to depend mostly on the chances of contact with the virus and not preexisting disease in the infant. Infants with chronic lung disease or congenital cardiac conditions are particularly susceptible to severe infection with respiratory syncytial virus and human metapneumovirus. Therefore, community activity of respiratory and gastrointestinal viruses and defects in the barriers to prevent spread, especially poor adherence to handwashing, within the unit appear to be the most important risk factors for viral infection.

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Table 94.1 Characteristics of prenatal, early-onset, and late-onset neonatal infections

	Prenatal onset	Early-onset infections	Late-onset infections
Age at onset	Prior to birth	Birth to 2–7 days	2–7 to 30 days
Primary route of transmission	Transplacental or ascending	Maternal flora transmitted peripartum	Hospital-acquired
Risk factors	Maternal infection Prolonged premature rupture of membranes	Prolonged premature rupture of membranes Septic or traumatic delivery Maternal infection, especially urogenital Fetal anoxia Male sex Maternal factors (poverty, pre-eclampsia, cardiac disease, diabetes)	Extreme prematurity Mechanical ventilation Contact with hands of colonized personnel Contact with aerosols of bacteria Contaminated equipment (e.g., isolettes, ventilators, IV lines) Debilitating illness, including bronchopulmonary dysplasia and short gut syndrome Congenital anomalies Surgery (including necrotizing enterocolitis) Prior exposure to broad-spectrum antibiotics
Most common pathogens	Cytomegalovirus Syphilis *Toxoplasma* Maternal vaginal flora Human immunodeficiency virus	*Escherichia coli* Group B streptococci, *Klebsiella* spp. *Enterococcus* spp., *Listeria monocytogenes* Other Enterobacteriacae (*Proteus, Citrobacter, Enterobacter*)	Those causing early-onset infections *Staphylococcus aureus* Coagulase-negative staphylococci *Pseudomonas aeruginosa* and other gram-negative rod species resistant to first-line antibiotics *Candida* spp.

Abbreviation: IV intravenous.

Microbiology

Table 94.1 lists the major bacterial organisms responsible for early and late postnatal sepsis. The organisms that cause meningitis in the neonate are the same. *Escherichia coli* and group B streptococci have accounted for about 80% of early-onset sepsis and meningitis in the past. The rate of group B streptococcal infection has declined about 80% since the widespread adoption of intrapartum antibiotic prophylaxis to prevent early-onset group B streptococcal disease.

Since the early 1990s the microbiology of late-onset sepsis has shifted, with an increase in commensal organisms, particularly staphylococci and *Candida* spp. This shift appears to be due to the increased survival of extremely premature infants with increased utilization of mechanical ventilation, central venous catheters, parenteral alimentation, and broad-spectrum antibiotics. Empiric therapy is guided by published information on the microbiology of neonatal infections as well as information about local bacterial and fungal isolates which should be kept by hospitals with neonatal units.

ANTIMICROBIAL THERAPY

Empiric therapy for early-onset sepsis

Antibiotics for early-onset infections are generally commenced prior to the identification of the infecting organism. Neonates, especially premature ones, typically fail to manifest classic signs and symptoms of infection. Thus, many schemata have been developed for empiric antibiotic treatment of infants with multiple epidemiologic risks alone or nonspecific signs and laboratory test abnormalities plus epidemiologic risk factors. The common features of these schemata are recognition of the risk factors listed in Table 94.1; the possibility that severe infection may present as temperature instability or other vital sign changes, unexplained hyperbilirubinemia, vomiting, or changes in feeding; and the recognition that a very short delay in treatment may result in overwhelming sepsis and death. Such schemata vary from hospital to hospital according to the population served, the type of hospital, and resources for screening. Screening tests may also include hematologic findings such as white blood cell count, the ratio of immature to mature cells of the granulocyte series, acute phase reactants such as erythrocyte sedimentation rate, C-reactive protein, procalcitonin, mannose-binding lectin, and serum amyloid A, upregulation of neutrophil cell surface adhesion molecules such as CD64 and CD11b, and concentrations of certain lymphokines such as interleukin-6 (IL-6), IL-8, and tumor necrosis factor-α, and each has been reported to have moderate positive and negative predictive values.

Treatment is designed to provide adequate antimicrobial activity against the organisms listed in

Table 94.2 Empiric antibiotic treatment for presumed neonatal sepsis (with or without meningitis)

Age and location of infant at onset	Antibiotic regimen	Alternative regimens
Early-onset sepsis	Ampicillin *plus* gentamicin[a]	Ampicillin *plus* cefotaxime
Late-onset sepsis (up to 1 month)		
Readmission from the community	Ampicillin *plus* cefotaxime (or ceftriaxone[b])	Ampicillin *plus* gentamicin[a] *with* or *without* cefotaxime (or ceftriaxone[b])
In the hospital, with no intravenous catheter(s)	Ampicillin *plus* gentamicin[a]	Ampicillin *plus cefotaxime* (or ceftriaxone[b])
In the hospital, with intravenous catheter(s)	Oxacillin or vancomycina *plus* gentamicin[a]	Vancomycin[a] *plus* cefotaxime (or ceftriaxone[b])

[a] Adjust dose according to concentration of the antibiotic in the blood once a steady state has been achieved.

[b] Ceftriaxone can displace bilibrubin from albumin thus intensifying hyperbilirubinemia and may also cause deposition of sludge in the gallbladder so it should be used with caution in newborns.

Table 94.1. Often the focus of infection is unknown initially but in the absence of a detectable extravascular source, therapy is directed against bacteremia and meningitis because experience demonstrates that these are the most likely foci. If pneumonia or a urinary tract infection is present, physical exam or screening tests, chest radiograph, and urinalysis will demonstrate these foci. Tables 94.2 and 94.3 list the antibiotics found to be effective and commonly used for neonatal infections. The recommended dosing (Table 94.3) takes into consideration the absorption, metabolism, distribution, and excretion, which differ from those of older children and change rapidly during early life.

Empiric treatment is generally an extended-spectrum penicillin with an aminoglycoside or extended-spectrum (third-generation) cephalosporin (Table 94.2). A majority of pediatric infectious disease practitioners continue to use an extended-spectrum penicillin, usually ampicillin, with an aminoglycoside, usually gentamicin. The advantages of this combination are low cost, considerable experience, and low toxicity. The advantages of the extended-spectrum cephalosporins are greater activity against many of the pathogens and excellent central nervous system penetration in the presence of inflammation. There is concern, however, about the development of resistant flora if these agents are used routinely. Prior treatment with third-generation cephalosporins increases the risk for invasive infections due to *Candida* species. Also *Listeria* and *Enterococcus* species which occur in ill neonates are resistant to the cephalosporins. If gram-negative bacillary meningitis is diagnosed, it is reasonable to use ampicillin plus an extended-spectrum cephalosporin as a first choice until the pathogen is identified.

When transmission of *Staphylococcus* from mother to infant is suspected, an anti-staphylococcal agent should be included.

Empiric therapy for late-onset sepsis

The neonates most likely to have late-onset infections are ill residents of an intensive care nursery. Ideal empiric antibiotic therapy takes into consideration the resident flora of the nursery, especially isolates from previously infected neonates, and the particular risk factors of the patient. If intravascular cannulas have not been used, if the infant has not been treated for a previous infection, and if there have not been isolates of gentamicin-resistant gram-negative aerobic bacilli, it is appropriate to use the same empiric treatment as for early-onset sepsis (see Table 94.2). In fact, this is usually not the case, and another regimen is often more appropriate. Ill infants frequently have one or more intravascular catheters in place, and these may be the focus of infection. The most common bacterial species causing catheter-associated infections are coagulase-negative staphylococci and *Staphylococcus aureus*. Although penicillinase-resistant semisynthetic penicillins (oxacillin, nafcillin) are usually the agents of choice against staphylococci, resistance to this class, commonly called methicillin-resistant *S. aureus* (MRSA), is rising in many institutions. Some institutions report high endemic rates of MRSA in neonatal intensive care units (NICUs). In addition, coagulase-negative staphylococci appear to have a higher incidence in very-low-birth-weight infants, and these pathogens are more likely to show methicillin resistance.

Table 94.3 Dose schedules of frequently used parenteral antibiotics for neonatal infections[a]

	<7 days of age		>7 days of age	
ANTIBIOTIC AGENT	DAILY DOSE (per kg)	DOSES/DAY	DAILY DOSE (per kg)	DOSES/DAY
Penicillins				
Penicillin G	50 000–100 000 units[b]	2–3[c]	100 000–200 000 units	3–4
Ticarcillin, ticarcillin–clavulanate	150–225 mg	2–3	225–300 mg	3–4
Piperacillin, piperacillin–tazobactam	150–225 mg	2–3	225–300 mg	3–4
Penicillinase-resistant penicillins (oxacillin, nafcillin)	50–100 mg	2	100–200 mg	3–4
Ampicillin	50–150 mg	2–3	100–200 mg	3–4
Aminoglycosides				
Amikacin[d]	7.5–20 mg	1–2	22.5–30 mg	3
Gentamicin[d]	5 mg	2	7.5 mg	3
Tobramycin[d]	5 mg	2	7.5 mg	3
Cephalosporins				
Cefotaxime	100 mg	2	100–200 mg	3
Ceftazidime	100–150 mg	2–3	100–150 mg	3
Ceftriaxone	50 mg	1	50–75 mg	1
Miscellaneous antibiotics				
Clindamycin	10–15 mg	2–3	15–20 mg	3–4
Vancomycin[d]	20–30 mg	2	30–45 mg	3
Chloramphenicol[d]	25 mg	1	25–50 mg	1–2
Aztreonam	60–90 mg	2–3	90–120 mg	3–4
Metronidazole	7.5–15 mg	1–2	15–30 mg	2
Antifungal agents				
Amphotericin B	0.5–1.0 mg	1	0.5–1.0 mg	1
Amphotericin B lipid complex or liposomal	3–5 mg	1	3–5 mg	1
Flucytosine (oral)[e]	100–150 mg	4	100–150 mg	4
Fluconazole[f]	3–12 mg	1	3–12 mg	1
Antiviral agents				
Acyclovir	45–60 mg	2–3	45–60 mg	2–3

[a] Dosing of very small premature infants (1200 g birth weight) may require longer dose intervals, and specialized literature or a pharmacy specialist should be consulted.

[b] Where there is a dose range the higher figure is used for treatment when meningitis is present. For sepsis without meningitis the higher end of the dose range is recommended for more severe infections or when the measured serum antibiotic concentration is lower than the therapeutic range.

[c] Where there is a range of number of doses/day the greater number and higher dose is used for neonates with a birth weight over 2 kg and the lower number doses with lower daily dose are for neonates with a birth weight under 2 kg.

[d] Dosing should be guided by laboratory determination of serum antibiotic concentrations once a steady state has been reached.

[e] Limited data on dosing neonates. Dose indicated is from cases in the literature.

[f] Limited data in neonates. Child dose is listed.

Therefore, in institutions with substantial methicillin resistance of staphylococci it is reasonable to use vancomycin for empiric treatment of late-onset catheter-associated infections until susceptibility is known. Generally an aminoglycoside is added. If an infant develops new symptoms of infection while receiving gentamicin, either amikacin or third-generation cephalosporin is substituted.

Penicillin is used for group B streptococci; ampicillin or ampicillin plus gentamicin is used for *Enterococcus* species or *Listeria*. For gram-negative bacillary infections ampicillin or ampicillin plus an aminoglycoside or third-generation cephalosporin (depending on susceptibility) is continued for 7 to 10 days unless there is a focal infection in addition that requires a longer

duration of treatment. For peritonitis due to necrotizing enterocolitis, the addition of clindamycin to the regimens recommended for sepsis may be of value for treatment of staphylococci and gram-negative rod anaerobes. The duration is determined based upon response to treatment.

If *Pseudomonas aeruginosa* is a likely pathogen, tobramycin is preferred to gentamicin because of higher activity. Extended-spectrum β-lactam agents such as ceftazidime and piperacillin–tazobactam are also used for *Pseudomonas* species. If infections due to gentamicin-resistant gram-negative bacilli have recently been encountered in the unit, amikacin or netilmicin are the aminoglycosides of choice. Ideally, each neonatal treatment unit would monitor pathogens isolated and adjust empiric treatment accordingly.

Isolation of *Candida* from blood or a closed space requires prompt institution of antifungal treatment. For candidemia, first remove intravascular catheters and treat with amphotericin B or one of the lipid-associated forms of amphotericin. Once there has been speciation, one may consider treatment with fluconazole or other azoles if it is a susceptible species. Although it is controversial, there is evidence that fluconazole prophylaxis is effective at reducing neonatal candidiasis and candidemia in NICUs. At this time, prophylaxis with fluconazole (3 or 6 mg/kg/day, twice weekly) is recommended primarily for neonates with a birth weight of <1000 g in units having a high rate of candidal infections.

Adjunctive therapy of sepsis

In addition to antibiotic therapy, infants with sepsis require intensive medical management. Care should be provided to address fluid and electrolyte, metabolic, nutritional, respiratory, cardiovascular, renal, and hematologic needs. Extracorporeal therapies, including continuous renal replacement therapy (CRRT), plasma-based removal techniques, and extracorporeal membrane oxygenation (ECMO), have been explored in the treatment of neonatal sepsis. The most experience is with ECMO, which has been used successfully for the treatment of refractory septic shock in neonates. The use of agents to support or enhance the neonate's immune response is controversial. Exchange transfusion, transfusion of concentrated white blood cells when there is severe neutropenia and bone marrow failure, commercial intravenous immunoglobulin preparations, and organism-specific immunoglobulin preparations are either ineffective or only slightly better than placebo. Hematopoietic growth factors, such as granulocyte colony-stimulating factor (G-CSF) and granulocyte–macrophage colony-stimulating factor (GM-CSF), have been studied in septic neonates with neutropenia, but results are inconclusive, and their use is not currently recommended. Steroids have not been proven to be of benefit in neonatal sepsis or meningitis.

Therapy and management of other focal infections

MENINGITIS

The doses of some antibiotics are increased when treating meningitis to allow for lower antibiotic concentrations in central nervous system tissue and cerebrospinal fluid (CSF) due to the blood–brain barrier. Bactericidal antibiotics are preferred to bacteriostatic agents. Routine intrathecal or intraventricular administration of antibiotics does not improve outcome. Intraventricular instillation may occasionally be warranted when resistant organisms are not eradicated using conventional antibiotics.

Ampicillin plus gentamicin or cefotaxime are recommended for empiric treatment of neonatal meningitis. Cefotaxime is preferred over ceftriaxone because the latter antibiotic has high protein binding which can increase free bilirubin in the blood. Complications and delayed sterilization are more common with gram-negative bacillary meningitis in the newborn than with meningitis in children beyond the neonatal period caused by the usual organisms for that age group. In evaluating the infant being treated for bacillary meningitis, it is recommended to repeat the lumbar puncture every 48 hours until the CSF is sterile to monitor antibiotic efficacy. Continued positive cultures may signal the need to change antibiotics or look for a focus such as a brain abscess with cranial imaging. Assuming no complications, antibiotics are usually continued for 3 weeks. For group B streptococcal meningitis repeat lumbar puncture has little value when there is a good clinical response and no late complications. Resistance of group B streptococci to penicillin and ampicillin has not been reported. Length of treatment is 2 to 3 weeks. Hydrocephalus is an unfortunately common complication of neonatal meningitis, usually associated with severe ventriculitis, and it is important to monitor the head circumference and serial head ultrasound examinations, if

indicated, throughout therapy. Infants who develop an increase in ventricular size should be evaluated by a neurosurgeon. At this time there are no data to suggest that adjunctive steroid treatment is either safe or beneficial for neonatal meningitis.

PNEUMONIA

Neonatal pneumonia can occur prenatally, in association with early-onset sepsis, as a complication of a noninfectious respiratory condition such as respiratory distress syndrome or meconium aspiration, or as a nosocomial pneumonia associated with mechanical ventilation. Prematurely born infants > 1 month of age may develop chronic lung disease of prematurity, which has not been determined to be an infectious disease. Rarely is diagnostic lower-lung tissue or sputum of good quality available for microbiologic diagnosis. Thus there is little information on optimal therapy for pneumonia as an isolated infection. In general, the bacterial pathogens are the same as those for early- and late-onset sepsis, and empiric antimicrobial treatment is the same. Antibiotic therapy is usually for 10 to 14 days and extended to 21 days for the rare cases of staphylococcal pneumonia. In addition, organisms of maternal origin such as *Chlamydia trachomatis*, which can be treated with erythromycin or sulfisoxazole, and genital mycoplasmas such as *Mycoplasma hominis* and *Ureaplasma urealyticum*, for which there is no proven treatment, may be encountered. There are reports of treatment of *U. urealyticum* with macrolide antibiotics but so far little convincing evidence of efficacy.

URINARY TRACT INFECTION

Percutaneous bladder puncture is the best method of culture to avoid contamination. Bladder catheterization is acceptable but is more likely to result in contamination of the urinary tract. If the same organism is recovered from the urine and the blood, it may not be clear whether the urinary tract was the initial focus of infection or was seeded from blood unless there is an obvious urinary tract anatomic abnormality. Late-onset urinary tract infections may be associated either with a congenital malformation or urinary tract instrumentation or be spontaneous, with no discoverable underlying cause. Initial antibiotic treatment should be similar to the approach to the neonate with sepsis according to Table 94.2 and, following identification of the pathogen continued with one of the agents listed in Table 94.3, according to the susceptibility of the isolate. Due to unpredictable absorption of oral antibiotics the treatment is generally with parenterally administered drug. Although treatment for 10 to 14 days with an agent that has renal concentration and excretion is conventional, the neonate, like older individuals, may have a poor response or relapse in the presence of obstruction, a foreign body, or incomplete voiding. Due to the high rate of congenital malformations in neonates with urinary tract infections or vesicoureteral reflux, imaging studies should be part of the evaluation and management.

SKELETAL INFECTIONS

Septic arthritis and osteomyelitis in the neonate are generally secondary to bacteremia. *S. aureus* is the most frequently isolated organism, and group B streptococci and gram-negative aerobes, especially *E. coli*, are also encountered. *S. aureus* skeletal infections in the neonate are often severely destructive and associated with later disabilities, and may be associated with multiple foci and rupture through the incompletely formed epiphyseal plate. Magnetic resonance imaging helps evaluate arthritis and osteomyelitis because metabolic bone disease of prematurity may make interpretation of radiographs difficult. Empiric therapy is similar to sepsis, but an agent active against *S. aureus* such as oxacillin or nafcillin (or vancomycin if MRSA is suspected) should be added. Management includes aspiration of infected bone or septic joint, and open drainage should be considered if aspiration is insufficient to drain the focus. Length of treatment is generally at least 3 weeks for septic arthritis and at least 4 weeks for osteomyelitis. A longer course may be necessary if there is delayed sterilization, late appearance of a second focus, unusual organism, or other complications. There is too little experience with oral agents for skeletal infections in the neonate to recommend this route.

VIRAL INFECTIONS

Herpes simplex infections

Herpes infections of the newborn are transmitted from the mother's genital tract to the infant, usually at delivery but, rarely, ascending infection may occur in utero. The incidence is approximately 1 in 3000 to 5000 deliveries although published rates vary considerably. Infants of mothers with primary genital herpes lesions at the time of delivery rather than recurrent herpes

are at highest risk, but mothers of infants with herpes infection are often unaware of ever having had genital herpes. The incubation period is generally from 3 or 4 days to a month after birth. Most neonatal herpes infections are due to herpes simplex virus type 2. The presentation of neonatal herpes may include (1) only cutaneous, eye, and mucous membrane manifestations (vesicles); (2) only central nervous system infection; or (3) disseminated visceral infection. Combinations of the three may also occur. Severity and prognosis are worst for disseminated visceral disease and best for cutaneous disease.

Acyclovir is the antiviral agent of choice. Moderately ill infants who are treated early in the course of infection benefit most. The recommended dose is now higher than that previously recommended. The usual dose in a term infant is 60 mg/kg/day divided every 8 hours. The optimal duration of treatment is unknown, but although early studies used a duration of 10 days, most practitioners extend the course to 14 to 21 days (the latter when the infection is disseminated or the central nervous system is involved) because of reports of recurrences with the shorter regimen. Some recommend repeat lumbar puncture to follow the polymerase chain reaction (PCR) and to extend treatment until the CSF PCR is negative.

Cytomegalovirus infection

Cytomegalovirus (CMV) infection of the neonate usually derives from mother to infant during gestation, but CMV may also be acquired by the infant at the time of delivery or postnatally. The diagnosis of congenital CMV infection is established by detecting virus by culture or other techniques in urine, blood, or other tissues during the first 3 weeks of life. Many laboratories utilize rapid culture techniques combined with direct immunofluorescence detection using antibodies against intermediate-early or early CMV antigens but PCR tests have taken over for diagnosis in some laboratories. The use of PCR and quantitative antigenemia in the blood, which have been useful in following older immunocompromised individuals, may be useful in confirming neonatal infection as well as in following the course of infection.

Numerous antiviral agents treat CMV infection, including ganciclovir, valganciclovir, foscarnet, cidofovir, and CMV immunoglobulin. However, there is limited experience in treating congenital infection with these agents. One study showed that infants with symptomatic congenital CMV infection and evidence of central nervous system involvement treated for 6 weeks with ganciclovir (6 mg/kg intravenously every 12 hours) have less hearing loss at 6 months and fewer developmental delays at 12 months compared to untreated controls. Concerns of marrow suppression and other potential long-term effects, such as germ cell toxicity and carcinogenicity, have led many to restrict the use of ganciclovir to treatment of congenital CMV with central nervous system involvement. A recent study demonstrated superiority of oral valganciclovir for 6 months compared to 6 weeks of treatment for congenital CMV disease.

Varicella-zoster virus

Infants born of mothers who have active varicella are in danger of developing overwhelming infection due to varicella-zoster virus (VZV) if the mother's lesions appear in the period between 5 days before delivery and 2 days after delivery. The rationale is that infants exposed during this period may have received a large dose of VZV intravenously by transplacental exposure. Infants exposed earlier in utero receive antibody transplacentally from the mother and generally develop a mild infection. Infants exposed after birth also develop mild varicella. If an infant is exposed to VZV during the critical perinatal period described above, treatment with varicella-zoster immunoglobulin (VariZIG) 125 units (one vial) or immune globulin, intravenous given as soon as possible after delivery or exposure is recommended. Neonates who develop severe perinatal VZV infections can be treated with acyclovir at a dose of 45 mg/kg/day in three divided doses for 5 to 7 days.

Viral pneumonia

Respiratory syncytial virus, influenza viruses, parainfluenza viruses, and adenoviruses can cause severe respiratory disease in neonates, and the diagnosis is made by viral culture or rapid antigen tests. In general, antimicrobial treatment is not available. Ribavirin by aerosol, which in earlier studies appeared to shorten the course of respiratory syncytial virus-associated bronchiolitis in infants, is no longer recommended for routine use because subsequent studies cast doubt on the efficacy of ribavirin even for older infants.

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95. Pregnancy and the puerperium: infectious risks

Raùl E. Istùriz and Jorge Murillo

Infectious diseases that occur during pregnancy and the puerperium pose special risks to the mother, fetus, and infant. Any intervention must be weighed against possible side effects.

URINARY TRACT INFECTIONS

For pregnant women it is recommended to culture urine at the first prenatal visit. Treatment should be provided if the urine culture is positive.

Short courses (3 days) of antimicrobial therapy are usually effective in eradicating asymptomatic bacteriuria. Penicillins, cephalosporins, aztreonam, ertapenem, imipenem, and meropenem are considered safe. Sulfonamides, including TMP–SMX, are avoided in the first trimester and near term (because of kernicterus).

Recommended regimens include amoxicillin, 500 mg orally three times a day; amoxicillin–clavulanate, 875 mg twice a day; nitrofurantoin, 100 mg every 12 hours; sulfisoxazole, 500 mg three times a day; cephalosporins, such as cefuroxime–axetil, 250 to 500 mg every 12 hours, or cefpodoxime, 100 mg every 12 hours, can also be used. Fosfomycin, 3 g PO as a single dose, was shown to be effective when compared with other drugs administered for a longer time.

Urine culture should be performed 1 week after therapy and monthly until the end of pregnancy. Suppressive therapy until delivery is recommended for women who have persistent bacteriuria after two or more courses of therapy.

In acute cystitis, pyuria is found in most patients, and urine culture should be performed. Patients should be treated for 3 to 7 days if symptoms suggesting pyelonephritis are absent. The same antibiotic regimens suggested for asymptomatic bacteriuria can be utilized. Quinolones are contraindicated in pregnancy. Follow-up urine culture should be obtained 1 week after therapy. For recurrent infections, antimicrobial prophylaxis should be considered for the duration of pregnancy.

When acute pyelonephritis is the presumptive diagnosis, we admit pregnant patients to the hospital, culture urine and blood, and treat with intravenous antibiotics until the patient is afebrile for 24 hours. Then, oral therapy can be used to complete 10 to 14 days of therapy. If fever and symptoms persist >48 hours after treatment imaging studies of the urinary tract and repeat urine culture should be obtained. Antibiotic prophylaxis should be considered in patients with recurrent pyelonephritis, with periodic urine cultures for the remainder of the gestation.

Empiric treatment of acute pyelonephritis includes the following: ceftriaxone, 1 g IV every 24 hours, ceftazidime, 2 g IV every 8 hours, cefepime, 2 g IV every 12 hours, piperacillin–tazobactam, 4.5 g IV every 8 hours, ertapenem, 1 g IM every 24 hours, meropenem and aztreonam, 1 to 2 g IV every 8 hours. We avoid aminoglycosides whenever possible.

PREMATURE RUPTURE OF FETAL MEMBRANES AND INTRA-AMNIOTIC INFECTION

Premature rupture of fetal membranes (PROM) can occur at any time before uterine contractions and labor start. Subclinical infection or inflammation of the chorioamniotic membranes causes an important proportion of cases. Intra-amniotic infection (IAI), present in 40% to 75% of women with PROM, is the infection of the membranes, the amniotic fluid, the placenta, and/or the uterus. It is associated with a 50% rate of preterm deliveries before gestation week 30.

Maternal fever and tachycardia and fetal tachycardia are common manifestations of IAI. Maternal leukocytosis is common. Maternal bacteremia occurs in up to 10% of cases but is more common when virulent organisms (*Escherichia coli* 15%, group B streptococcus 18%) are causing the infection. Abnormal labor, necessity for C-section, hemorrhage, wound infection, and endometritis

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are maternal complications. Fetal and neonatal complications include sepsis, pneumonia, respiratory distress, intraventricular hemorrhage, and low apgar score.

When IAI is suspected amniocentesis is performed. Amniotic fluid is obtained for aerobic (group B streptococcus, *E. coli*, enterococci) and anaerobic (*Peptostreptococcus, Bacteroides*, and *Fusobacterium* species, *Gardnerella vaginalis*, and *Mobiluncus* species) cultures. Samples for Gram stain (48% sensitivity, 99% specificity), glucose level (sensitive when below 15 mg/dL), white blood cell count (above 30/mm^3), and leukocyte esterase activity (trace or greater) and measurement of amniotic fluid cytokines (interleukin [IL]-1a, IL-6, IL-8, and tumor necrosis factor [TNF]) can be obtained at the same time. Antibiotics are used immediately. Ampicillin, 2 g IV every 6 hours, plus gentamicin, 5.1 mg/kg once daily, continued for 1 dose after delivery; clindamicin, 900 mg IV every 8 hours, can be added after cord clamping in cesarean deliveries to reduce endometritis. Alternatives include ampicillin–sulbactam, 1.5 to 3 g every 6 hours; or piperacillin–tazobactam, 3.375 to 4.5 g every 6 hours. For serious infections due to resistant bacteria, such as extended-spectrum β-lactamase-producing gram negatives, carbapenems (meropenem, doripenem, ertapenem) can be substituted.

MYCOBACTERIAL INFECTION IN PREGNANCY

The diagnosis and treatment of pregnant women with active tuberculosis (TB) follows the same steps as in the nonpregnant individual. A human immunodeficiency virus (HIV) serology is mandatory. PPD is safe and accurate during pregnancy. Provided no multidrug resistance is suspected, the initial regimen consists of isoniazid (with pyridoxine 50 mg/day), rifampin, and ethambutol, for 2 months, followed by rifampin and isoniazid for 7 months. Isoniazid may exhibit increased maternal liver toxicity during pregnancy. Pyrazinamide is not currently recommended in the United States for routine use. Expert consultation is advised.

Therapy for latent TB infection (LTBI) may be started even during the first trimester, with isoniazid (5 mg/kg/day, maximum 300 mg) for 9 months (supplemented with pyridoxine) or rifampin (600 mg/day) for 4 months. Breastfeeding is not discouraged.

In pregnant AIDS patients, the treatment of disseminated disease due to *Mycobacterium avium* complex (MAC) is difficult. Azithromycin (Food and Drug Administration [FDA] category B) is the preferred macrolide for MAC prophylaxis and treatment (see Chapters 157, Tuberculosis, and 158, Nontuberculous mycobacteria). Again, expert consultation is advised.

MALARIA AND PREGNANCY

Pregnant women are more vulnerable to high parasitemia, severe infection, and mortality; fetuses are more vulnerable to low birth weight (LBW), prematurity, stillbirth, congenital disease, and death. Hence, exposure to malaria should be avoided, and diagnosis and treatment of identified cases should be prompt.The geographic distribution of drug-resistant malaria parasites, the clinical features in obstetric patients, and the laboratory diagnosis are the same as described in Chapter 200, Malaria. We recommend hospitalization for all pregnant women with malaria. All antimalarial drugs have potential fetal toxicity. Chloroquine phosphate, the blood schizonticide of choice for oral prophylaxis (500 mg [300 mg base] once a week beginning a week prior to potential exposure and continued for 4 weeks afterwards) and therapy (1 g [600 mg base] stat, and then 500 mg in 6 hours and 500 mg daily for two doses) is generally considered safe and is effective for treatment of plasmodial species other than chloroquine-resistant *Plasmodium falciparum*. Pregnant women should receive chloroquine once a week until the end of pregancy when primaquine can be administered to eradicate dormant hypnozoites that may be in the liver. Mefloquine appears safer than other antimalarial drugs, but concerns remain about stillbirth, LBW, and neuropsychiatric and cardiac side effects. Tetracyclines are contraindicated during pregnancy, but IV clindamycin (10 mg/kg followed by 5 mg/kg every 8 hours) is an alternative. Artesunate plus clindamycin is indicated during any trimester of pregnancy; for treatment in the second or third trimester, an artemisinin-based combination regimen known to be effective in the region of acquisition of malaria may be preferable. Atovaquone (250 mg) combined with proguanil (100 mg) is highly effective against chloroquine- and mefloquine-resistant *P. falciparum* malaria, but data in pregnancy are scarce. Rescue has been successful with atovaquone–proguanil combined with artesunate in multidrug-resistant *P. falciparum* infections without recorded toxicity. Small studies suggest that artemisinin-derived

antimalarials are well tolerated. Quinine sulfate or quinidine gluconate with or without clindamycin are alternative regimens that require continuous monitoring of vital signs, blood glucose, and electrocardiogram (ECG). For severe malaria in the second and third trimester, parenteral artesunate is preferred over quinine/quinidine. Treatment should be started immediately with the most readily available drugs. Exchange transfusions might be added in severe malaria during pregnancy, but their benefit is controversial.

During pregnancy, chloroquine alone or with proguanil remains preferred for chemoprophylaxis where still effective; where not, mefloquine may be used. Doxycycline and primaquine must be avoided. Pregnant women should not visit malarial zones; when unavoidable, dedicated chemoprophylaxis, intermittent preventive treatment, and antivector strategies that include insecticide-treated nets are paramount.

TOXOPLASMOSIS

The rationale for early treatment of toxoplasmosis acquired during gestation is to decrease fetal infection. When the maternal diagnosis is established during pregnancy, spiramycin, a macrolide antibiotic with an antibacterial spectrum similar to erythromycin (1 g orally three times a day) reduces the rate of transmission of infection to the fetus by approximately 60%. The drug, available in the United States through the FDA (1–301-827–2335), is continued until delivery, assuming fetal infection has been excluded. If fetal infection is confirmed (the diagnostic method of choice is amniotic fluid polymerase chain reaction [PCR] examination for *Toxoplasma gondii* DNA after 18 weeks of gestation), oral pyrimethamine, 25 mg/day, plus sulfadiazine, 4 g/day, is superior and therefore should be started together with folinic acid, 10 mg/day, as soon as the diagnosis is established.

Serologic screening is to be performed before pregnancy or at the first prenatal visit, before gestational week 22, and finally near term in previously seronegative women. If the tests are or become positive, acute immunoglobulin M (IgM) (requires confirmation in a reference laboratory), IgA, or IgE can prove recent infection and mandate therapy. Maintenance trimethoprim–sulfamethoxazole (TMP–SMX) for *Pneumocystis jirovecii* (*carinii*) pneumonia (PCP) prophylaxis may prevent toxoplasmosis.

HERPES SIMPLEX VIRUS INFECTION OF THE GENITAL TRACT

Maternal fetal transmission occurs by direct contact during vaginal delivery. Ascending or transplacental infection rarely occurs. Acyclovir, an antiviral drug with an excellent safety profile, has been used in pregnancy including the first trimester. The same experience is accumulating with the use of valacyclovir and famciclovir.

For primary genital infection, acyclovir is recommended at a dose of 400 mg PO, three times a day for 10 to 14 days. For one or more symptomatic recurrences of genital herpes simplex virus during pregnancy, acyclovir, 400 mg PO three times a day, given at 36 weeks through delivery is beneficial. In preterm premature rupture of membranes at less than or equal to 31 weeks in women with active genital herpetic lesions, expectant management is warranted, and acyclovir therapy may shorten the duration of the lesions, but no further data are available.

The greatest risk for neonatal herpes is in women who shed virus during delivery, which is most common in those who acquired herpes in the third trimester. Additional risk factors include mothers younger than 21 and the use of fetal scalp electrodes. Although cesarean section does not prevent all neonatal lesions, for women with a history of genital herpes and either active genital lesions, vulvar pain, or burning at the time of delivery, cesarean section should be offered.

Prophylactic cesarean delivery is not indicated for women with a history of recurrent herpetic lesions and no evidence of active lesions at the time of delivery. In such women, acyclovir prophylaxis from week 36 is preferred to cesarean delivery.

The use of antiviral therapy during delivery is controversial; antiviral therapy can reduce the rates of viral shedding (and thereby reduce newborn exposure) but data are incomplete and the approach should be individualized. The benefit of treating asymptomatic mothers at delivery is unknown. After delivery, a high index of suspicion and immediate isolation and treatment of infants with early infections are warranted.

VACCINATION DURING PREGNANCY

Yearly inactivated influenza vaccine (IIV) is indicated during pregnancy; Tdap vaccination is recommended during each pregnancy regardless of the interval since prior dose. Antipneumococcal vaccination may be given if other risk factors are

present; meningococcal and hepatitis vaccines may be indicated on the basis of medical or epidemiologic indications. Live-virus vaccines such as varicella, zoster, and MMR are contraindicated. Always consult the current vaccine recommendations and updates.

INFLUENZA

The risk of complications is increased in pregnant women with influenza. Vaccination is the best protection for the mother and protects the infant for 6 months. The Centers for Disease Control and Prevention (CDC) recommends influenza vaccination to all women who are pregnant or will be pregnant during influenza season regardless of trimester. Live attenuated influenza vaccine (nasal route) should not be utilized during pregnancy. A trivalent or tetravalent vaccine should be utilized.

The diagnosis during pregnancy is clinical and treatment should be initiated within 2 days of symptoms, although data suggest a benefit of treatment if started later. Treatment of influenza outweighs the potential risk to the fetus. Women within 2 weeks postpartum should also be treated promptly. Pregnant women with presumptive influenza should be treated with antivirals, despite an updated vaccination history, since vaccine is not 100% effective.

Oseltamivir and zanamivir are antiviral drugs to which the majority of influenza viruses are susceptible since 2009. Although they are Pregnancy Category C drugs, prenatal exposure to these drugs has not shown increased fetal risk.

Oseltamivir is preferred to inhaled zanamivir because of greater experience using the drug during pregnancy. The dosing for oseltamivir is 75 mg orally every 12 hours and for zanamivir 10 mg (2 inhalations) every 12 hours administered for 5 days. Longer treatments have been used in patients who persist very ill after 5 days of therapy. Antiviral prophylaxis should be considered for pregnant women and for women up to 2 weeks postpartum. Zanamivir is considered the drug of choice for prophylaxis in pregnancy due to its low systemic absorption. Secondary respiratory complications may be seen especially in asthmatic patients. The dose recommended for prophylaxis is zanamivir 10 mg (2 inhalations) once a day for 10 days or oseltamivir 75 mg orally daily for 10 days. When fever develops during the first trimester, acetaminophen should be added to the antiviral therapy.

HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION

Antiretroviral therapy during gestation includes two separate issues: treatment of maternal HIV infection and prevention of prenatal transmission. Treatment with antiretrovirals during pregnancy reduces the HIV viral load to undetectable levels and lowers the risk of perinatal infection from 25% to 30% without therapy to less than 2%. Therefore, combination antiretroviral therapy is indicated to all pregnant women with HIV regardless of the baseline CD4 count and HIV viral load. The goal of therapy is to achieve an undetectable HIV viral load using the most sensitive assay. Certain antiretroviral drugs should be avoided in pregnancy, e.g., efavirenz, because of teratogenic effects; didanosine and stavudine are more toxic than the available preferred nucleoside reverse transcriptase inhibitors (NRTI). Nevirapine, a non-nucleoside reverse transcriptase inhibitor (NNRTI), has caused hepatotoxicity in women with CD4 counts >250 cells/mm^3. The recommendations for the use of antiretroviral drugs to prevent or reduce perinatal transmission of HIV are updated periodically, and the reader is encouraged to consult the web site http://AIDSinfo.nih.gov for current guidelines.

For HIV-infected pregnant women on antiretroviral therapy and failure of virologic suppression, there is no clear recommendation. Raltegravir has been used later in pregnancy; however, the reports on safety and efficacy are anecdotal. Intrapartum care using IV zidovudine as therapy or prophylaxis depends on the maternal viral load. If the patient receiving antiretroviral combination has a viral load < 400 copies/mL, IV zidovudine is no longer necessary. However, if the viral load is > 400 copies/mL or unknown at the time of delivery, IV zidovudine is indicated during labor, regardless of the mode of delivery or antiretroviral regimen. IV zidovudine during labor and delivery or before a cesarean section (started 3 hours prior to surgery) should be initiated at the following doses: 2 mg/kg IV as a loading dose followed by continuous IV infusion of 1 mg/kg/hour until delivery. Continue other antiretrovirals on schedule and minimize the duration between rupture of membranes and delivery through stimulating labor. Additionally, cesarean section at 38 weeks of gestation is recommended to all patients if the viral load is above 1000 copies/mL near the time of delivery.

PARVOVIRUS B19 INFECTION

Infection with parvovirus B19 during pregnancy can lead to vertical transmission complicated by fetal heart failure, anemia, hydrops fetalis, and death.

All pregnant women exposed to or with symptoms suggestive of parvovirus infection should have IgM and IgG antibody testing. Those found to have a positive IgM who are beyond 20 weeks of gestation should have weekly ultrasounds for at least 8 weeks after the acute infection to look for signs of fetal hydrops. When hydrops fetalis develops, usually maternal IgM antibodies are absent. If pregnant women with recent parvovirus B19 exposure have negative IgM and IgG serologies, then testing maternal plasma for parvovirus B19 DNA should be performed, since it is a more sensitive test. There is no effective drug treatment for parvovirus B19 infections and it is difficult to avoid contact with infected individuals since they are contagious before symptoms develop; hand washing and avoiding sharing drinks, food, or utensils, may reduce transmission.

POSTPARTUM ENDOMETRITIS

Infection of the uterine cavity remains a significant cause of postpartum fever. Fever, tachycardia, suprapubic pain reflecting uterine tenderness, and purulent cervical drainage are characteristic findings. Purulent foul-smelling lochia and uterine subinvolution are also found in some women. A fever of greater than or equal to 38° C after 24 hours of delivery and within 10 days postpartum is significant. Endometrial cultures are not routinely done since it is difficult to obtain uncontaminated samples through the cervix. Cervical cultures for gonorrhea and samples for chlamydia nucleic acid amplification should be obtained if not done previously, as well as blood and urine cultures.

Early onset of suspected infection suggests group A streptococci; onset between day 3 and 7 postpartum suggests enteric bacteria and anaerobes and late onset after 7 and even 14 days suggest *Chlamydia* infection. Cesarean delivery, especially after the onset of labor, is more frequently associated with endometritis.

Ultrasound and/or computed tomography can establish the presence and characteristics of a mass, especially if palpated, and guide decisions for aspiration or further procedures. Therapy includes draining pelvic collections and the uterus if indicated. Initial antibiotic therapy is empiric and should be broad spectrum covering aerobes and anaerobes.

Clindamycin and gentamicin are commonly used; alternative drugs with similar efficacy include piperacillin–tazobactam and carbapenems (imipenem, meropenem, doripenem, or ertapenem). Doxycycline should be added to the previous antibiotics if *Chlamydia* is suspected or diagnosed. Therapy is continued until the patient is clinically improved and afebrile for at least 24 hours; oral antibiotics are rarely prescribed after successful parenteral therapy. If bacteremia is present, at least 7 days of antibiotic therapy is recommended, switching to PO therapy if appropriate oral alternatives are available. Defervescence is expected after 48 to 72 hours of therapy; persistent fever may suggest resistance, abscess, absence of therapeutic drug blood levels, or septic pelvic thrombophlebitis.

CESAREAN SECTION

The risk of infection after cesarean delivery is higher than after vaginal delivery. Surgical site infections usually develop between 4 and 7 days after the surgical procedure and wound infections are diagnosed in 2.5% to 16% of these patients. It has been reported that a subcutaneous hematoma is a major risk factor for infection in a high percentage of patients after discharge. Group A or B β-hemolytic streptococci usually cause an early infection manifested by fever and cellulitis. Infections caused by *Staphylococcus aureus*, enteric bacteria, or vaginal flora usually appear later. A wound containing pus may require drainage, debridement, irrigation, and vacuum wound therapy may also be useful once local infection is controlled. Cellulitis at the wound site can be treated with broad-spectrum antibiotics alone if there are no signs of fluid collections.

For severe infections, especially if deeper tissue extension is suspected, broad-spectrum antibiotics covering *S. aureus* (including methicillin-resistant *S. aureus* [MRSA]) and microbial flora at the site of surgery should be started immediately. This can be accomplished with vancomycin or daptomycin. The antibiotic therapy for deeper pelvic infections is described in the section on postpartum endometritis.

LACTATIONAL MASTITIS

Acute breast infections during breastfeeding cause fever and breast discomfort, and occur in 2% to 10% of lactating women. Risk factors include

nipple excoriations or cracking, prolonged unilateral engorgement with inadequate milk drainage, and previous mastitis. *S. aureus*, and more frequently MRSA have become the most important pathogens. Group A or B streptococcus, *E. coli*, anaerobes (*Bacterioides* species), coagulase-negative staphylococci and *Corynebacterium* species are frequently isolated. These microorganisms penetrate the nipple, colonize the stagnant milk, and then produce mastitis. Ultrasound is an effective method to diagnose abscesses and is useful to guide abscess drainage.

In patients with mild to moderate infection and with risk factors for MRSA, trimethoprim–sulfamethoxazole DS (1 tablet PO every 12 hours) or clindamycin (300 to 450 mg PO every 6 hours) can be used. Linezolid (600 mg PO every 12 hours) is also an acceptable effective alternative. In patients with mild to moderate infections and with no risk factors for MRSA, dicloxacillin (500 mg PO every 6 hours), or clindamycin (300 to 450 mg PO every 6 hours) can be used if the patient is allergic to β-lactam drugs.

In patients with severe infections (systemic toxicity, hemodynamic instability) vancomycin at 15 mg/kg IV every 12 hours should be immediately started, and if Gram stain of the abscess or drainage shows the presence of gram-negative bacilli, broad-spectrum empiric antibiotic therapy including a third-generation cephalosporin or a β-lactam/β-lactamase inhibitor combination should be promptly added. Patients should be treated for at least 10 days. Continuation of lactation is encouraged during therapy. Breast pumps are useful until the mother can resume nursing.

HEPATITIS

Acute hepatitis A during pregnancy is similar to the nonpregnant population. So far, there has not been perinatal transmission reported. Premature labor is a risk if severe disease develops during the third trimester. Other complications include PROM, premature contractions, vaginal bleeding, and placental detachment. Overall, children have a favorable outcome. When acute hepatitis B is diagnosed during gestation, it is usually not linked to high mortality or fetal malformations. The infection is not severe and termination of pregnancy is not considered. If hepatitis B occurs earlier in pregnancy, there is a 10% transmission rate during the perinatal period; however, transmission increases significantly if the acute infection is diagnosed near or at the time of delivery. Perinatal transmission occurs most efficiently when the infant mucosal membrane comes in contact with infected maternal secretions during birth, especially if the mother is HBeAg positive. Transmission can also happen in utero or after birth.

Universal maternal screening for hepatitis B virus infection is strongly recommended, and any women in labor with known hepatitis B status should be considered potentially infectious. The use of prophylactic hepatitis B immunoglobulin immediately after birth followed by hepatitis B recombinant vaccine within 12 hours, and completion of three doses within the first 6 months of life, reduces hepatitis B virus transmission to rates of 10% or less. Hepatitis B maternal vaccination is not contraindicated during pregnancy or lactation.

Hepatitis D coinfection during pregnancy is managed as described for hepatitis B. The risk of transmission of hepatitis C from mother to infant is approximately 2%. Cesarean section delivery and avoidance of breastfeeding are not recommended for hepatitis C-infected women.

Hepatitis E virus infection and fulminant hepatic failure have a mortality rate of 10% to 25% in women during the third trimester. Vaccines are presently in development. Also, there is no evidence that immunoglobulin protects against hepatitis E, including lots produced where infection is endemic.

VARICELLA

Varicella-zoster virus infection is more severe during pregnancy. The risk of congenital varicella syndrome appears to be low, between 0.4% and 2%.

Varicella pneumonia during gestation is a severe disease, usually developing within 1 week of the rash, may rapidly progress to respiratory failure, and it is a medical emergency. Patients are febrile, hypoxemic, with chest x-rays showing diffuse nodular infiltrates. Intravenous acyclovir is indicated at a dose of 10 mg/kg every 8 hours.

Uncomplicated varicella infections in a pregnant female can be treated with acyclovir (20 mg/kg PO every 6 hours) for 5 days. Although the use of this drug has not been studied in pregnancy, a prospective registry of acyclovir use during gestation has not revealed an increased rate of birth defects.

Pregnant women who have been exposed to varicella-zoster virus are eligible for prophylaxis with varicella immune globulin, if they have no history of disease or negative serologic evidence

of prior exposure. VariZig, which is a purified immune globulin made from plasma containing a high level of antivaricella antibodies, should be administered within 10 days of exposure. The dose recommended is 125 units/10 kg of body weight given intramuscularly, the maximum dose is 625 units. There are no data to support the use of acyclovir for reducing the risk of varicella in exposed pregnant women.

Neonatal varicella-zoster virus infection is a serious disease that results from the transmission of the virus from the mother to the fetus within 5 days before to 2 days after delivery. The management of newborns exposed to varicella-zoster virus is discussed in Chapter 94, Neonatal infection.

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96. Dialysis-related infection

Peter Mariuz and Roy T. Steigbigel

Data from the US Renal Data System (USRDS) 2012 Annual Report show that the adjusted incident rate for end-stage renal disease (ESRD) was 348 per million persons. The December 31, 2010 prevalent population included 383 992 patients on hemodialysis (HD) and 29 733 on peritoneal dialysis (PD). Infections are the second most common cause of death of patients receiving long-term dialysis (12% to 22%), and a leading cause of hospitalization. Sepsis is responsible for more than 75% of these deaths. Abnormalities of cellular immunity, neutrophil function, and complement activation are associated with chronic renal failure and cited as risk factors for the increased susceptibility to infection. Additional predispositions for bacteremia include comorbid conditions (diabetes mellitus, hepatitis C infection), receipt of immunosuppressive therapy, and anemia. Most dialysis-related infections are caused by common microorganisms rather than by opportunistic pathogens and are primarily related to access site for vascular and PD. This chapter focuses on the treatment of infections related to dialysis access devices.

Table 96.1 Vascular access devices for hemodialysis

Temporary venous access (usually less than 2–3 weeks)	Permanent access for ESRD
Single- or double-lumen (Mahurkar type) catheter into the subclavian vein	Arteriovenous fistula using autogenous saphenous vein or graft using PTFE
Silastin-Teflon shunt for CAVH or CAVHD	Dacron-cuffed double-lumen silicon catheter (Permcath) surgically inserted into the subclavian or internal jugular vein through a subcutaneous tunnel; rarely used.
Twin wide-bore femoral catheter for CAVH or CAVHD	Scribner arteriovenous shunt, now used infrequently
Temporary venous access in ESRD: single- or double-lumen venous catheter inserted over guidewire into the subclavian, femoral,[a] or internal jugular vein	

Abbreviations: ESRD = end-stage renal disease; PTFE = polytetrafluoroethylene; CAVH = continuous arteriovenous hemofiltration; CAVHD = continuous arteriovenous hemodialysis.

[a] Femoral vein placement is associated with high rate of infection, so it is usually removed by 72 hours.

TYPES OF ACCESS DEVICES FOR DIALYSIS

The wide variety of catheters available for hemodialysis (Table 96.1) differ according to the duration of use (acute versus chronic) and intraperitoneal versus extraperitoneal designs. The peritoneal catheters for acute use (≤3 days) have the same basic design, a relatively stiff length of straight or slightly curved nylon or polyethylene tubing with side holes at the distal portion. They are placed at the bedside over a guidewire. These catheters lack cuffs that may protect against bacterial migration from the skin to the outer surface of the catheter, and consequently have a high rate of infection when used for longer than 3 days. Peritoneal access devices for chronic use are made of silicone rubber or polyurethane, usually with 1 or 2 Dacron cuffs, and side holes at the distal end. They can be placed by use of guidewire and dilators, peritoneoscopy, or, less frequently, laparoscopy. The silicone rubber or polyurethane surface elicits growth of squamous epithelium in the subcutaneous tunnel and at the catheter's entry and exit sites. The Dacron cuffs provoke a local inflammatory response resulting in the formation of fibrous and granulation tissues within 4 weeks. Both epithelial and fibrous tissues inhibit bacterial migration along the tunnel. Additionally, the fibrous tissue anchors the catheter. Examples of peritoneal catheters for chronic use include the straight or curled Tenckoff catheter, which is widely used in the United States, and the Oreopoulos–Zellerman, Lifecath, and Toronto Western II catheters. It is not known whether

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these newer catheters provide any advantage over the Tenckoff design.

An arteriovenous (A-V) fistula is an anastomosis of the radial artery to the cephalic vein. Other vessels in the upper arm can also be used. An A-V graft uses a tube made of polytetrafluoroethylene (PTFE, Teflon) to make the A-V connection.

INFECTIOUS COMPLICATIONS OF VASCULAR ACCESS DEVICES

In 2006, over 80% of patients began HD with catheter access while in 2007, 23% of patients on HD were using a catheter. Each dialysis session requires four tubing connections, thus a high risk for introduction of microbes through the hub and lumen of catheters. The reported catheter infection rate ranges from 3.8 to 6.6 episodes per 1000 days for nontunneled catheters vs. 1.6 to 5.5 episodes per 1000 days for tunneled catheters, both of which are markedly higher than for A-V fistulas and grafts. The relative risk for infection-related hospitalization and death is increased 2- to 3-fold for catheter-dependent HD patients compared to those with A-V fistulas. Local infections occur at the exit site or in the tunnel of percutaneously inserted silicone catheters. The clinical presentations of exit-site infection include pain, erythema, tenderness, induration, and purulent discharge within 2 cm of the site. Tunnel infections are associated with pain, erythema, tenderness, or induration involving the subcutaneous tract of the catheter. Infection of autologous A-V fistulas and prosthetic PTFE A-V grafts manifests as cellulitis, perifistular abscess, false aneurysm, draining sinus, and in PTFE fistulas, bleeding when the grafts' suture lines are involved. Fever, leukocytosis, or left shift in the differential leukocyte count may be present.

Both exit-site and tunnel infections may be complicated by concomitant bacteremia, sepsis, and suppurative thrombophlebitis. Bacteremia may lead to metastatic foci of infection, including septic arthritis, septic pulmonary emboli, endocarditis, osteomyelitis, brain abscess, and splenic abscess. Bacteremia and sepsis often present without signs or symptoms of infection at the vascular access site. Catheter-related colonization without clinical manifestations of infection has been reported in up to 55% of HD catheters. Most catheter-related bloodstream infections (CR-BSI) arise from the lumen following bacterial colonization and biofilm formation. Eradication of bacteria in endoluminal biofilm requires very high concentrations of antibiotics (up to 1000 times the concentrations needed to kill bacteria in solution). Systemic antibiotic therapy alone without catheter removal yields cure in only one-third of these CR-BSI.

Table 96.2 Microbiology of access device infections

Hemodialysis	Peritoneal dialysis
Staphylococcus aureus (50%–80%) Other gram-positive bacteria (*S. epidermidis*, streptococci, including enterococci, diphtheroides), gram-negative organisms (*Escherichia coli, Pseudomonas aeruginosa, Acinetobacter* spp., and other enteric gram-negative bacteria) (15%–30%) Occasionally fungi	*Staphylococcus epidermidis* and *S. aureus* (50%) Other gram-positive bacteria (streptococci, including enterococci, diphtheroides) Gram-negative organisms (*E. coli, P. aeruginosa, Acinetobacter* spp., and other enteric gram-negative bacteria) Occasionally fungi

Percentages in parentheses are approximate proportional incidence from numerous references.

Microbiology

A specific microbiologic diagnosis of access-related infection can frequently be made by Gram stain and culture of purulent material from the cannula exit site or with A-V fistulas from needle exit sites or abscess fluid. In addition, blood cultures drawn from the access device along with other peripheral sites should be obtained to aid in identification of access site as origin of infection. Access site origin of bacteremia is suggested if either quantitative blood cultures have colony counts from catheter blood that are 3-fold greater than from peripheral blood cultures or catheter blood cultures have an earlier time to positivity (at least 2 hours) compared to the time to positivity of blood cultures from another site. The organisms responsible for access device infection are shown in Table 96.2.

Therapy

Therapy is based on the results of cultures from infected sites and blood. Initial management plans are shown in Table 96.3. Additionally, relative indications for removal of either catheter or A-V fistula or graft include: suppurative thrombophlebitis, septicemia, bacteremia with metastatic foci of infection, infections caused by *Staphylococcus aureus, Pseudomonas aeruginosa,*

Table 96.3 Treatment of hemodialysis access-site infections

Type of infection	Therapy
Exit-site infection in a temporary access device with or without bacteremia[b]	Catheter removal and vancomycin,[a] 1 g IV; subsequent doses based on serum levels; aminoglycosides or broad-spectrum β-lactam antibiotics if gram-negative organisms suspected
Tunnel infection[b]	Catheter removal and antibiotics as above
Catheter-related sepsis	Catheter removal; empiric broad-spectrum antimicrobial therapy with vancomycin and gentamicin, 1.5 mg/kg IV in a single dose; subsequent antimicrobial therapy based on pathogen and sensitivity pattern
Suppurative thrombophlebitis	Catheter removal, antimicrobial therapy based on pathogen and sensitivity pattern; surgical consultation for possible exploratory venotomy
Arteriovenous fistula infection	Vancomycin and gentamicin as above; incision and drainage of abscess; ligation or removal of prosthetic arteriovenous fistulas for occlusion or tunnel infection or if response to treatment is not prompt; surgical repair of a malfunctioning infected shunt may be possible

[a] Alternatives to vancomycin include daptomycin and linezolid (see text).
[b] 10–14 days is often used for exit and tunnel infections with catheter removal; if the catheter remains in place, 2–3 weeks of antimicrobials.
Abbreviation: IV = intravenously.

mycobacteria, and fungi, lack of response to medical therapy within 48 to 72 hours, and recurrent infection in a catheter with the same pathogen. Tunnel infection associated with catheter access requires removal of the catheter. Any associated fluid collections associated with an A-V fistula or graft should be drained. In the absence of exit-site and tunnel infection, sepsis, or metastatic foci of infection, exchange of the catheter over a guidewire may be attempted. If there is no resolution of fever, bacteremia, or fungemia in 48 to 72 hours the catheter should be removed. CR-BSI caused by coagulase-negative staphylococci (not *S. aureus* or fungi) seem very amenable to guidewire exchange. Intravenous (IV) vancomycin is often used in initial therapy for access device infections as methicillin-resistant *Staphylococcus aureus* (MRSA) staphylococci are the most common pathogen. The type of dialyzer, dialysis flow rate, patient size, and level of residual renal function can make vancomycin serum levels difficult to predict. Therapy should be initiated with a loading dose of 15 to 25 mg/kg of vancomycin given preferably after dialysis. The second dose, 5 to 10 mg/kg, is given after the next dialysis session. Before the third dialysis session a predialysis serum vancomycin level should be done and used to determine the vancomycin dose to be given after the third dialysis session. A standard postdialysis dose can be started once target serum concentrations have been achieved. Other antimicrobials with good activity against staphylococci are alternatives to vancomycin. Linezolid or daptomycin can be used in patients with allergy to vancomycin or for organisms with reduced sensitivity to vancomycin. Dose of daptomycin is 4 mg/kg or if bacteremia is present, 6 to 8 mg/kg, every 48 hours (preferably after dialysis), and for linezolid, 600 mg IV every 12 hours. Methicillin-sensitive staphylococci (MSSA) should be treated with nafcillin, 1 to 2 g IV every 4 to 6 hours.

Fifteen to thirty percent of infections are caused by gram-negative bacilli. If gram-negative organisms are suspected, an aminoglycoside, cefepime, or aztreonam should be used in combination with the antibiotic noted above for suspected infection caused by gram-positive organisms. Vancomycin-resistant enterococci (VRE) resistant to ampicillin should be treated with linezolid or daptomycin. The initial choice of antimicrobials should be influenced by the sensitivity of organisms prevalent in the patient's geographic region. Surveillance blood cultures should be obtained 1 week after completion of antimicrobial therapy.

When catheter salvage is attempted, antibiotic lock therapy (ALT) has been recommended in addition to parenteral antibiotics for uncomplicated catheter infections. The rationale for this is the known difficulty to eradicate bacteria in endoluminal biofilm with parenteral therapy. With ALT the catheter lumen is filled with several milliliters of antimicrobial solution at concentrations several fold higher than the minimum inhibitory concentration (MIC) of the antibiotic for the infecting organism in combination with 50 to 100 U of heparin. Vancomycin (1 to 5 mg/mL), gentamicin, or amikacin (1 to 2 mg/mL); ciprofloxacin (0.2 mg/mL); and cefazolin (5 mg/mL) have been used most often. The solution is allowed to remain (lock) in the catheter for as long as possible and changed every 48 hours. The same volume of solution is removed before the next dose of antibiotic or other medications or solutions are administered. The optimal duration of ALT is not known but it has been used most frequently for 10 to 14 days after each dialysis

session. ALT is also used to prevent CR-BSI. Well-designed, appropriately powered, randomized, controlled trials that show efficacy of ALT to treat CR-BSI are lacking.

Lock therapy rather than catheter removal should not be used when the patient has sepsis, septic thrombophlebitis, endocarditis, osteomyelitis, neutropenia, *Staphylococcus aureus*, mycobacterial or fungal infection, or exit-site or tunnel infections.

INFECTIONS ASSOCIATED WITH PERITONEAL DIALYSIS CATHETERS

There are several types of chronic PD: continuous ambulatory peritoneal dialysis (CAPD), continuous cycling (CCPD), and nightly PD with a dry day. CAPD has a relatively high incidence of exit-site and tunnel infections (0.6 to 0.7 per dialysis-year). Whether PD catheter infections are less frequent with CCPD or nightly PD with a dry day remains controversial. Thirty percent of patient transfers from peritoneal to hemodialysis are a consequence of catheter complications and peritonitis. PD catheter exit-site and particularly tunnel infections may result in peritonitis and catheter loss. Peritonitis accounts for 15% to 35% of hospital admissions for patients on PD.

Exit-site infections present with purulent discharge from the exit site. Erythema may or may not be present. Pericatheter erythema without purulent drainage may be an early sign of infection. A tunnel infection can present with erythema, induration, tenderness, and abscess in the area between the catheter cuffs but is often occult as demonstrated by ultrasonography. Ultrasonography will reveal an area of hypoechogenicity (fluid collection) between the tube or the cuff of the catheter and surrounding tissues. Indications for tunnel sonography include presence of exit-site infection, recurrent peritonitis, and for assessment of the efficacy of therapy and prognosis of tunnel infections. A sonolucent area around the exit-site greater than 1 mm thick following therapy and the involvement of the proximal cuff are associated with poor outcome. A specific microbiologic diagnosis can be made by performing a Gram stain and culture of purulent exudate. The organisms responsible for PD catheter infections are shown in Table 96.2. *Staphylococcus aureus* and *Pseudomonas aeruginosa* exit-site infections are frequently associated with concomitant tunnel infections and often result in catheter-associated peritonitis.

Table 96.4 Treatment of peritoneal dialysis access device infections

Type of infection	Therapy
Exit-site erythema without purulent discharge	Topical mupirocin, chlorhexidine, hydrogen peroxide, or povidone iodine bid; avoid mupirocin with polyurethane catheter
Gram-positive exit-site infection	For MSSA dicloxacillin, 250–500 mg PO q6h, or cephalexin, 500 mg PO BID, or trimethoprim–sulfamethoxazole, 160/800 mg PO BID. Clindamycin may also be used. IV or IP route can be used. For methicillin-resistant staphylococci: vancomycin, IV 1 g every 3–5 days dependent upon blood levels. Rifampin, 600 mg PO qd, can be added for possible synergistic effect. Ultrasound to rule out tunnel or cuff involvement; 2–3 weeks of therapy generally recommended; shave external cuff and explore tunnel if infection persists; if this fails, catheter removal
Gram-negative exit-site infection	*Pseudomonas aeruginosa* should be suspected pending culture results. Ciprofloxacin, 250 mg PO BID; not to be taken within 2 hours of phosphate binders or antacids; alteration of therapy based on culture and sensitivity results. If infection is slow to resolve or recurrent *Pseudomonas* infection add a second drug such as IP aminoglycoside, cefepime, piperacillin–tazobactam, or a carbapenem. Therapy should be continued for 2–3 weeks. Catheter removal if infection persists beyond 2–3 weeks; early catheter removal should be considered if *Pseudomonas* or *Stenotrophomonas* isolated.
Tunnel infection	Antimicrobials as for exit-site infections with removal of catheter.

Abbreviations: BID = twice a day; MSSA = methicillin-sensitive *Staphylococcus aureus*; PO = orally; IV = intravenously; IP = intraperitoneally.

Therapy

Therapy is ultimately based on the results of microbiologic culture data. Initial management plans are shown in Table 96.4. Therapy should be continued until the exit site appears normal. Indications for catheter removal include: peritonitis, bacteremia, sepsis, recurrent peritonitis with same pathogen, and infection caused by fungi. Relative indications for catheter removal are tunnel infections (particularly if there is no response to therapy noted on serial ultrasound examinations), involvement of the deep cuff (which often leads to peritonitis), chronic exit-site infections (no cure after 2 to 4 weeks of therapy), and exit-site infections associated with

involvement of the superficial cuff as noted on ultrasound. Ultrasonographic evidence of tunnel involvement is associated with frequent catheter loss (50%) because of refractory or recurrent peritonitis. A 30% or greater decrease in the size of the fluid collection after 2 weeks of therapy is often associated with catheter salvage. Prolonged courses of antimicrobial therapy, although sometimes necessary, should be avoided to decrease the chance of development of antimicrobial resistance. Infections with VRE and, more ominously, vancomycin-insensitive strains of *S. aureus* and *S. epidermidis* reported in dialysis patients receiving prolonged (months of) treatment make the judicious use of this drug imperative. In chronic exit-site infections, adjunctive surgical therapy may help control infection and result in catheter salvage. Surgical procedures that have been used include cuff shaving (removal of the external cuff), debridement and curettage of the exit site and sinus tract, incision, and debridement along the subcutaneous tunnel with exteriorization of the superficial cuff and relocation of the exit site. It is not known which of these is most effective. Among gram-positive organisms, *S. aureus* is more commonly associated with poor response to medical therapy, tunnel infections, and catheter loss.

PERITONITIS ASSOCIATED WITH CAPD INFECTIONS

Peritonitis is a common complication of PD. Although the incidence varies from center to center, the average incidence is 1.3 episodes per patient per year. Peritonitis may be less common in CCPD and nocturnal intermittent peritoneal dialysis (NIPD) than in other forms of CAPD. An additional, modest reduction in the incidence of peritonitis has been achieved with use of Y-set transfer kit and "flush before fill" (particularly infections from skin flora). Bacteria gain entry to the peritoneum from the catheter, often after improper technique in connecting the transfer set to the dialysate bag or the catheter to the transfer set from the outside surface of the catheter; as a consequence of exit-site or tunnel infection; or by hematogenous spread or from the bowel or pelvis. Clinical manifestations include abdominal pain, fever, chills, malaise, nausea, vomiting, constipation, or diarrhea with abdominal tenderness, rebound tenderness, and leukocytosis. The peritoneal fluid may appear cloudy and will almost always contain >100 white blood cells per cubic millimeter of fluid after a dwell time of at least 2 hours, with 50% or more polymorphonuclear leukocytes. In any suspected CAPD infection, including those that appear to be localized to the exit site, a Gram stain and culture, cell count and differential of the peritoneal fluid should be done.

Microbiology

A single pathogen is usually involved. Polymicrobial infection suggests a perforated viscus or other intra-abdominal or pelvic pathologic process. Most cases of peritonitis (70%) are caused by gram-positive bacteria. Collectively, *S. aureus* and *S. epidermidis* account for almost 50% of infections. *Pseudomonas aeruginosa* and enteric gram-negative bacilli constitute 20% to 30%, and fungi, mostly *Candida albicans*, <1% to 10%. Some 5% to 20% of cases are culture negative. Though infrequent, fungal peritonitis is associated with significant morbidity and mortality with death rates as high as 25%. Up to 40% of patients cannot resume PD because of damage to the peritoneal membrane that prevents effective dialysis.

Therapy

Antibiotics may be given by the IV, oral (PO), or intraperitoneal (IP) route. The IP route is preferred because of its convenience. Fourteen days of therapy is usually adequate. There is no therapeutic advantage to IV therapy for peritonitis. Helpful information for the initial choice of antimicrobials includes peritoneal fluid Gram stain results, history of microbe-specific peritonitis, coexistent exit-site infection, and intra-abdominal pathology. If the Gram stain does not show gram-positive bacteria or gram-negative bacteria or is unavailable, empiric therapy should be initiated with vancomycin and gentamicin. However, because of the increasing prevalence of MRSA with reduced sensitivity to vancomycin, initial therapy with linezolid or daptomycin may become preferable to initial use of vancomycin.

After 24 to 48 hours, 70% to 90% of dialysate fluid cultures will yield a specific pathogen, and therapy should be modified accordingly. For *S. aureus* or *S. epidermidis* sensitive to nafcillin this may be given at 125 mg/L in each exchange or a first-generation cephalosporin or clindamycin may be used. Addition of rifampin, 600 mg/day PO, can be considered for patients responding slowly to the initial regimen but should not be used for more than a week as resistance to this

drug often develops with prolonged use. In areas where tuberculosis is endemic, the use of rifampin to treat *S. aureus* peritonitis should be avoided. If the patient does not improve within 5 days, evaluation for tunnel infection should be done. For MRSA, vancomycin, 2 g (30 mg/kg) IP every 7 days should be given if there is evidence of clinical response. If the patient is not responding to vancomycin consideration should be given to substituting linezolid 600 mg IV every 12 hours, or daptomycin 6 to 8 mg/kg every 48 hours especially if the vancomycin MIC is > 1 μg/mL. If the organism is sensitive, clindamycin, 300 mg/L loading dose and then 150 mg/L maintenance, can be used. For enterococci sensitive to ampicillin, it should be given at 125 mg/L in each exchange, and consider continuing the aminoglycoside. In penicillin-allergic patients, vancomycin, 2 g IP per week, should be used. Treatment of VRE depends on the antimicrobial sensitivities of the specific organism. If VRE is ampicillin susceptible, this is the drug of choice. Linezolid, 600 mg IV every 12 hours, or daptomycin, 4 mg/kg (6 to 8 mg/kg if bacteremia present) every 48 hours, preferably after dialysis, is useful for VRE resistant to ampicillin and for the penicillin-allergic patient. Because enterococci are part of the intestinal flora, intra-abdominal pathology should be considered. For other gram-positive organisms, therapy should be based on antibiotic sensitivity results. For gram-negative organisms other than *P. aeruginosa* and *Stenotrophomonas maltophilia*, a first-generation cephalosporin may suffice. If the microbe is resistant to cefazolin, the choice of another cephalosporin should be based on sensitivity testing. For *P. aeruginosa* or *S. maltophilia*, consider use of two agents (one being an aminoglycoside) chosen based on sensitivity testing results and continue for at least 3 weeks. However, eighth nerve toxicity may complicate aminoglycoside use, particularly after 2 to 3 weeks of therapy. If the infection is catheter related, the catheter should be removed with continued administration of antibiotics for 1 week.

Polymicrobial or anaerobic infections suggest a perforated viscus and therefore surgical consultation is required. Vancomycin and an aminoglycoside should be continued or changed to a cephalosporin based on sensitivity testing, with addition of metronidazole, 500 mg IV or PO every 8 hours.

If yeast are identified on Gram stain fluconazole, 200 mg PO or IP daily, should be used. The catheter should be promptly removed and treatment continued for at least 10 more days. Voriconazole, caspofungin, and amphotericin B are alternatives to fluconazole for patients who do not respond or who have organisms insensitive or less sensitive to fluconazole such as *Candida krusei* and *Candida glabrata*. After catheter removal, infections with filamentous fungi should be treated with amphotericin B or voriconazole.

Most patients with peritonitis demonstrate significant clinical improvement within 2 to 4 days. Patients who do not respond to therapy should be re-evaluated. Peritoneal fluid should be obtained for cell count and differential, Gram stain, and culture. In addition, intra-abdominal or gynecologic pathology requiring surgical intervention, unusual pathogens (fungi, mycobacteria), and sclerosing peritonitis must be considered. The catheter should be removed and cultures obtained for patients whose original cultures are negative and remain symptomatic after 2 to 4 days.

LESS COMMON PATHOGENS

There are conflicting data regarding the intrinsic risk of dialysis patients for developing tuberculosis. It is likely that any predisposition of patients to pulmonary tuberculosis is related more to the prevalence of tuberculosis in the community than to host factors. However, there is a higher incidence of extrapulmonary tuberculosis in patients receiving PD. Treatment is the same as for patients without end-stage renal disease (ESRD) except dosing of some agents must be adjusted for renal failure and others should be avoided. Isoniazid is given at 150 mg/day PO with a supplemental dose after dialysis. Rifampin requires no dosage adjustment. The dosage of ethambutol is 5 mg/kg/day PO with a supplemental dose after dialysis. Some believe that pyrazinamide use should be avoided if possible; ethionamide is given at 250 to 500 mg/day PO.

Listeria monocytogenes septicemia, meningitis, and endocarditis have been rarely described in patients with ESRD, usually as a complication of iron overload or during immunosuppressive therapy. Yersiniosis complicating iron overload has also been reported. Disseminated or rhinocerebral phycomycosis in nondiabetic patients receiving hemodialysis may be related to deferoxamine use. Treatment includes amphotericin B, posaconazole, and surgical debridement of infected sites.

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97. Overwhelming postsplenectomy infection

Larry I. Lutwick

What more thou didst deserve than in thy name,
And free thee from the scandal of such senses
As in the rancor of unhappy spleen
Measure thy course of life, with false pretenses
Comparing by thy death what thou hast been.
– *"A Funeral Elegy," W. Shakespeare, 1612*

INTRODUCTION

The human spleen (Figure 97.1) (in German: *milz; ohnemilz*: without a spleen), an organ that at one point had been deemed as nonessential as the appendix, has been associated in history as the source of melancholy thoughts. This concept brought forth the expression of "venting one's spleen" as a way of improving a person's overall situation. A similar therapeutic process, laughter ("If you desire the spleen, and will laugh yourself into stitches, follow me," Shakespeare [Figure 97.2], *Twelfth Night*, Act III, Scene 2), is also linked to the spleen.

It seems ironic, therefore, that these concepts reflect that this collection of immune cells in the left upper quadrant of the abdomen appeared to function as a way of cleansing the body. Indeed, Shakespeare's "unhappy spleen," one that has been removed from residence (by splenectomy) or whose function is embarrassed by one or another disease (hyposplenism), predisposes (by not appropriately performing its cleansing function) its former owner to an infectious disease process with substantial morbidity and mortality by becoming *ohnemilz*.

This disease, overwhelming postsplenectomy infection (OPSI), also referred to as postsplenectomy sepsis (PSS), is one of a group of infectious disease processes, such as bacterial meningitis and meningococcemia, for which diagnosis and therapeutic intervention are required immediately to minimize the disease impact. Using Ben Franklin's (Figure 97.3) "ounce of prevention is worth a pound of cure" concept, prevention as well as therapeutic intervention is an important part of any discussion of OPSI.

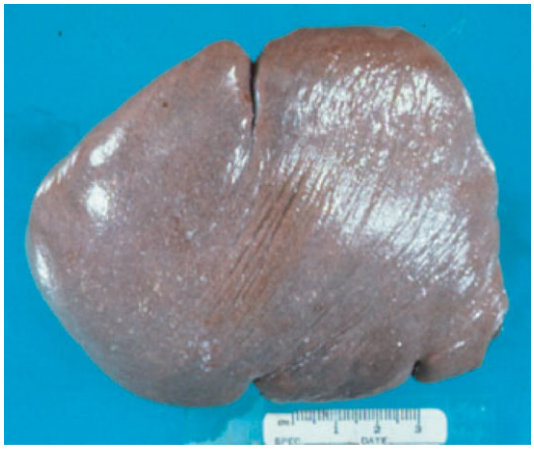

Figure 97.1 The spleen.

RISKS AND TIMING OF OPSI

The individual risk of OPSI is dependent on the cause of splenectomy as well as the time after the procedure. Overall, the lifetime risk of 1% to 2% is estimated related to trauma or idiopathic thrombocytopenic purpura (ITP), 3% for spherocytosis, 6% for Hodgkin's disease and portal hypertension, and as high as 11% for thalassemia. Although some asplenic conditions clearly have a lower risk of OPSI, if OPSI develops the morbidity and mortality are not lower in these cohorts. About 5% to 6% of total OPSI cases occur in individuals with poorly functioning spleens. A partial

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Figure 97.2 William Shakespeare.

list of diseases associated with hyposplenism can be found in Table 97.1.

No ideal assay is available to measure adequate splenic function. The presence of Howell–Jolly bodies (nuclear remnants in circulating red blood cells [RBCs]) is too insensitive. Quantification of red cells containing "pocks" (actually vacuoles containing hemoglobin found in older RBCs) as seen by interference microscopy, however, appears to be a valuable tool.

About 50% of cases of OPSI following a splenectomy occur within 2 years of the event and about 75% within 5 years. It is important to know, however, that 2% to 3% of cases occur 20 years or longer after the event and there have been reports of OPSI four decades after the onset of *ohnemilz*.

PRESENTATION AND DIAGNOSIS

The classical presentation of OPSI is one that often begins with an alert, relatively nontoxic patient who might walk into an emergency department complaining of fever and chills associated with myalgias and diarrhea. The individual deteriorates quickly, developing lactic acidosis due to organ hypoperfusion, disseminated intravascular coagulation (DIC), and multiorgan failure. This gastroenteritis-like presentation can, but should not, divert attention away from OPSI in the at-risk individual.

The progression to septic shock and death in these individuals can happen within hours of initial presentation. Overall mortality rates

Table 97.1 Common causes of hyposplenism

Blood diseases
Primary thrombocytosis
Sickle cell hemoglobinopathies
Gastrointestinal diseases
Celiac disease
Ulcerative colitis
Splenic infiltration
Amyloidosis
Sarcoidosis
Malignant infiltration
Vasculitic diseases
Autoimmune thyroiditis
Lupus erythematosus
Rheumatoid disease
Others
Ethanolism
Long-term parenteral nutrition
Spleen irradiation
Splenic vein thrombosis

Figure 97.3 Benjamin Franklin.

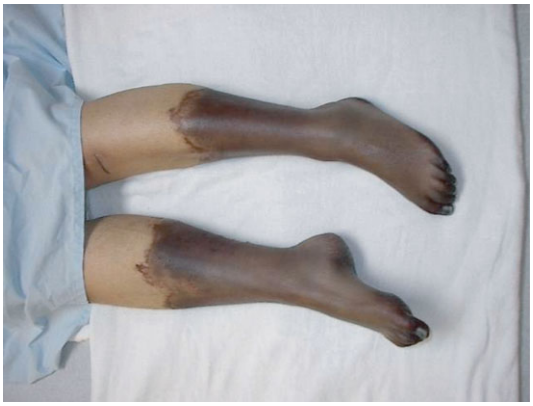

Figure 97.4 Purpura fulminans.

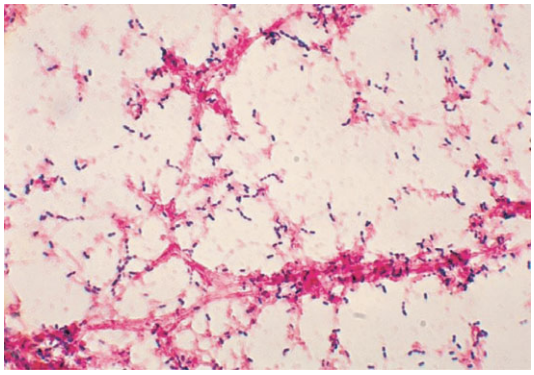

Figure 97.5 Pneumococcus.

are 50% to 60%, with a majority of the deaths within 24 hours. Encouragingly, relatively recent pediatric data suggest that increased survival rates can result from prompt recognition and overall incidence can decrease with preventative measures. Purpura fulminans (Figure 97.4) has been associated with OPSI as well as with meningococcemia. It causes considerable endothelial injury, resulting in arterial thrombosis and gangrene of one or multiple extremities. If the affected individual survives, multiple extremity amputations can result.

Prompt diagnosis requires knowledge of the issue with spleen function or absence in an appropriately ill patient. Confirmation especially awaits finding positive blood cultures for the bacterial etiology. Blood cultures are often positive within 6 to 8 hours due to the high initial bacteremia, which is as much as 10 000 times the organism load of a more routine bacteremia. Because of this massive bacteremia, organisms can be found in the buffy coat of the peripheral blood and sometimes on a standard peripheral smear. It should be noted that Wright stain, routinely used on peripheral blood smears, will stain all bacteria blue, even the usual "red" organisms on Gram stain of gram-negative bacteria.

PATHOGENS

Streptococcus pneumoniae (the pneumococcus)

The pneumococcus is without question the most canonical cause of OPSI. This α-hemolytic, polysaccharide-encapsulated, gram-positive diplococcal bacterium has a distinctive morphology on staining, a so-called lancet shape (Figure 97.5). Its capsule is a well-recognized virulence factor, interfering with phagocytosis by preventing effective C3b opsonization of the bacterial cells. Overall, *S. pneumoniae* is involved in 50% to 90% of OPSI cases, with the percentage of pneumococcal OPSI cases tending to increase with age. In series that include single case reports, pneumococci are often underrepresented because many case reports relate to less common causes of infection in asplenic hosts.

No single type or group of the 90 different capsular types appears to be more associated with OPSI than other forms of invasive pneumococcal disease. With the use of pneumococcal polysaccharide vaccination, however, especially in places with universal immunization using the newer 13-valent conjugated product, a shift of serotypes can occur.

It is important to note that antimicrobial drug resistance has become increasingly prevalent. Some isolates are only less sensitive to penicillin (particularly relevant in bacterial meningitis), some are fully resistant to penicillin, and some may be resistant to penicillin as well as the extended-spectrum cephalosporins such as ceftriaxone. The local epidemiology of pneumococcal resistance must be considered in the empiric treatment of OPSI. High levels of penicillin resistance are reported in Spain, parts of eastern Europe, and South Africa (Figure 97.6). In the United States, resistance is more prevalent in Alaska and the South but can be found anywhere. It is yet to be determined whether changes in serotypes in the post-conjugate vaccine era will in the long run increase or decrease antimicrobial resistance.

Haemophilus influenzae type b

Although studies report the frequency of *Haemophilus influenzae* type b (Hib)-associated

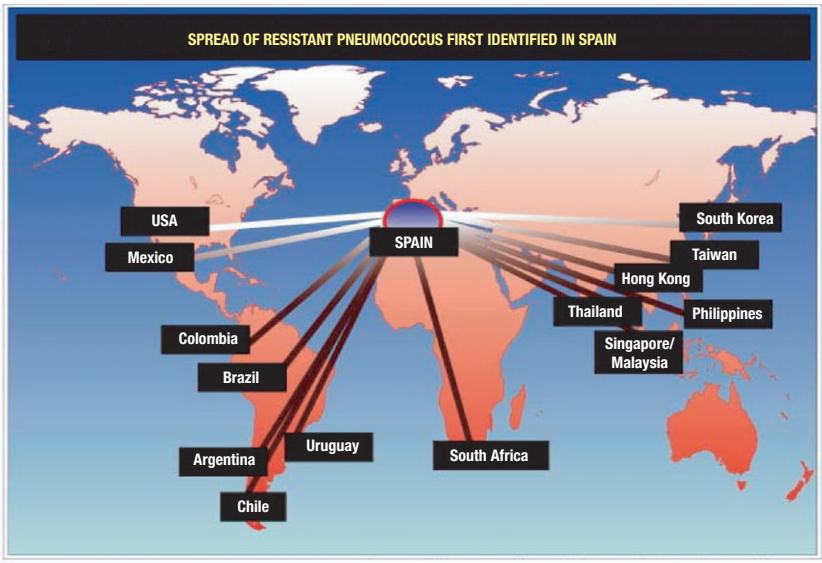

Figure 97.6 Spread of resistant pneumococcus.

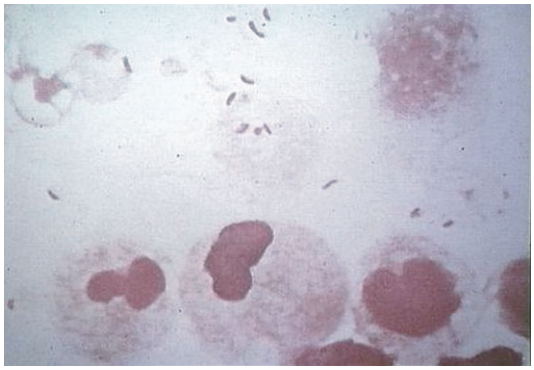

Figure 97.7 *Haemophilus influenzae*.

OPSI to be about 10 times lower than that of the pneumococcus, Hib is classically the second most common cause of OPSI. It has primarily affected children younger than 15 years. *Haemophilus influenzae* is a small polysaccharide-encapsulated pleomorphic gram-negative coccobacillus (Figure 97.7) that can be confused with pneumococcus if the Gram stain technique is poor (over- or underdecolorized). Like pneumococcus, the type b capsule is a major virulence factor for invasive disease.

The incidence of invasive Hib disease (and correspondingly of Hib-related OPSI) has dramatically decreased because of the use of the conjugated Hib vaccine. Neither nontypeable strains nor non-b capsular organisms have been found to be significant causes of OPSI, although nontypeable organisms may cause usually non-invasive infection in the human respiratory tract. When choosing antimicrobial therapy, it is important to know that many *H. influenzae* strains produce β-lactamases.

Other bacterial organisms

Capnocytophaga canimorsus, a fastidious gram-negative rod formerly referred to as CDC group DF-2, is usually transmitted to humans from dog bites. Human infection with this part of canine and feline oral normal flora is relatively mild when occurring in the eusplenic host. Of reported severe cases, however, predisposing conditions can be identified in 80%, primarily asplenia or a hyposplenic condition. The presence of an eschar at the bite site 1 to 7 days after the bite, or observation of gram-negative bacilli in the blood buffy coat or peripheral smear, is highly suggestive of *C. canimorsus* infection.

The organism does not have a capsule as the pneumococcus and Hib do but appears to escape from immune surveillance by blocking the typical proinflammatory response of human macrophages perhaps related to the inability of Toll-like receptor 4 to respond to the organism. β-lactamase activity can be seen in 30% of strains.

Although *Neisseria meningitidis* (the meningococcus) is often cited as the third most common cause of OPSI and does occur in the asplenic host, it does not appear that meningococcemia is either more severe or more frequent than in

eusplenic individuals. Because meningococci are encapsulated and can cause quite severe invasive infection, most authorities include preventative strategies for it in dealing with the noneusplenic person.

Salmonellosis has been associated with, but does not play a large role in, OPSI. Most reports are associated with illnesses where cell-mediated immunity defects from either the illness or its treatment predispose to salmonellosis, such as in children with sickle cell anemia. Sickle cell disease, however, does cause hyposplenism as previously noted.

INTRAERYTHROCYTIC PARASITEMIAS

The human spleen plays a key role in malarial parasite clearance by removal of intraerythrocytic parasites from the RBC without red cell destruction (pitting). Because pitting is absent or much diminished in the splenectomized or hyposplenic person, removal of malarial parasites (either killed by medication or viable) is delayed and disease may falsely appear to be more severe. During antimalarial therapy, delayed clearance in the noneusplenic does not, therefore, necessarily reflect antimalarial resistance. In partially malaria-immune individuals, the course of *Plasmodium falciparum* infection is not much changed by asplenia, but more fever and higher levels of parasitemia occur and there seems to be a risk for more symptomatic malaria episodes. How this relates to the nonimmune splenectomized person traveling into a malarious area is not clear but appropriate prophylaxis is indicated, regardless of splenic function.

In babesiosis, however, splenectomized patients are clearly at higher risk for illness with much higher levels of parasitemia (Figure 97.8) due to the lack of a spleen. This high parasitemia is associated with significant hemolysis. In the United States, infections have been reported from many states, but the most endemic areas are the islands off the coast of Massachusetts (including Nantucket and Martha's Vineyard) and New York (including eastern and south-central Long Island, Shelter Island, and Fire Island) and in Connecticut. Many of the initial individuals diagnosed with babesiosis were asplenic prior to the recognition that mild and even asymptomatic infections with babesiosis may occur in areas of endemicity for this tick-borne organism. These noneusplenic individuals are responsible for most cases of morbidity and mortality related to babesiosis. These individuals may also acquire the infection by blood transfusion without travel into a highly endemic area because their underlying diseases associated with noneusplenism may cause the need for transfusion.

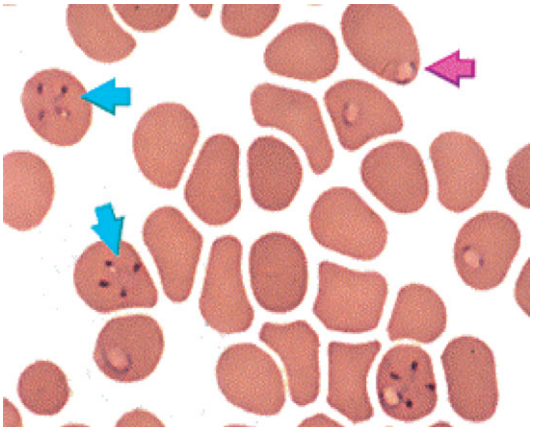

Figure 97.8 Babesiosis.

THERAPEUTIC INTERVENTIONS

Active intervention early on in the form of antimicrobial therapy administration is crucial to patient survival. For this reason, two modalities should be utilized in the prehospital stage of this process aimed at shortening the time to first dose of antimicrobial treatment. For these to be relevant, the asplenic or hyposplenic person has to be aware of the condition and communicate this knowledge to the physician involved. One modality often mentioned in reviews of this infection is having the asplenic person fill and keep current and carry with him/her a prescription for an appropriate orally administered antimicrobial agent (Table 97.2). The drug should be taken, ideally after talking with a physician by telephone, if a febrile illness develops, especially with prostration while the person is coming to seek health care. It is not a substitute for medical care. The second prehospital modality comes into play when a potential OPSI case presents at a physician's office. Similar to suggestions for a patient with suspected bacterial meningitis, if available, a dose of an antimicrobial such as ceftriaxone should be given intravenously or intramuscularly. This should be done even if blood cultures cannot be performed. For obvious reasons, no controlled trials of these methods of early treatment have been or will be done.

Upon emergency department arrival, it is imperative for the patient to impart the

Table 97.2 Suggested regimens for initial extramural oral therapy[a]

Ampicillin or amoxicillin
Dose: 2 g
Contraindicated in β-lactam hypersensitivity
Not active against β-lactamase-producing organisms
Not active against penicillin-resistant pneumococci
Amoxicillin–clavulanate
Dose: Two 875 mg amoxicillin/125 mg clavunate tablets
Contraindicated in β-lactam hypersensitivity
Trimethoprim–sulfamethoxazole
Dose: Two 800 mg sulfamethoxazole/160 mg trimethoprim tablets
Contraindicated in sulfonamide hypersensitivity
Inconsistent activity for pencillin-resistant pneumococci
Clarithromycin or azithromycin
Dose: 2 g
Inconsistent activity for pencillin-resistant pneumococci
Moxifloxacin
Dose: 800 mg

[a] Minimal to no data on any of these regimens in overwhelming postsplenectomy infection.

Table 97.3 Treatment options for suspected bacterial OPSI

Rationale: Adequate coverage for *S. pneumoniae* and *H. influenzae*
Ceftriaxone 2 g IV q12h
Alternative in severe β-lactam allergy
Moxifloxacin 400 mg IV q24h
Plus
Vancomycin 1 g IV q12h
Alternatives in vancomycin-intolerant patients
Moxifloxacin 400 mg intravenously q24h

Abbreviations: OPSI = overwhelming postsplenectomy infection; IV = intravenously.

appropriate information regarding the spleen and the new symptoms at once to facilitate immediate triage. Specific therapy (Table 97.3) could consist of an extended cephalosporin such as ceftriaxone, a β-lactam/β-lactamase inhibitor, a newer fluoroquinolone, and/or vancomycin. The therapy must afford adequate activity against the encapsulated pathogens commonly implicated in OPSI. Choice of initial antimicrobial therapy should be guided by the community antimicrobial resistance profile.

In addition to antimicrobial therapy, aggressive cardiovascular and hemodynamic support is given as needed. Whether adjuvant immunologic interventions decrease morbidity and/or mortality is not known but, in animal models, granulocyte-stimulating factor and intravenous immunoglobulin have been studied.

Table 97.4 Treatment options for intraerythrocytic protozoa in OPSI

Babesiosis
(The usual adult dose treatment is for 1 week, but consideration is needed for longer lengths of treatment in asplenics with significant hemolysis. Exchange transfusions have been used as an adjunct in severe cases.)
Atovaquone 750 mg PO q12h
plus
Azithromycin 500 mg PO on day 1 then 250 mg PO per day
OR
Clindamycin 600 mg PO q8h
plus
Quinine 650 mg PO q8h
Falciparum malaria
(Most strains except from parts of Central America, the Caribbean, and the Middle East should be considered to be chloroquine-resistant and that antimalarial should not be used except with cases from known "sensitive" areas.)
Usual adult dose oral therapies (for parenteral treatment of severe falciparum malaria, consult WHO reference)
Atovaquone–proguanil fixed combination
4 tablets daily for 3 d
OR
Artemether–lumefantrine fixed combination[a]
4 tablets 2× daily for 3 d
OR
Quinine 650 mg q8h for 7 d
plus
Doxycycline 200 mg daily for 7 d
or
Clindamycin 600 mg 2× daily for 7 d

[a] Not US Food and Drug Administration (FDA) approved.
Abbreviations: OPSI = overwhelming postsplenectomy infection; PO = orally; WHO = World Health Organization.

If an intraerythrocytic protozoan is involved, therapy should be directed in that direction. Table 97.4 lists some of the current therapies for falciparum malaria and babesiosis. Response to therapy for babesiosis in the noneusplenic person, however, clinically appears to be much slower independent of the delayed clearance of parasitized erythrocytes.

PREVENTION

Education

The importance of patient (and the respective family) education cannot be overemphasized. A philosopher once reflected that the half-life of truth is 8 months, underscoring the importance of physicians to continue to remind asplenic or hyposplenic patients and/or their families to tell any physician involved in their medical care

of the splenic defect. A medical alert bracelet or necklace could also assist in this task. Early knowledge of asplenia can prompt earlier treatment of presumptive OPSI.

The widespread knowledge of OPSI has also changed the landscape of surgical splenectomy. Whenever possible, the organ or part of it is retained in an effort to provide adequate organ function. In trauma situations, repair instead of removal is preferred. Splenectomy, however, can still be required in the management of a variety of disease states.

Vaccination

The current Centers for Disease Control and Prevention (CDC) guidelines recommend administering the 23-valent unconjugated pneumococcal polysaccharide vaccine (PPV23) to all children older than 2 years with anatomic or functional asplenia at least 8 weeks after the last 13-valent conjugated pneumococcal vaccine (PCV13). A second dose 5 years later is then suggested. In asplenic adults who have been previously immunized with PPV23, a dose of PCV13 should be given 1 or more years after the last PPV23. If no PPV23 had been given, a single dose of PCV13 should be given followed by a PPV23 at least 8 weeks later. Another PPV23 can be given 5 years later and again at age 65. It is not unreasonable to consider revaccination with these vaccines more frequently. Additional repeated immunizations with this vaccine are not recommended by CDC, probably due to the lack of adequate safety studies (Table 97.5). A number of case reports have surfaced documenting occurrence of OPSI with vaccine-related strains of pneumococci sepsis despite administration of the pneumococcal polysaccharide vaccine. This may be related to lack of an adequate response to the polysaccharide of the infecting type.

Table 97.5 Bacterial vaccines to consider in patients with asplenia/hyposplenia

23-valent unconjugated pneumococcal vaccine Contains types 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F
13-valent conjugated pneumococcal vaccine[a] Contains types 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F
Conjugated *H. influenzae* vaccine Contains type b
Quadrivalent meningococcal vaccine Contains types A, C, Y, and W-135

[a] Not formally approved by the FDA for adults <65 years of age.

Both meningococcal polysaccharide and the *H. influenzae* type b (Hib) conjugated vaccines are also part of CDC recommendations for asplenic adults. Meningococcal vaccination is now available as a quadrivalent conjugated polysaccharide product for types A, C, Y, and W-135; it is not yet part of routine immunization in young children but is recommended in teenagers. For asplenic children, however, a two-dose primary series of the vaccine, with at least 8 weeks between doses, is recommended. To this point, there is no licensed vaccine for type B due to issues of immunogenicity of the antigen, and trials of outer membrane protein vaccines are in progress. One dose of Hib vaccine is suggested for the asplenic child or adult who had not been adequately vaccinated previously.

Hyposplenia or functional asplenia is not a contraindication to receiving any otherwise indicated live, attenuated vaccines such as MMR (measles, mumps, and rubella), varicella-zoster virus (either for varicella or zoster), or yellow fever. Influenza vaccine should be administered yearly.

Antimicrobial prophylaxis

Prophylactic antimicrobial therapy after splenectomy has been advised by some experts, but this has primarily been advocated in the pediatric population. Children are usually started on penicillin prophylaxis for the first 2 years, and studies conducted in sickle cell disease patients have demonstrated significant reduction in the incidence of pneumococcal sepsis. Sustained lifelong prophylaxis has been advocated by some authorities, but the issues of noncompliance and selection of resistant strains along with adverse drug reactions have prevented this from becoming the rule. There are no controlled trials to recommend lifelong antimicrobial prophylaxis in asplenic adults; however, the practice should be strongly considered if a patient has had an episode of OPSI.

ACKNOWLEDGMENTS

This chapter includes contributions from Amy Wecker and Monica Panwar

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PART XII

HIV

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98. HIV infection: initial evaluation and monitoring

Fouad Bouharb and Aaron E. Glatt

Infection with human immunodeficiency virus (HIV) can be devastating news to newly diagnosed patients. Early recognition of the infection, monitoring of the immune deficiency both clinically and quantitatively, prophylaxis and treatment of opportunistic infections, and starting antiretroviral treatment have made such infection a chronic disease with documented increase in survival rate. More than 34 million people worldwide, and more than one million in the United States are living with HIV infection. Primary care physicians need to be familiar with the history, clinical presentation, complications, early detection, and treatment of HIV infection, especially during the early stages of the infection, when they are expected to care for these patients. US Preventive Services Task Force (USPSTF) made a Grade A recommendation to screen all patients (18 to 65 years) for HIV. If implemented, primary care physicians will care for a growing population of newly identified relatively asymptomatic HIV patients, and they will need to adhere to the latest recommendations for early treatment and prevention of transmission.

HIV CLINICAL PRESENTATION

Patients can present with different complaints ranging from an acute nonspecific retroviral syndrome (mononucleosis like) lasting 1 to 4 weeks after HIV-1/HIV-2 acquisition with an incubation period as long as 6 weeks, to an AIDS-defining illness suggesting advanced immunosuppression, most commonly *Pneumocystis jirovecii* (*carinii*) pneumonia, esophageal candidiasis, wasting syndrome, or Kaposis's sarcoma. During this initial presentation, it is important for clinicians to establish the route and risks for acquisition of HIV with open, nonjudgmental questions because this is essential for potentially reducing further transmission and recognizing complications.

HISTORY AND PHYSICAL EXAMINATION

HIV infection causes and predisposes to multiple organ diseases. Evaluation should be systematic and comprehensive. After a detailed chief complaint and history of present illness are obtained, a thorough review of past medical, surgical, and social histories; medications; allergies; and systems on all patients is necessary. Detailed physical examination, with careful documentation of baseline observations, is essential for early recognition of new problems. It is important to recognize that antiretroviral therapy (ART) may significantly alter the natural history of HIV infection. In addition, ART may be associated with significant side effects such as lipodystrophy, lipoatrophy, and other signs and symptoms.

General

Fever, weight loss, malaise, fatigue, shaking chills, night sweats, and loss of appetite can be initial findings of significant illness. They are less common in early HIV infection. They may signify worsening immunosuppression. Weight and nutritional assessment should be recorded at each visit.

Skin

The skin of nearly all HIV-infected persons will eventually be affected secondary to infectious and noninfectious dermatologic disorders. Skin or nail pigmentation and rashes of all varieties can occur in disseminated or sporadic fashion. They may be clues to underlying serious illness, coinfection, or worsening immunosuppression. Needle tracks or skin popping indicate intravenous drug abuse and an indication to discuss rehab, and/or prevention of transmission by not sharing needles (Table 98.1).

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Table 98.1 Commonly seen cutaneous manifestations in HIV patients

Etiology	Clinical features
Bacterial infection	
Bacillary angiomatosis	Fleshy, friable, protuberant papules-to-nodules that tend to bleed very easily
Staphylococcus aureus	Folliculitis, ecthyma, impetigo, bullous impetigo, furuncles, and carbuncles
Syphilis	May occur in different forms (primary, secondary, or tertiary); chancre may become painful due to secondary infection
Fungal infection	
Candidiasis	Mucous membranes (oral, vulvovaginal), less commonly *Candida intertrigo* or *paronychia*
Cryptococcoses	Most common on the head and neck; typically present as pearly 2- to 5-mm translucent papules that resemble molluscum contagiosum papules; other forms include pustules, purpuric papules, and vegitating plaques
Seborrheic dermatitis	Poorly defined, faint pink patches, with mild-to-profuse fine, loose, waxy scales in the hair-bearing areas such as the eyebrows, scalp, chest, and pubic area
Arthropod infestations	
Scabies	Pruritus with or without rash; generalized but can be limited to a single digit, more severe in Norwegian type
Viral infection	
Herpes simplex	Painful vesicular lesion in clusters; perianal, genital, orofacial, or digital; can be disseminated
Herpes zoster	Painful dermatomal vesicles that may ulcerate or disseminate (polydermatomal)
HIV	Discrete erythematous macules and papules on the upper trunk, palms, and soles are the most characteristic cutaneous finding of acute HIV infection
Human papilloma virus	Genital warts (may become unusually extensive)
Kaposi's sarcoma (herpesvirus)	Erythematous macule or papule, enlarge at varying rates, violaceous nodules or plaques, occasionally painful
Molluscum contagiosum	Discrete umbilicated papules commonly on the face, neck, and intertriginous site (axilla, groin, or buttocks)
Noninfectious	
Drug reactions	Mild rash to Stevens–Johnson syndrome
Nutritional deficiencies	Mainly seen in children and patients with chronic diarrhea; diffuse skin manifestations, depending on the deficiency
Psoriasis	Scaly lesions; diffuse or localized; can be associated with arthritis
Vasculitis	Palpable purpuric eruption (can resemble septic emboli)

Abbreviation: HIV = human immunodeficiency virus.

Lymph nodes

Nonspecific small, symmetric, mobile nodes are commonly seen in patients with HIV infection; these often reflect nonspecific reactive hyperplasia. Acute generalized lymphadenopathy can be seen during seroconversion. Non-Hodgkin's lymphoma (NHL) and infectious pathogens can present as single or multiple nodes. At each visit lymph node groups should be assessed for size, quantity, texture, and tenderness. Biopsy is usually not indicated and is not helpful, unless the etiology is unclear, the nodes are rapidly enlarging, and/or they are associated with fever and weight loss.

Head, eyes, ear, nose, and throat

Candida and herpes simplex virus often cause painful cheilitis, stomatitis, or pharyngitis and can manifest at any stage of HIV infection. Candida (oral thrush), cytomegalovirus (CMV) (oral ulcers), Epstein–Barr virus (EBV) (oral hairy leukoplakia), varicella-zoster virus, mycobacterial infection, *Cryptococcus neoformans, Histoplasma capsulatum*, Kaposi's sarcoma, squamous cell carcinoma, and NHL may be visible on oral examination, and idiopathic aphthous ulcers are a significant cause of troublesome oral pain. Toothache and dental tenderness may indicate periodontal disease or abscess and may cause both fever and headache. Gingival and periodontal infection are particularly aggressive in patients with HIV infection.

Facial pain, nasal obstruction, postnasal drip, and headache can be caused by sinusitis, which occurs frequently in HIV infection. Atopy may coexist.

Blurred vision, scotoma, floaters and/or decreased visual acuity may suggest CMV retinitis or other opportunistic infectious retinochoroiditis. Complete eye examinations at baseline and when retinitis is a consideration are essential, especially in hosts with CD4 cell count below $50/mm^3$. This is especially important if ART is not successful and/or patients are noncompliant with ART.

Headache of new onset or changing character may be an early manifestation of a central nervous system opportunistic process.

Cardiopulmonary

Precise baseline pulmonary and cardiovascular examinations are important because of increasing pulmonary and cardiac complications in

advancing HIV disease. Shortness of breath at rest or with exertion, its duration and progression, whether a cough is dry or productive, sputum color, amount, and odor may help with the differential diagnosis. Hemoptysis can be caused by tuberculosis, thrombocytopenia, bacterial pneumonia, or other lung pathology. Chest pain can be caused by pneumonia, spontaneous pneumothorax (often *Pneumocystis*-related), pericarditis, herpes zoster, or HIV-related cardiomyopathy. Palpitations and postural hypotension may suggest symptomatic anemia.

Gastrointestinal

Gastrointestinal diseases are increasingly frequent as HIV disease progresses. Odynophagia, dysphagia, retrosternal chest pain, nausea, anorexia, and weight loss are commonly associated with esophagitis due to *Candida*, herpes simplex, CMV, or more rarely, lymphoma. Hepatic or splenic enlargement may be an early manifestation of HIV-related complications and baseline size should be accurately quantified and documented.

Right upper quadrant pain associated with fever and elevated liver enzymes may indicate viral or drug-induced hepatitis, cholelithiasis, or acalculous cholecystitis related to *Mycobacterium avium* complex (MAC), cryptosporidiosis, microsporidia, or CMV.

Epigastric or left upper quadrant pain may indicate drug-induced pancreatitis. Abdominal distension, tenderness, masses, constipation, or fecal incontinence may be caused by Kaposi's sarcoma, lymphoma, carcinoma, gastrointestinal opportunistic infections (CMV, histoplasmosis, tuberculosis), or parasitic infestation. Diarrhea occurs in 30% to 66% of adults with HIV. *Salmonella, Cryptosporidium, Isospora*, CMV, microsporidia, and other enteric pathogens commonly occur. Constipation is commonly seen in patients taking methadone, heroin, or opioids, as well as other medicines. Antibiotic use predisposes patients to *Clostridium difficile* infection.

Painful defecation or rectal pain can be caused by trauma, perirectal abscess, herpes, squamous cell carcinoma, or other sexually transmitted diseases (e.g., lymphogranuloma venereum, LGV), all of which are increased in persons having anal intercourse. Careful sexual and social histories may help identify pathogens. Perirectal areas should be carefully examined for lesions, abscess, fissures, proctitis, and ulcerations. Stools should be tested for occult blood.

Genitourinary, obstetric, and gynecologic manifestations

Painful, frequent urination may indicate urinary tract infection, sexually transmitted disease, or vulvovaginitis. The latter are more common and possibly more difficult to treat in HIV infection. Recurrent or severe vaginitis, vaginal discharge, and pruritus are common and may not be related solely to sexual practices. Prompt evaluation of all genital discharges, ulcers, and lesions will allow correct identification of any sexually transmitted disease.

Women should be queried regarding menstrual history, fertility, method of birth control, and numbers and dates of pregnancies and abortions. Menstruation may become irregular in worsening HIV infection, and fertility declines as well. Prior tubal scarring from salpingitis or pelvic inflammatory disease predisposes to ectopic pregnancy and infertility. An external genital, rectal, and complete pelvic examination (speculum and bimanual), including Pap tests and appropriate cultures and stains, should be performed initially and at least annually if exams are normal.

Neurologic

Neuropsychiatric complications eventually occur in many HIV-infected patients, yet symptoms may go unrecognized because of coping strategies and the large reserve available until significant deterioration is noted. Subtle neurologic deterioration, memory loss, and poor concentration may be the only early signs of HIV dementia. Central and peripheral neurologic complications may be caused by HIV infection, opportunistic infections, medications, or malignancy. Illness can occur at any stage of HIV infection, albeit with different manifestations. Symptoms depend greatly on the location of the abnormality and the pathophysiology involved. Progressive multifocal encephalopathy or peripheral neuropathy can occur years or even decades after seroconversion; intracranial mass lesions are usually a late complication of HIV disease.

Distal predominantly sensory polyneuropathy, chronic inflammatory demyelinating polyneuropathy, mononeuropathy, herpesvirus and CMV radiculitis, and neuropathies of vitamin deficiency are commonly seen. Neurologic evaluation and appropriate diagnostic testing may differentiate treatable from less responsive pathology. A carefully documented baseline

neurologic examination, including mental status assessment; cranial nerve testing; and evaluation of sensation, strength, coordination, and reflexes, should be part of an initial and yearly comprehensive evaluation. Mini-mental status test results should be clearly documented.

Musculoskeletal

Myalgia and proximal muscle weakness, tenderness, and wasting may be manifestations of primary HIV or drug-related myositis. Severe, persistent oligoarthritis, primarily affecting the large lower limb joints with exquisite pain, psoriatic arthritis with erosive changes and crippling deformities, and septic arthritis caused by *Staphylococcus aureus*, especially in substance abusers, are not uncommon. Changes in fat distribution secondary to ART may also be present.

Medical history

A clear history of prior HIV-related events, CD4 cell counts, viral load, resistance patterns, ART, complications, opportunistic infections, and malignancies will help stage HIV infection, provide prognostic information, and clarify therapeutic options. Opportunistic infections signify marked immunocompromise and are discussed at length in Chapter 101, Differential diagnosis and management of HIV-associated opportunistic infections.

HIV infection significantly increases the risk of tuberculosis and increases the yearly rate of conversion from latent to active tuberculosis to 7% to 8%, compared with an approximate 10% *lifetime* conversion rate in non-HIV patients. Tuberculosis also appears to make HIV infection worse, with a more rapid progression to AIDS. Purified protein derivative (PPD) status, previous exposure to tuberculosis, and previous prophylaxis or treatment (date, duration, outcome, and medications) are critical. Noncompliance, prior hospitalizations, and geographic and social factors play major roles in development of drug resistance and empiric management. Syphilis may increase the rate of HIV acquisition as other sexually transmitted disease (STDs) and initial presentation can be varied in coinfected patients.

Medications

Polypharmacy, with prescription agents and vitamin, mineral, and herbal supplements, and alternative medications are very common. They can cause or change disease manifestations and be associated with adverse effects and toxicity, which can be confused with symptoms of HIV-related disease. For example, vitamin overdosing may cause diarrhea, abdominal cramps, peripheral neuropathy, increased intracranial pressure, headache, anorexia, nausea, and vomiting. Drug interactions, sometimes leading to ART failure, are also common and must be diligently sought, for both prescription and nonprescription medicines.

Allergy

The astute physician should differentiate between allergic reaction and intolerance, which is commonly misinterpreted as allergy. The specific reaction, duration, and resolution of toxicity for each medication should be noted, as well as a clear temporal relationship with all factors potentially involved. Rash and fevers are the most common type of adverse drug manifestations and must be differentiated from infectious etiologies common in HIV.

Social history

Particular attention must be given to all aspects of the psychosocial history, especially residence status, occupational history, substance abuse, and sexual history. A complete sexual history should be obtained, including orientation, practices, lifetime number of partners, prostitution, and any previous STDs. Care should be taken to take the sexual history in a nonjudgmental fashion, and in privacy. If at all possible, one should never take a sexual history in the presence of the spouse, parent, or immediate family member. Dietary habits and water sources are important for certain pathogens.

Travel history

Because certain opportunistic infections occur predominantly in particular geographic regions (e.g., southwestern United States – coccidiomycosis; Ohio River Valley – histoplasmosis), place of birth and a complete travel history are particularly useful in formulating an accurate differential diagnosis. History of travel to developing or tropical countries may raise suspicion of travelers' diarrhea, malaria, leishmania, kala-azar, strongyloidiasis, *Penicillium* infection (Southeast Asia), HIV-2, etc.

Pets

Certain opportunistic infections have been associated with particular animals. Patients should be queried regarding exposure to animals and advised about methods of avoiding zoonoses. *Bartonella* (formerly *Rochalimaea*) species have been associated with cat scratch disease and bacillary angiomatosis, and exposure to cats is associated with toxoplasmosis.

LABORATORY STUDIES

Laboratory testing is sometimes the only way to absolutely establish or confirm a diagnosis. Laboratory studies should be individualized, but several general principles apply (Tables 98.2 and 98.3).

A complete blood count may reveal mild normocytic, normochromic anemia, which often develops as HIV progresses. Macrocytosis frequently develops while on zidovudine and can be an important adjuvant method of assessing compliance. Pancytopenia may suggest bone marrow involvement or infiltration; isolated thrombocytopenia may be an early finding of HIV infection; and leukopenia and/or a blunted neutrophil response to infection is a common finding. Neutropenia often becomes more pronounced with various drug therapies (e.g., zidovudine, trimethoprim–sulfamethoxazole, pentamidine) and may require treatment with colony stimulating factors.

Assessment of chemistries, liver function tests, and hepatitis serologies/viral levels are useful in diagnosing new or chronic illnesses, making vaccination recommendations, and as a guide to monitoring drug toxicities. Hepatitis A, B, C, and others are more common in HIV infection based upon underlying risk behaviors, and choosing initial ART may be influenced by co-infections, especially such as hepatitis B.

Nonspecific syphilis (RPR or VDRL) tests, with confirmatory fluorescent treponemal antibody absorbed (FTA-ABS) tests, should be performed initially and repeated annually in patients at risk.

Table 98.2 Purposes of laboratory testing in HIV infection

1. Establish baseline parameters
2. Identify underlying disease
3. Determine appropriate therapy
4. Estimate the likelihood and rate of disease progression
5. Monitor response to therapy
6. Monitor adverse reactions and toxicities
7. Screen for common/preventable illnesses

Abbreviation: HIV = human immunodeficiency virus

Lumbar puncture may be indicated for patients with reactive serologies (RPR of 1:16 and above), for patients with positive treponemal tests of uncertain duration, late latent syphilis, and/or secondary to symptoms.

A TST (tuberculin skin test) should be placed on initial evaluation and at least annually except in patients with a history of tuberculosis or known prior reactive TST. IGRA (interferon-gamma release assay) is recommended when TST is negative but the HIV-infected patient was exposed to an active tuberculosis patient or is at high risk of tuberculosis infection. An initial chest radiograph is usually indicated to establish baseline status, regardless of TST or IGRA status.

Baseline antitoxoplasma IgG antibodies may influence prophylaxis decisions and help with the evaluation and empiric treatment of central nervous system mass lesions. Baseline CMV and EBV serologies, and cryptococcal antigen testing have no value.

Pap smears are recommended initially, and at 6 months time, and thereafter at least annually, if normal. For high-risk patients based upon sexual activity, more frequent evaluation may be prudent, with referral to a gynecologist for atypia or other Bethesda scale findings. The role of screening HPV testing has not yet been finalized, but will possibly replace Pap testing in the future. An anal Pap or equivalent screening test is recommended in those who have engaged in anal sex. The frequency of such testing remains to be finalized.

Cholesterol, lipid, and blood sugar evaluations are important to monitor for the metabolic abnormalities common in patients with HIV, especially those on ART.

CD4 lymphocyte counts (marker of immune status) and viral load counts (marker of disease status and response to therapy) should be obtained initially and at 3-month intervals as a guide for treatment and prophylactic interventions. Less frequent testing can be utilized in stable patients or those not on any therapy with initially low risk of progression. Resistance status should be obtained at initial evaluation and thereafter as appropriate based upon ART, compliance, and other clinical and laboratory factors. There is significant variability in CD4 cell counts; the aggregate picture over time is more useful than a single reading for major therapy decisions.

Viral load testing is essential for monitoring the efficacy of ART and the most ultrasensitive assays, capable of detecting as low as 10 viral particles per mL, should be used. Viral

Table 98.3 Routine laboratory studies guidelines for HIV-infected adults

Test	Indication	Interval
Antitoxoplasma IgG antibody	Screening for previous exposure Guide diagnostic and empiric management	Baseline ? Yearly in patients with negative results
Chemistry and liver functions	Evaluation of baseline renal and liver function, and nutritional status Diagnosis of concurrent hepatitis Monitoring of drug toxicities Monitoring of efficacy of therapy	Baseline Every 6–12 mo More frequently in patients with advanced disease, baseline abnormalities, or with drug toxicity
Chest radiograph	Screening for disease Diagnosis of active disease	Baseline If pulmonary disease suspected
Complete blood count	Evaluation of anemia, leukopenia, or thrombocytopenia Monitoring of drug toxicities Monitoring of efficacy of therapy Assessment of compliance	Baseline Every 6 mo More frequently in patients with abnormalities or those taking marrow-suppressing agents
Hepatitis profile	Diagnosis of viral hepatitis Evaluation for vaccination Response to vaccination	Baseline During potential acute infection Postvaccination
Lymphocyte subset testing (CD4 cells)	Guiding initiation of prophylactic and/or antiretroviral therapy Prognostic information Monitoring of efficacy of therapy	Baseline Every 6 mo if >500 Every 3 mo if <500
HIV viral load	Diagnostic in acute infection before seroconversion (>10 000/mL) Monitoring of HIV activity Monitoring of efficacy of therapy	Baseline Every month until antiretroviral therapy efficacy is established Every 3 mo if clinically stable
RPR or VDRL	Screening for syphilis Monitoring response to therapy Use specific test (i.e., FTA) for confirmation and/or false-negative specimen	Baseline Yearly (at least) in patients at risk/prior infection Monthly for 6 mo, and at 9 and 12 mo after therapy
Tuberculosis skin test (TST; purified protein derivative)	Screening for infection or previous exposure	Baseline, then yearly More frequently if at risk
IGRA (interferon-gamma release assay)	Identification of new converters Exposed to active TB and TST is negative	

Abbreviations: HIV = human immunodeficiency virus; TB = tuberculosis.

genotyping and phenotyping are commonly used to detect for resistance and to guide the choice of individual ART regimens in treatment-naïve patients and in patients who fail therapy.

VACCINATIONS

Patients should receive appropriate immunizations as early as possible in the course of HIV infection to optimize response. While clinical efficacy is difficult to prove or even assess, it is assumed that higher CD4 cell counts, preferably more than 500/mm^3, are associated with better vaccine efficacy (Table 98.4).

In previously unvaccinated patients, pneumococcal vaccine PCV13 (Prevnar 13) is administered first, followed by PPSV23 (Pneumovax 23) 8 weeks thereafter. Some recommend an additional booster after 5 years. If previously vaccinated with PPSV23, PCV13 can be administered at some point as well, although the optimal timing of this is unclear (1 year later?). Efficacy is very questionable if the CD4 cell count is less than 200 cells/mm^3. *Haemophilus influenzae* vaccination is not indicated as per latest recommendations.

Patients without serologic evidence of hepatitis B exposure or immunity should be given hepatitis B vaccine. Booster vaccinations, while

Table 98.4 Vaccination guidelines for HIV-infected adults

Vaccine	Frequency
Pneumococcal vaccine Naïve patients Exosed to PPSV23 All patients	PCV13 first; PPSV23 8 weeks later PCV13 after 1 year PPSV23 booster at 5 years
Hepatitis B vaccine series	Series of three (0, 1, and 6 months) (booster in 5 years)
Influenza	Yearly, only injectable; no live attenuated
Human papillomavirus (HPV4; HPV2)	Three doses: both females and males (through age 26); (males receive HPV4 only)
Diphtheria/tetanus/ pertussis	1 shot Tdap, then Td booster every 10 years
Measles (MMR), varicella	1–2 shots, if CD4 >200
Haemophilus influenzae, zoster, anthrax, small pox	Not recommended
Meningococcal, hepatitis A	Vaccination when CD4 cell count is >200 cells/mm^3 In special groups. Refer to CDC for guidelines

Abbreviations: HIV = human immunodeficiency virus; MMR = measles, mumps, and rubella vaccine; CDC = Centers for Disease Control and Prevention.

not proven, are sometimes recommended for healthcare workers (and others) no earlier than 5 years after the initial vaccination series is completed.

Influenza vaccine (*only inactivated*) is recommended annually. MMR and VZV are contraindicated in severly immunocompromised patients. Inactivated polio vaccine, standard childhood vaccinations, and booster diphtheria and tetanus immunizations can be given as per published guidelines. Hepatitis A vaccine may also be indicated among selected at-risk populations.

GUIDELINES FOR FOLLOW-UP

Patients receiving ART need to be followed closely to ensure compliance, efficacy, and optimal management. Once stabilized clinically, follow-up of asymptomatic patients should be individualized, but patients should be seen between two and four times per year if not on ART. Stable asymptomatic patients on ART without significant lab abnormalities can be seen every 3 to 4 months if they have no complications and are compliant. Symptomatic HIV patients should be examined and re-evaluated as frequently as indicated, and additional screening testing should occur when immune status worsens. Most patients have numerous psychosocial needs that also must be addressed; referral to the appropriate staff is essential for complete and compassionate care.

SUGGESTED READING

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99. HIV infection: antiretroviral therapy

Kathleen Squires and Christopher T. Miller

INTRODUCTION

The first cases of the human immunodeficiency virus (HIV) were first described in the early 1980s, prompting an aggressive search for a cure for this deadly virus. In 1987, the approval of zidovudine, the first medication approved for the treatment of HIV, ushered in a new age in HIV management. As our understanding of HIV evolved, new therapies gradually emerged in the 1990s, as did hope that a curative medication regimen may be discovered.

Single-drug nucleoside reverse transcriptase inhibitor therapy initially conferred only 6 to 12 months of benefit to patients before viral resistance rendered this approach ineffective. Therapeutic strategy then evolved into dual-drug therapy, which extended benefit to 2 to 3 years. Eventually the use of a three-drug regimen (i.e., highly active antiretroviral therapy, or HAART) in the mid 1990s became the predominant regimen and remains the standard of care today.

Along with these new drug developments came new frustrations, however, manifested as mutated and resistant HIV strains, high pill burdens, and significant toxicities. These multidrug regimens subsequently have been refined over the past 10 years, to the point where many patients are able to maintain an intact immune system with no detectable virus on single-pill, triple-drug coformulated, minimally toxic antiretroviral therapy (ART) regimens. While the goal of HIV eradication has remained elusive, the modern age of ART has commonly rendered HIV disease a chronic condition that, when ideally managed, can lead to a reasonable life expectancy in patients who once considered this infection a death sentence.

This article provides a brief overview of HIV replication along with a more detailed review of the currently approved ART medications and classes as well as their indications and combinations. Use of ART in the setting of a variety of host and viral characteristics, monitoring, and a brief discussion of the immune reconstitution inflammatory syndrome (IRIS) are included as well. Note that most recommendations in this article apply only to HIV-1 virus.

Antiretroviral medications will be referred to by their three-letter abbreviations. Refer to Table 99.1, Table 99.2, and Table 99.3 and the sections on integrase and entry inhibitors for abbreviation associations.

HIV REPLICATION CYCLE

A better understanding of the HIV replication cycle (Figure 99.1) has led to the development of antiretroviral medications targeted against viral enzymes and even host proteins. A visualization of this replication cycle is essential to understanding how these medications function. Current ART medications inhibit entry of virus into host cells, reverse-transcription of viral DNA from an RNA template, integration of this viral DNA into the host genome, and processing of newly transcribed viral proteins.

Fusion of HIV with the host cell membrane with subsequent viral RNA entry into the host cell is the first step of HIV viral replication (Figure 99.1). Viral glycoproteins 120 and 41 group together and interact with host cell CD4 receptors and CCR5 or CXCR4 co-receptors, causing fusion of the viral and host membranes and entry of viral factors (Figure 99.2).

After fusion, viral RNA is released into the host cell along with essential viral enzymes, including the viral reverse transcriptase enzyme (RT). RT then uses host cell nucleosides and nucleotides to construct a double-stranded viral complementary DNA (cDNA). Viral cDNA interacts with the viral integrase protein in the host cell cytoplasm. Viral cDNA is then transported into the nucleus of the host cell, where integrase incorporates viral cDNA into the host DNA genome. Once incorporated

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Table 99.1 Summary of NRTIs

Agent (trade name in *italics)*	Analog	Metabolism	Dosing	Resistance	Adverse effects	Miscellaneous
Zidovudine (AZT, ZDV) ***Retrovir***	Thymidine	Hepatic glucuronidation Renal excretion	300 mg PO q12h or 200 mg PO q8h 100 mg PO q8h for dialysis patients	TAM1 TAM2	Headache Malaise Anorexia Nausea Vomiting Anemia Granulocytopenia Lactic acidosis Hepatic steatosis Peripheral neuropathy Lipodystrophy Myopathy	**Third-line NRTI** Generally used in combination with lamivudine First antiretroviral Still first-line therapy in combination with lamivudine for pregnant patients with HIV Antagonizes stavudine and should not be coadministered
Stavudine (d4T) ***Zerit***	Thymidine	Renal excretion	≥60 kg: 40 mg PO q12h <60 kg: 30 mg PO q12h	TAM1 TAM2	Peripheral neuropathy Hyperlactatemia Lactic acidosis Hepatic steatosis Lipoatrophy Pancreatitis Hyperlipidemia	Antagonizes zidovudine and should not be coadministered Risk of fatal lactic acidosis in combination with didanosine and should not be coadministered
Didanosine (ddI) ***Videx***	Adenosine	Cellular metabolism	≥60 kg: 400 mg PO qd <60 kg: 250 mg PO qd Decrease dose with renal dysfunction Poor absorption with food	L74V 69 insertion Q151M	Peripheral neuropathy Pancreatitis Myocardial infarction (possible) Mitochondrial toxicity (worst of all NRTIs)	Should not coadminister with stavudine (see above) Concentration increase in combination with ganciclovir, allopurinol, tenofovir Concentration decrease with methadone
Abacavir (ABC) ***Ziagen***	Guanosine	Hepatic glucuronidation	300 mg PO q12h or 600 mg PO qd 200 mg PO q12h with mild hepatic dysfunction Contraindicated with moderate to severe hepatic dysfunction	K65R L74V Y115F M184V 69 insertion Q151M	Hypersensitivity syndrome (possibly fatal) Myocardial infarction (possible)	**Current alternative NRTI** Generally used in combination with lamivudine Screen patients for HLA-B5701 allele to assess risk for hypersensitivity Possibly less efficacious in patients with viral load >100 000 copies/mL
Tenofovir (TDF) ***Viread***	Adenosine	Renal excretion	300 mg PO qd (as prodrug tenofovir disoproxil fumarate) Decrease dose with renal dysfunction (GFR<50 mL/min), discontinue with GFR<30 mL/min	K65R TAM1 69 insertion	Possible decline in GFR Decrease in bone mineral density Fanconi syndrome	**Current preferred NRTI** Generally used in combination with emtricitabine Active against hepatitis B virus Discontinue GFR<30 mL/min
Lamivudine (3TC) ***Epivir***	Cytosine	Renal excretion	300 mg PO qd or 150 mg PO q12h	M184V May still be continued in face of M184V mutation, as this mutation leads to	Headache Fatigue Neutropenia	**Current preferred NRTI** Generally used in combination with abacavir or zidovudine

Agent (trade name in *italics)*	Analog	Metabolism	Dosing	Resistance	Adverse effects	Miscellaneous
				decrease in viral load and hypersensitivity of HIV to zidovudine, even in presence of TAMs		Similar to emtricitabine First-line NRTI in pregnancy Active against hepatitis B virus
Emtricitabine (FTC) ***Emtriva***	Cytosine	Renal excretion	200 mg PO qd	M184V Often continued in face of M184V mutation, as this mutation leads to decrease in viral load and hypersensitivity of HIV to zidovudine, even in presence of TAMs	Headache Fatigue Neutropenia	**Current preferred NRTI** Generally used in combination with tenofovir Similar to lamivudine Active against hepatitis B virus

Abbreviation: NRTI = nucleoside and nucleotide reverse transcriptase inhibitors; TAM = thymidine analog mutation; GFR = glomerular filtration rate.

Table 99.2 Summary of NNRTIs

Agent (trade name in italics)	Metabolism	Dosing	Resistance	Adverse effects	Miscellaneous
Nevirapine (NVP) ***Viramune***	Hepatic CYP3A4, CYP2B6	200 mg PO qd for 2 weeks, then 400 mg PO qd Adjustment needed for dialysis patients	**K103N** V106A/M Y181C Y188L G190A/S	Rash, including Stevens–Johnson syndrome Hepatic necrosis	First-generation NNRTI Preferred NNRTI in pregnancy Contraindicated in women with baseline CD4 >250 cells/mm^3 and men with CD4 >400 cells/mm^3 owing to risk of hepatic toxicity Can precipitate acute methadone withdrawal
Efavirenz (EFV) ***Sustiva***	Hepatic CYP3A4, CYP2B6	600 mg PO qd on empty stomach	**K103N** 100 106 181 188 190 225	Rash Hepatotoxicity Vivid dreams Insomnia Dizziness Poor concentration **Teratogenicity (Pregnancy Category D)**	**Current preferred NNRTI** First-generation NNRTI Must be taken on empty stomach (usually before bed) to minimize side effects Can precipitate acute methadone withdrawal **Pregnancy Category D**
Etravirine (ETR) ***Intelence***	Hepatic CYP3A4, CYP2C9, CYP2C19	200 mg PO q12h Absorption decreased with food 50%	Y181C G190A Multiple other mutations	Rash Nausea	Second-generation NNRTI Only medication of this class that cannot be inactivated by a single point mutation
Rilpivirine (RPV) ***Edurant***	Hepatic CYP3A4	25 mg PO qd, taken with minimum 400-kcal meal Caution in severe renal impairment	V90I K101E/P/T **E138K/G** V179I/L Y181I/C V189I H221I F227C/L M230L	Depression Insomnia Headache Rash QT prolongation	**Current alternative NNRTI** Second-generation NNRTI **Take with minimum 400-kcal meal** **Contraindicated with PPIs**, anticonvulsants, rifampin/rifabutin/rifapentine, dexamethasone, St. John's wort (all decrease RPV levels) H2Bs must be taken 12 h before or 4 h after RPV Antacids should be taken 2 h before or 4 h after RPV Caution with combination with medications that prolong QT interval **Contraindicated when initial HIV viral load >100 000 copies/mL (more virologic failure than efavirenz)**

Abbreviations: NNRTI = non-nucleoside reverse transcriptase inhibitor; PPI = proton pump inhibitor; H2B = H_2 histamine receptor blocker.

Table 99.3 Summary of PIs

Agent (trade name in italics)	Metabolism	Dosing	Resistance	Adverse effects	Miscellaneous
Ritonavir (RTV) ***Norvir***	Hepatic CYP3A4, CYP2D6	For boosting, 100–200 mg PO q12h Stand-alone, 300 mg PO q12h, increase to 600 mg PO q12h over 5 days	M46L V82A I84V Minor mutations at 10, 20, 24, 32, 36, 54, 71, 73, 76, 77, 90	Diarrhea Nausea/vomiting Altered taste Paresthesias Dyslipidemia	**Powerful CYP3A4 inhibition exploited at low doses to boost levels of other PIs** Rarely used as stand-alone agent due to toxicity Also inhibits CYP2D6 Induces CYP3A, CYP1A2, CYP2C9, CYP2C19, CYP2B6
Indinavir (IDV) ***Crixivan***	Hepatic CYP3A4	800 mg PO q12h boosted with ritonavir 100 mg PO q12h	M46L V82A I84V Minor mutations at 10, 20, 24, 32, 36, 54, 71, 73, 76, 77, 90	Nephrolithiasis Unconjugated hyperbilirubinemia (no jaundice) Abdominal pain Nausea Dry skin	Must increase water intake to avoid nephrolithiasis Infrequently used secondary to toxicity
Saquinavir (SQV) ***Invirase***	Hepatic CYP3A4	1000 mg PO q12h boosted with ritonavir 100 mg PO q12h Take within 2 h of high-calorie/fat meal	L90M G48V Minor mutations at 10, 24, 54, 62, 71, 73, 77, 82, 84	Nausea/vomiting Diarrhea Abdominal pain Hyperlipidemia	Alternate PI in pregnancy May prolong PR/QT intervals One randomized trial showed noninferiority to atazanavir and better side effect profile
Nelfinavir (NFV) ***Viracept***	Hepatic CYP2C19, CYP3A4, CYP2D6	1250 mg PO q12h Take with meals	D30N L90M Minor mutations at 10, 36, 46, 71, 77, 82, 84, 88	Diarrhea Hyperlipidemia	Poor efficacy compared to other PIs Ritonavir does not boost levels Should not be used in treatment-experienced patients
Fosamprenavir (FPV) ***Lexiva/Telzir***	Hepatic CYP3A4 Biliary excretion	700 mg PO q12h boosted with ritonavir 100 mg PO q12h	I50V I84V Minor mutations at 10, 32, 46, 47, 54, 73, 76, 82, 90	Diarrhea Rash Hyperlipidemia May increase risk cardiovascular disease	Prodrug of amprenavir Sulfonamide component may cause reaction in sulfa-allergic patients
Lopinavir (LPV) ***Kaletra*** **(lopinavir/r combination pill)**	Hepatic CYP3A4	400 mg PO q12h boosted with ritonavir 100 mg PO 12h	V82A V32I I47A Minor mutations at 10, 20, 24, 33, 46, 50, 53, 54, 63, 71, 73, 76, 84, 90 Concurrent V32I, I47A, and position 46 mutation confers high resistance	Diarrhea Nausea/vomiting Hyperlipidemia May increase risk cardiovascular disease	**Current alternative PI** Preferred PI in pregnancy Coformulated in fixed pill with ritonavir Often compared with newer PIs for noninferiority Generally six or more mutations required for significant drug resistance
Tipranavir (TPV) ***Aptivus***	Hepatic CYP3A4	500 mg PO q12h boosted with ritonavir 200 mg PO q12h Take with high-fat meal		Hepatotoxicity Intracranial hemorrhage Nausea Diarrhea Gastrointestinal side effects largely due to higher dose of ritonavir used	Used in treatment-experienced patients with resistance to other PIs, efficacy demonstrated in RESIST-1 and -2 trials for this population Contraindicated in patients at risk for serious bleeding Sulfonamide component may cause reaction in sulfa-allergic patients

Agent (trade name in italics)	Metabolism	Dosing	Resistance	Adverse effects	Miscellaneous
Atazanavir (ATV) ***Reyataz***	Hepatic CYP3A4	300 mg PO qd boosted with 100 mg ritonavir PO qd 400 mg PO qd unboosted if not given with TDF/FTC Take with food Absorption requires low pH, avoid H_2 blockers and PPIs	I50L I84V Minor mutations at 10, 16, 20, 24, 32, 33, 34, 36, 46, 48, 53, 54, 60, 62, 64, 71, 73, 85, 90, 93	Nausea Hyperbilirubinemia with jaundice/ scleral icterus Nephrolithiasis Hyperlipidemia	**Current preferred PI** Preferred PI in pregnancy Should not be used in treatment-experienced patients on renal dialysis Does not affect methadone levels Should not be used in combination with ddI/FTC owing to inferiority Can prolong PR interval PI with least effect on lipids Avoid coadministration with H2Bs and PPIs Only PI shown to be noninferior to efavirenz
Darunavir (DRV) ***Prezista***	Hepatic CYP3A4	800 mg PO qd boosted with 100 mg RTV PO qd in treatment-naïve patients 600 mg PO q12h boosted with ritonavir 100 mg PO q12h in patients with documented DRV resistance Should be taken with food	I50V V11I I54L G73S L89V V32I L33F I47V I54M I76V I84V	Diarrhea Nausea Headache Nasopharyngitis Acute hepatitis Hyperlipidemia	**Current preferred PI** Alternate PI in pregnancy Sulfonamide component may cause reaction in sulfa-allergic patients Should be taken with food

Abbreviations: PI = protease inhibitor; PPI = proton pump inhibitor; H2B = H_2 histamine receptor blocker.

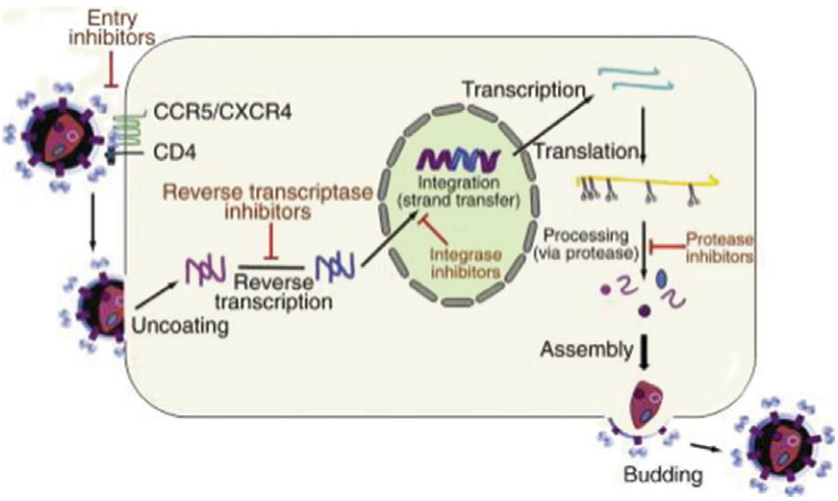

Figure 99.1 HIV replication cycle.

into the host genome, viral DNA is transcribed and translated into polyproteins by host enzymes and ribosomes. Viral proteases then cleave these polyproteins into functional and mature viral proteins. Full HIV virions are constructed. These new virions then bud from the host cell surface, detach, and infect new host cells, repeating the cycle (Figure 99.1).

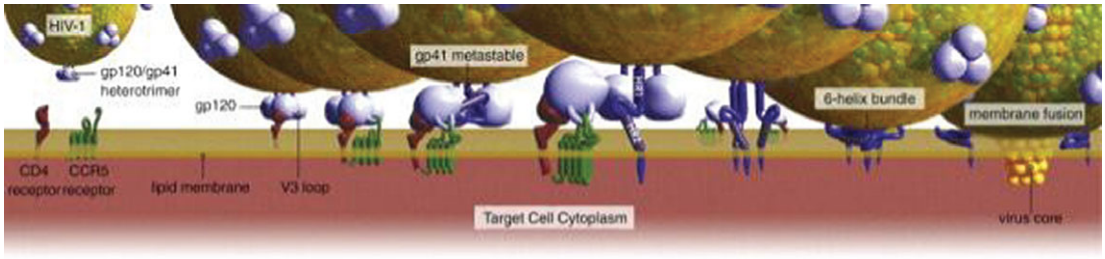

Figure 99.2 Fusion of the viral and host membranes.

HIV ANTIRETROVIRAL DRUG CLASSIFICATIONS

Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs)

Viral RT uses a pool of available host cellular nucleosides and nucleotides to construct viral cDNA from a viral RNA template. NRTIs are designed to mimic the structure of these natural nucleosides and nucleotides. When viral RT erroneously incorporates an NRTI into the growing viral cDNA chain, the chain is prematurely terminated. NRTIs block further chain elongation in the 3′ direction. Table 99.1 presents a summary of the drugs in the NRTI class.

With few exceptions, two NRTI agents are combined to form an "NRTI backbone" that comprises two of the three active drugs in a modern ART regimen. A third active agent is then added to this NRTI backbone.

Emtricitabine (FTC) and lamivudine (3TC) are similar, roughly equivalent cytosine analogs, and are both very well tolerated. One of these two medications is typically combined with a second preferred, alternative, or third-line agent of this class to form most front-line NRTI backbones. They have the additional advantage of being able to be dosed once daily.

Tenofovir disoproxil fumarate (TDF) is currently the preferred NRTI and is generally used in combination with FTC. TDF is extremely well tolerated with regard to side effects, can be given once daily, and has activity versus hepatitis B virus. It has the advantage of once-daily dosing. Its major disadvantages are a potential for renal dysfunction and osteoporosis with long-term use. It must be adjusted for renal function and is not recommended for glomerular filtration rate (GFR) <30 mL/min (Table 99.1).

Abacavir (ABC) is the main alternative NRTI and is generally combined with 3TC. Like TDF, it is also extremely well tolerated by patients and is given once daily. Some data have suggested a possible increase in risk of myocardial infarction using ABC, and some conflicting data exist suggesting that ABC may not be as effective in patients with higher baseline viral loads (discussed later). The primary disadvantage of ABC, however, is a severe, life-threatening hypersensitivity reaction that can occur in patients positive for the HLA-B5701 allele. ABC should not be administered to patients positive for the HLA-B5701 allele.

Zidovudine (AZT) is still occasionally used as a third-line NRTI, generally in combination with 3TC. It is poorly tolerated compared with the other commonly used NRTIs previously mentioned, and side effects such as lipodystrophy, peripheral neuropathy, myopathy, anemia, and hepatic steatosis can occur (Table 99.1). An additional disadvantage with AZT is that it must be administered twice daily.

Resistance to NRTIs generally occurs due to RT mutations. Mutations resulting in resistance to NRTIs and to all classes of ART medications occur most commonly in the setting of incomplete adherence to a full ART regimen. Prolonged viremia is often necessary for the development of such mutations. With the exception of the M184V and K65R mutations, significant resistance to a drug may take several serial mutations, which may require several months of viremia.

Table 99.1 contains a listing of specific mutations conferring resistance to each drug in the NRTI class, but there are several major mutations of notable importance. Thymidine analog mutations (TAMs) were commonly seen prior to the use of triple-drug therapy, especially in patients taking AZT or stavudine (d4T). They allow for excision of NRTIs from the growing viral cDNA strand. TAM1 mutations occur at positions 41, 210, and 215 on RT and can confer resistance to multiple drugs across the NRTI class, including

newer NRTIs such as TDF (for example, TAMs can decrease TDF activity by a factor of 4). TAM2 mutations cluster at RT positions 67, 70, and 219 and do not confer class resistance to the extent that TAM1 mutations do. Insertion mutations can be significant as well, with an insertion at position 69 conferring class-wide resistance. Important substitution mutations include the K65R mutation, which can decrease TDF activity as well as the activity of other NRTIs (excluding AZT), and the M184V substitution mutation, which may reduce FTC and 3TC activity by a factor of 1000.

The M184V mutation does confer a fitness disadvantage to the HIV virus and reduces the viral load. M184V also renders HIV highly sensitive to AZT, even in the face of TAM mutations. Therefore, FTC or 3TC therapy may be continued in patients with known M184V mutation as an inactive drug to exploit such secondary advantages. This strategy may prove especially useful in patients with multidrug-resistant (MDR) HIV strains.

Certain general toxicities of this drug class can be attributed to the mechanism of action of NRTIs. In addition to terminating viral DNA transcription, they can also inhibit host DNA transcription enzymes. Mitochondrial DNA polymerase is particularly susceptible to these drugs, and lactic acidosis, peripheral neuropathy, hepatic steatosis, myopathy, and lipoatrophy can all result from inhibition of this enzyme (see description of AZT). Insulin resistance and diabetes may also be potential adverse effects. The first-line NRTIs have minimal overlapping interaction with mitochondrial DNA polymerase, and therefore are much better tolerated than their predecessors.

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)

NNRTIs are allosteric RT inhibitors that bind to a dedicated site that lies apart from the enzyme's active functional site. The result of NNRTI binding is a change to the enzyme's conformation, rendering it ineffective at viral DNA transcription. Table 99.2 presents a summary of the drugs in the NNRTI class.

First-generation NNRTIs include nevirapine (NVP) and efavirenz (EFV). EFV is considered the preferred medication of this class. It has demonstrated superior virologic suppression compared with triple-NRTI regimens or protease inhibitor (PI)-based regimens with nelfinavir (NFV), indinavir (IDV), and ritonavir-boosted lopinavir (LPV/r) and noninferior suppression compared with atazanavir-based (ATV) therapy. EFV can be administered once daily. EFV should be taken on an empty stomach to minimize side effects, which can be substantial. Neuropsychiatric side effects such as vivid dreams and fogginess have been described in approximately 50% of patients, but are generally mild and self-limited (within 2 to 6 weeks). EFV is the only US Food and Drug Administration (FDA) pregnancy category D antiretroviral and should not be initiated during pregnancy. NVP should not be administered to men with a CD4 count >400 cells/mm^3 and women with a CD4 count >250 cells/mm^3, as usage in these groups has been associated with hepatic necrosis.

Second-generation NNRTIs include etravirine (ETV) and rilpivirine (RPV). These NNRTIs have been chemically altered from their predecessors with the theoretical goal of rendering them more effective against drug-resistant HIV. RPV, the newest drug from the NNRTI class, has been demonstrated to have a higher rate of virologic failure compared with EFV in patients with higher HIV viral loads, thus earning it a designation as an alternative NNRTI. The E138K mutation is commonly seen in the setting of RPV virologic failure, and the M184V/I and K65R/N mutations are seen with greater frequency than with EFV in this setting. Administration of RPV in patients with a viral load >100 000 copies/mL should be avoided, and its use is only approved in treatment-naïve patients. RPV must also be taken with a high-calorie meal. Its absorption requires an acidic environment, so care must be taken to avoid direct coadministration with antacids and H_2-blocking medications. Proton pump inhibitors should be avoided altogether in patients on RPV. RPV may cause an artifactual rise in creatinine that does not reflect a true change in the GFR.

ETV has only been studied in treatment-experienced patients and is approved only in this setting (see ART selection in patients with multidrug-resistant HIV, below).

Unfortunately, since it is not directly involved in the action of the RT enzyme, the conformation of the dedicated NNRTI binding site is not important for RT functionality. Therefore, mutations at this site may block NNRTIs from binding, but generally do not affect RT functionality. Simple single-point mutations to the enzyme can render every first-generation NNRTI ineffective (hence the development of second-generation NNRTIs mentioned previously). Currently, ETV

is the only NNRTI that is approved in the setting of NNRTI mutations. The low barrier to resistance with the NNRTIs may limit the use of these medications in patients with a history of poor compliance to ART.

NNRTIs are hepatically metabolized by cytochrome P450 (CYP) enzymes, making drug–drug interactions a concern. Particular care must be taken when combining these medications with anticonvulsant, antimycobacterial, and certain antifungal therapies. PIs may have strong interactions with NNRTIs as well, and their combination should generally be avoided, except in special cases.

Protease inhibitors (PIs)

PIs inhibit HIV aspartyl protease, an enzyme used by the virus to cleave and construct gag and pol proteins. Gag proteins form structural aspects of the virus, while pol proteins comprise the vital viral enzymes RT, protease, and integrase. PIs are primarily metabolized by hepatic CYP enzymes, especially CYP3A4. They may also induce or inhibit these enzymes. Drug–drug interactions are therefore significant, especially in the setting of coadministration with immunosuppressants, antiarrhythmics, antibiotics, statins, opiates, oral contraceptives, benzodiazepines, or other ART medications. For example, acute withdrawal may occur when PIs are administered to patients taking chronic opiates such as methadone. Efficacy of contraceptives may be reduced significantly. Table 99.3 presents a summary of the drugs in the PI class.

The metabolism of PIs by CYP3A4 is exploited with the concept of "boosting." The PI ritonavir (RTV) is an especially powerful inhibitor of CYP3A4. Owing to pill burden, toxicity, and a host of potential drug–drug interactions via its effect on other CYP enzymes, RTV is no longer considered a viable stand-alone PI. However, when RTV is given at subtherapeutic doses in combination with another "primary" active PI, CYP3A4 metabolism becomes saturated, allowing plasma concentrations of the primary PI to become higher ("boosted") and more stable (increased half-life) with less frequent dosing. The overall effect of this strategy is that fewer pills are required to be taken on a less frequent basis with less toxicity to the patient. This boosting effect also minimizes viral protease mutations by keeping the steady state of drug well above the minimum inhibitory concentration required to suppress HIV replication, even in the face of occasional missed doses. However, while boosting does allow for higher fidelity concentrations of less toxic drugs, adverse effects and drug–drug interactions still do exist and may become accentuated as well. RTV toxicity is also limited at this subtherapeutic dose, yet some effects such as nausea and vomiting may become clinically relevant.

Currently, darunavir (DRV) and atazanavir (ATV) are the preferred medications of the PI class, both boosted by RTV. Each has the advantage of once-daily dosing in treatment-naïve patients. ATV was found to be noninferior with respect to virologic response compared with EFV. Boosting with RTV was clearly shown to be effective when RTV-boosted ATV (ATV/r) was compared with unboosted ATV and with LPV/r. Once-daily DRV/r was demonstrated to be noninferior to LPV/r in treatment-naïve patients. DRV has also shown to be an effective choice in treatment-experienced and MDR HIV, although it must be given twice daily if any DRV mutations exist (see section below on selection of PI and MDR HIV).

Dyslipidemia is a toxicity seen with drugs from this class (ATV having the least effect in this regard). Propensity toward insulin resistance and diabetes may potentially occur as well. Gastrointestinal symptoms are well documented, including abdominal pain, nausea, vomiting, and diarrhea. With regard to the primary preferred PIs, ATV has the notable effect of causing reversible indirect hyperbilirubinemia due to inhibition of UDP-glucuronosyltransferase. Jaundice or scleral icterus may even become evident in patients taking ATV, and a change to an alternative agent should be considered if cosmetic concerns exist. While isolated hyperbilirubinemia itself does not constitute hepatic failure in this setting, the presence of elevated hepatic transaminases should raise concern for alternative pathology.

As mentioned previously, newer boosted PIs have a high barrier to viral resistance. Several mutations to viral protease are usually required for resistance, and generally one or more mutations must be major. DRV is especially robust in the setting of multiple PI mutations.

Entry inhibitors

Entry inhibitors are drugs targeted at inhibition of HIV fusion and entry into host cells. The primary drugs of this class are enfuvirtide (ENF) and maraviroc (MVC). Neither of these

medications is currently considered amongst the preferred ART medications.

ENF is an amino acid polypeptide fusion inhibitor and is used primarily as a salvage drug for patients who have prior experience with ART and multiple resistance mutations to primary ART medications. Two randomized trials with median patient CD4 count <100 cells/mm^3 demonstrated significantly improved viral suppression when ENF was added to an optimized ART regimen. ENF is dosed as a 90-mg subcutaneous injection administered twice daily. Advantages of this drug include no need to adjust dose for renal or hepatic function and no known drug interactions. There is also no evidence of teratogenicity in animal models (although experience in pregnant humans is lacking). A major disadvantage, however, is the need for twice-daily injections to avoid gastrointestinal denaturation of the medication. Not only is the need for injection a potential psychological barrier to home, but there is also a 98% incidence of local injection reactions. Injections must be administered away from recent previous injection sites or areas of reactive skin, and care must also be taken to avoid blood vessels, large nerves, injured skin, and tattoos. Nausea, vomiting, diarrhea, fatigue, and insomnia are additional adverse effects that have been described. Viral resistance can occur with amino acid substitutions on viral glycoprotein 41, usually at position 36, 38, 40, and 43.

MVC is a CCR5 allosteric antagonist. It is the only approved ART medication that targets a host, not a viral, receptor. It is designed to prevent interaction of viral gp120 with host CCR5, thereby inhibiting viral attachment. It has been demonstrated to effectively lower viral load and raise CD4 counts in two randomized, double-blind, placebo-controlled trials. Patients must be screened with a tropism test prior to initiation to ensure their specific HIV strain does not use CXCR4 for entry, either in lieu of or in conjunction with reliance on CCR5, as MVC has not been shown to be of benefit in this patient population. MVC was shown to be most effective in these two studies when combined with at least two other effective antiretroviral medications. If used in combination with ENF for salvage regimens, patients responded best when there was no ENF resistance and when ENF was being administered to the patient for the first time. The 48-week MERIT study in which MVC plus AZT/3TC was compared with EFV plus AZT/3TC (a standard primary initial HAART regimen at the time of that study) failed to demonstrate that the MVC regimen conferred as much viral suppression as the EFV regimen. However, reanalysis of these data in the MERIT-ES study with a newer Trofile test demonstrated improved efficacy. MVC can be used in combination with two NRTIs in special circumstances for treatment-naïve patients, although it is considered to be a less satisfactory regimen compared to preferred or alternative NNRTI-, PI-, or integrase inhibitor-based regimens.

MVC is dosed at 300 mg twice daily. There is little data to date to suggest dose adjustment in patients with renal or hepatic dysfunction. MVC is metabolized by CYP3A, and therefore dose adjustment is necessary with CYP3A inducers or inhibitors. Concurrent medications that inhibit CYP3A that may be encountered in the HIV population include PIs and clarithromycin, while common inducers encountered in this population include EFV, NVP, and anticonvulsants. Dosing should be decreased to 150 mg twice daily in the presence of an inhibitor, and increased to 600 mg twice daily with an inducer. Side effects of MVC include dizziness, cough, rash, upper respiratory tract infection, and fever. There are two major pathways of viral resistance to MVC. The first occurs with an amino acid substitution on viral gp120. The second, and much more common, pattern of resistance occurs when selection of CXCR4-binding virus occurs (patients initially screened for CXCR4-using virus may have low levels present that are undetectable by the lab assay), as was demonstrated in the MOTIVATE trials.

Aside from drug resistance, selection of CXCR4 virus in patients prescribed MVC may have additional consequences. Patients with CXCR4-predominate virus may develop a faster drop in CD4 cell count and more aggressive progression to AIDS. Discontinuation of MVC in patients who develop CXCR4 tropism may lead to a resurgence of CCR5-predominate infection in such patients (however, MVC should not be reconsidered as a viable therapeutic option in such patients, even if CCR5-predominate virus returns).

Integrase strand transfer inhibitors (INSTIs)

INSTIs are a class of antiretroviral medications designed to block HIV integrase-mediated incorporation of HIV cDNA into the host DNA genome.

Raltegravir (RAL) was the first drug developed in this class and is considered the

Table 99.4 Fixed-dose combination pills

Combination (trade name)	Components	Dosing
Atripla[a]	600 mg EFV + 200 mg FTC + 300 mg TDF	1 tablet once daily before bed on empty stomach
Combivir	300 mg AZT + 150 mg 3TC	1 tablet twice daily
Complera[a]	25 mg RPV + 200 mg FTC + 300 mg TDF	1 tablet once daily with a meal
Epzicom	300 mg 3TC + 600 mg ABC	1 tablet once daily
Trizivir	300 mg AZT + 150 mg 3TC + 300 mg ABC	1 tablet PO twice daily
Truvada	200 mg FTC + 300 mg TDF	1 tablet once daily
Stribild[a]	150 mg EVG + 150 mg cobicistat + 200 mg FTC + 300 mg TDF	1 tablet once daily
DTG/ABC/3TC (trade name pending)[a]	50 mg DTG + 600 mg ABC + 150 mg 3TC	1 tablet once daily

[a] Complete ART regimen.

preferred INSTI. It has been demonstrated to be noninferior and better tolerated than EFV-containing primary ART regimens for treatment-naïve patients. RAL was also shown to decrease the viral load faster within 24 weeks compared to EFV-based regimens (the clinical significance of this class-wide INSTI effect is unknown).

RAL also has demonstrated efficacy in treatment-experienced patients. It showed greater suppression of HIV viral load at 48 weeks compared to placebo when added to an optimal ART backbone in two randomized, double-blinded phase III studies. Of note, in one of these studies patients with resistant virus concurrently started on DRV and ENF for the first time had even greater response, although the study was not powered to assess this effect. In another investigation of RAL use in treatment-experienced patients, substituting RAL for ENF maintained virologic suppression.

Despite its utility in treatment-experienced patients, RAL has a low barrier to resistance. Primary RAL resistance mutations to the viral integrase protein exist as substitutions at Y143, Q148, and N155 on the integrase enzyme.

RAL is administered orally at 400 mg twice daily. Dose adjustment is not necessary in renal or hepatic insufficiency, unless hepatic insufficiency is severe. It is metabolized by glucuronidation and therefore has few drug–drug interactions. RAL should be administered as 800 mg twice daily if coadministered with rifampin.

Elvitegravir (EVG) is the second INSTI to be developed. It is currently approved only for treatment-naïve patients as part of a four-drug fixed-dose combination pill trade (EVG/COBI/TDF/FTC) and is considered an alternative INSTI. This regimen contains 150 mg of EVG, 150 mg of cobicistat (COBI) for boosting EVG levels (COBI discussed below), as well as 200 mg FTC + 300 mg TDF. Boosting EVG levels with COBI in this single-pill fixed-dose combination allows for once-daily administration (Table 99.4), conferring a potential convenience and adherence advantage over a RAL-based regimen. Separate phase III clinical trials comparing the EVG/COBI/TDF/FTC fixed-dose combination pill with preferred regimens EFV/TDF/FTC (fixed-dose combination) and ATV/r + TDF/FTC demonstrated noninferiority at 48 weeks with regard to viral suppression and better tolerability than either of these preferred regimens.

EVG is also under investigation as therapy for treatment-experienced patients. Salvage regimens for such patients often include a boosted protease inhibitor and RAL in addition to another class of medication. In a prospective, randomized, double-blinded phase III trial, EVG and RAL were compared in patients with a minimum of 6 months' experience with or resistance to at least two classes of ART drugs. Either EVG or RAL was added to a backbone regimen consisting of an RTV-boosted PI and one additional drug from a separate class (note that RTV acted as a booster for EVG as well as the PI in this trial, allowing EVG to be administered once daily, as opposed to use of COBI for boosting in the fixed-dose combination pill). Efficacy and safety appeared equal in both groups; however, more patients experienced diarrhea and elevated liver enzymes in the EVG group. Again, the theoretical advantage of once-daily EVG dosing versus twice-daily RAL may offset such mild side effects in terms of improved adherence.

EVG is primarily metabolized by CYP3A4, making drug–drug interactions more of a concern compared to RAL. Use of rifamycins is contraindicated with EVG, making EVG a poor choice

in patients with tuberculosis coinfection. EVG is also contraindicated in combination with currently approved hepatitis C protease inhibitors and statins such as simvastatin and lovastatin. Dose adjustments are required with azole antifungals and clarithromycin. The dose of EVG should be decreased to 85 mg once daily when used in combination with ATV/r or LPV/r. When EVG is used in combination with MVC, the dose of MVC should be reduced to 150 mg twice daily. These CYP3A4 interactions are a major disadvantage of EVG and contribute significantly to its distinction as an alternative ART backbone medication.

Gastrointestinal side effects (nausea) were significantly notable with the EVG/COBI/TDF/FTC combination, although these side effects might be most attributable to the COBI portion of the new pill.

As with RAL, EVG has a low barrier to resistance. Primary viral integrase substitution mutations demonstrated to confer resistance to EVG include E92Q, H51Y, S147G, and E157Q.

Dolutegravir (DTG) is a recently-approved, promising INSTI discussed below in the "New and investigational medications" section.

Cobicistat

Cobicistat (COBI) is a pharmacoenhancer medication that strongly inhibits CYP3A4 and is used as a dedicated boosting agent. It is FDA-approved as part of the EVG/COBI/TDF/FTC regimen. It has been designed with the intent to replace RTV for boosting. COBI has the theoretical benefit of interacting with fewer CYP enzymes compared to RTV. It has also been studied as a booster for ATV head-to-head versus RTV-boosted ATV, each in combination with TDF/FTC. The COBI-boosted regimen was found to be noninferior at 48 weeks compared to the RTV-boosted regimen with regard to viral suppression and was noted to have similar safety. Based on these results, COBI may see a wider application as a PI booster in place of RTV in the future.

COBI has been shown to competitively inhibit creatinine excretion in the kidney, causing an increase in serum creatinine levels. This increase in creatinine does not represent a true reduction in GFR. This artifact elevation in serum creatinine seen in approximately 7% of patients studied on EVG/COBI/TDF/FTC was sustained at 48 weeks of therapy. In two trials comparing EVG/COBI/TDF/FTC with EFV/TDF/FTC and ATV/r + TDF/FTC, more patients dropped out of the EVG/COBI/TDF/FTC groups than with the other regimens due to renal intolerance (some was not completely reversible despite cessation of therapy). This potential for renal intolerance was one of the key factors in designating an "alternative" recommendation for EVG/COBI/TDF/FTC in treatment-naïve patients instead of a "preferred" recommendation. A rise in serum creatinine above 0.4 mg/dL or a drop in GFR below 50 mL/min while on therapy with EVG/COBI/TDF/FTC should prompt consideration of alternative therapy. EVG/COBI/TDF/FTC should not be initiated in patients with baseline serum creatinine clearance of less than 70 mL/min, a recommendation that virtually excludes this medication as a viable option for patients with any degree of baseline renal dysfunction.

Fixed-dose combination pills

The emergence of several commercial fixed-dose combination (FDC) pills has made the administration of several ART regimens a more practical venture (Table 99.4). These combination pills lead to increased adherence by limiting the number of pills patients must consume. Some of these formulations have the advantage of offering a complete ART regimen in one pill taken once daily. Toxicities and drug–drug interactions must still be considered for each individual component of these FDCs.

The most noteworthy FDCs are the four once-daily complete regimen pills. The first was NNRTI-based EFV/TDF/FTC (trade name Atripla). Atripla has remained a gold standard with regard to virologic suppression success and revolutionized ease of dosing. It is currently the only "preferred" single-pill regimen. Its major drawback is adverse reactions due to EFV, primarily neurologic side effects as well as drug rash. There is also a low genetic barrier to resistance. As with many of these formulations, renal function and bone density are of concern with regard to the TDF component. It is taken on an empty stomach at night to minimize side effects.

The second complete regimen pill is another NNRTI-based regimen RPV/TDF/FTC (trade name Complera). Patients may tolerate Complera a bit better than Atripla owing to less frequent side effects with RPV compared to EFV. There are several major drawbacks, however. It must be taken with a sizable amount of food at a time of day as previously discussed for RPV. There is a low genetic barrier to resistance. Due to increased rates of virologic failure in patients on RPV with

viral load >100 000 copies/mL, it is contraindicated in this group of patients. Proton pump inhibitors are strictly contraindicated, and alternative acid-blocking medications such as H_2 blockers must be appropriately timed to avoid interactions. Such drawbacks have led to the designation of "alternative" for Complera.

The third complete regimen is INSTI-based EVG/COBI/TDF/FTC (trade name Stribild). It is probably the best tolerated with regard to side effects when compared with Atripla and Complera. It should be taken with food, but the requirement is not as strict as with Complera. Drug–drug interactions (rifamycins are contraindicated in patients with tuberculosis coinfection, for instance), low genetic barrier to resistance, and strict limitations in patients with baseline renal dysfunction have led to an "alternative" designation, however.

A fourth complete regimen consisting of DTG/ABC/3TC may soon become a popular single-dose pill. Indications from studies with DTG (see below) are that this regimen will be very well tolerated, have the highest genetic barrier to resistance amongst these four regimens, and have no food requirement. Due to metabolism of DTG by glucuronidation, drug–drug interactions are minimal. Use of ABC in favor of TDF has the theoretical advantage of less renal dysfunction and less osteoporosis. Patients with the HLA-B5701 allele will not be able to take this regimen due to possible ABC hypersensitivity, and patients with hepatitis B coinfection will need an alternative regimen, as ABC is not active against hepatitis B (see discussion of hepatitis B coinfection below).

Fixed-dose, once-daily combination regimens employing COBI-boosted DRV are currently under investigation as well. Such a regimen would be the first PI-based FDC and would potentially simplify pill burden to patients already on DRV-based regimens and extend use of FDCs to patients with HIV mutations.

NEW AND INVESTIGATIONAL MEDICATIONS

Dolutegravir

Dolutegravir (DTG) is a promising INSTI that was recently FDA approved on August 12, 2013. It is dosed at 50 mg once daily and does not require boosting. It will be offered in a once-daily, complete-regimen fixed-dose combination pill along with ABC and 3TC in the future. Impressive results from four phase III trials combined with once-daily dosing, lack of drug–drug interactions, excellent tolerability, and higher barrier of resistance compared to other INSTIs may make DTG a popular future choice in HIV therapy.

Two phase III studies in treatment-naïve patients are ongoing. The SINGLE trial is a 96-week comparison of DTG in combination with ABC/3TC versus EFV/TDF/FTC in treatment-naïve patients. At 48 weeks, the DTG regimen is the first regimen to demonstrate superiority to EFV/TDF/FTC with regard to virologic suppression in this patient population. The DTG regimen also demonstrated fewer adverse effects. The SPRING-2 trial is a 96-week comparison of DTG head-to-head with RAL in treatment-naïve patients, each in combination with either TDF/FTC or ABC/3TC. At 48 weeks, DTG was found to be noninferior to RAL with regard to viral suppression and equal with regard to safety. There were no DTG or background regimen resistance mutations that developed during therapy in either of these studies.

DTG has also demonstrated efficacy in treatment-experienced patients. SAILING is a 48-week study comparing DTG with RAL in INSTI-naïve patients with virologic failure on a current ART regimen with resistance to two or more ART classes. DTG or RAL was added to an investigator-selected regimen with a minimum of one effective ART medication. DTG was superior with regard to virologic suppression, equal with regard to safety, and superior with regard to fewer new INSTI class mutations and fewer background regimen mutations. In the VIKING-3 study, DTG was examined in patients on failing HIV regimens with known resistance to RAL and/or EVG in addition to two or more other ART classes. DTG 50 mg twice daily was added to an investigator-selected optimized background regimen consisting of at least one fully active ART agent. Results demonstrated that the use of DTG for such an application significantly improved rates of virologic suppression.

Similar to RAL, DTG is primarily metabolized by glucuronidation and therefore has few drug–drug interactions. Its dose should be increased to 50 mg twice daily when given with rifampin. However, it requires no adjustment with rifabutin.

Adverse effects of DTG are minimal and include nausea, diarrhea, headache, and nasopharyngitis. DTG also inhibits renal creatinine secretion causing a slight increase in serum creatinine. This increase does not reflect a true decline in GFR.

Primary DTG resistance mutations have not yet been identified. As mentioned, the drug appears to have a higher genetic barrier to resistance compared to RAL and EVG. Integrase mutations E138K, G140S, R148H, R263K, and Q148HRK may cause some level of DTG resistance, however.

In summary, DTG may soon become one of the most popular HIV medications on the market. It can be administered once daily in a complete-regimen fixed-dose combination pill, it is very well tolerated, it appears to have excellent efficacy with regard to viral suppression in treatment-naïve patients, it is efficacious in treatment-experienced patients with resistance to multiple drug classes, including INSTIs, and it has a higher barrier to resistance compared to the other INSTIs.

Tenofovir alafenamide

Tenofovir alafenamide (TAF) is an investigational NRTI that is the prodrug of TDF. Early phase studies indicate that TAF taken once daily achieves higher intracellular drug levels and lower serum drug levels compared to TDF with minimal side effects. As mentioned, the primary concern with TDF is progressive renal dysfunction and osteoporosis with long-term use. Fanconi syndrome is another potential adverse effect of TDF. The higher levels of serum tenofovir seen with TDF contribute to such undesirable effects. Theoretically, the high intracellular tenofovir levels achieved by TAF may provide the same efficacy and activity against hepatitis B virus that has made TDF a preferred NRTI. At the same time, the low extracellular/serum tenofovir levels seen with TAF may limit side effects seen with TDF. Should these effects prove true with further studies, TAF may have the potential to replace TDF as one of the most commonly prescribed NRTI medications.

TAF is currently in phase II and III trials and is being used in fixed-dose combination pills. EVG/COBI/TAF/FTC is being compared with EVG/COBI/TDF/FTC and DRV/COBI/TAF/FTC is being compared with DRV/COBI/TDF/FTC.

USE OF ART THERAPY

Guidelines for ART initiation

Expert consensus continues to evolve with regard to criteria for initiation of ART. When ART first became available, consensus was initially to push for early therapy for every patient. It soon became clear, however, that toxicities of these early regimens were not benign, the high pill burden made compliance difficult, and resistance to these regimens quickly developed if adherence was not strict. As the pendulum swung back toward delayed therapy, however, obvious detriments arose such as increased progression to AIDS or death, increased risk of opportunistic infection, increased risk of HIV-associated organ dysfunction (such as HIV-associated nephropathy), and decline in absolute ability to regain maximal CD4 counts and full viral suppression. However, as newer therapies have developed, toxicity profiles of newer ART regimens have become better tolerated and pill burdens have lessened owing to boosting, more potent formulations, and FDCs. The potential for greater patient compliance and improved mortality has experts once again recommending earlier initiation of these newer ART regimens.

While HIV cure has never been achieved with any current regimen, four other major goals exist with ART treatment. These goals are to reduce HIV-associated morbidity and to extend and improve patient life, to restore and maintain a patient's immune system, to suppress the HIV viral load to undetectable levels, and lastly, to prevent HIV transmission. Because evidence indicates that these goals are increasingly achievable with current treatment regimens, HIV treatment guidelines now recommend initiating ART for any HIV-infected patient, regardless of their CD4 cell count. The strength of the recommendation increases with lower CD4 counts. Other compelling indications for ART initiation and strength of recommendation are listed in Table 99.5.

These most recent recommendations to start ART in all HIV patients are backed by several studies. The HIV-CAUSAL study demonstrated a 38% increase in AIDS or death in patients initiated on ART at a CD4 $\leq$350 cells/mm^3 compared to a group in which ART was initiated at CD4 $\leq$500 cells/mm^3. The CASCADE and COHERE trials confirmed these results in patients with CD4 $\leq$500 cells/mm^3. Expert consensus, rather than randomized trials, have extended the recommendation to start ART at CD4 counts >500 cells/mm^3.

Benefit seen from administering ART to HIV-positive patients who were sexually active with HIV-negative partners is yet another compelling reason to extend the universal ART treatment recommendation (not mentioned in Table 99.5). The HPTN 052 trial demonstrated a 96% reduction in HIV transmission to a noninfected partner

Table 99.5 Indications for ART initiation

Condition	Level of evidence
CD4 $\leq$500 cells/mm^3	AIa
Pregnancy	AIa
Opportunistic infection (within 2 weeks)[a]	AIa
Active tuberculosis infection with CD4 <50 cells/mm^3 (within 2 weeks of anti-TB therapy)[¶]	AIa
Active tuberculosis infection with CD4 $\geq$50 cells/mm^3 (within 8–12 weeks of anti-TB therapy)[b]	AIa
Chronic HBV coinfection	AIIa
HIV-associated nephropathy	AIIa
Age >60 years	BIIa
CD4 >500 cells/mm^3	BIII
Acute primary HIV infection	BIII
Tuberculosis meningitis (within 2–8 weeks anti-TB therapy)	BIII
Chronic HCV coinfection	CIII

[a] Initiation of ART in patients with cryptococcal meningitis should be used with caution and is discussed in the section on IRIS.
[b] Does not include tuberculosis meningitis.

when the HIV-positive partner was on ART therapy. This effect was demonstrated in HIV-positive partners with CD4 counts of 350 to 500 cells/ mm^3, and these results have been extrapolated to higher CD4 counts. Any of the approved ART regimens can be used to achieve the specific benefit of minimizing transmission. Ideally, maximum viral suppression should be achieved before onset of sexual activity (or before attempts at conception begin in HIV-discordant couples desiring natural pregnancy). Patients should be advised that even use of ART cannot prevent HIV transmission with absolute certainty. It also cannot prevent the transmission of other sexually transmitted infections. Therefore, condom usage should be discussed with patients. Pre-exposure prophylaxis therapy may be considered for HIV-negative patients who engage in sexual contact with patients who have confirmed HIV or who have high risk for HIV infection (see section on pre-exposure prophylaxis).

Selection of regimen

Selection of an antiretroviral regimen is based upon multiple considerations. Since noncompliance can lead to ART resistance, barriers to compliance must be addressed prior to ART initiation. Specifically, untreated mental illness such as depression, untreated chemical dependency, homelessness, and a chaotic life circumstance are all potential barriers to compliance. A patient's additional medical conditions must be taken into account as well, as should interactions with any medications the patient is taking for these conditions. The pregnancy status or desire to become pregnant should be assessed with female patients. Medication cost and access to coverage or assistance may become a factor. Prior exposure to ART and a patient's HIV genotype are additional factors.

Table 99.6 Preferred ART regimens for treatment-naïve patients

NNRTI-based	EFV + TDF/FTC	
PI-based	ATV/r + TDF/FTC	DRV/r + TDF/FTC
INSTI-based	RAL + TDF/FTC	

All of the preferred regimens for treatment-naïve patients contain two NRTI medications (an "NRTI backbone") combined with an additional anchoring agent. The preferred additional agent can be either an NNRTI, a boosted PI, or an INSTI. See Table 99. 6, Table 99.7, and Table 99.8 for listings of preferred, alternative, and third-line NRTI-backbones.

NRTI BACKBONE

Three NRTI combination formulations are currently available (Table 99.4): TDF/FTC, ABC/3TC, and AZT/3TC. Currently the TDF/FTC backbone is preferred, and ABC/3TC is considered the primary alternative. A 48-week head-to-head comparison study of TDF/FTC and AZT/3TC (each combination combined with EFV) demonstrated that TDF/FTC therapy resulted in noninferior viral load suppression (primary end point) as well as better CD4 improvement and less drug resistance and side effects. At 96 weeks, patients in the TDF/FTC arm had less lipodystrophy and better serum triglyceride levels. TDF/FTC has the additional advantage of being administered once daily, as opposed to AZT/3TC, which is administered as twice daily. A 48-week study comparing ABC/3TC with AZT/3TC (each combined with EFV) also demonstrated that ABC/3TC is noninferior to AZT/3TC with respect to viral suppression. Again, ABC/3TC offers the advantage of being administered once daily.

Two important studies have compared TDF/FTC and ABC/3TC. The HEAT trial compared each backbone in combination with LPV/r and demonstrated equally effective efficacy with

Table 99.7 Alternative ART regimens for treatment-naïve patients

NNRTI-based	EFV + ABC/3TC[a]	RPV/TDF/FTC[b]	RPV[b] + ABC/3TC[a]	
PI-based	DRV/r + ABC/3TC[a]	LPV/r + (TDF/FTC or ABC/3TC[a])	ATV/r + ABC/3TC[a]	FPV/r + (TDF/FTC or ABC/3TC[a])
INSTI-based	RAL + ABC/3TC[a]	EVG/COBI/TDF/FTC		

[a] ABC-based NRTI combination should be avoided in patients with presence of HLA-B5701 allele and used with caution in patients with HIV viral load >100 000 copies/mL.

[b] RPV-based regimens should be avoided in patients with HIV viral load >100 000 copies/mL.

Table 99.8 Third-line ART regimens for treatment-naïve patients in special circumstances

NNRTI-based	EFV + AZT/3TC	NVP[a] + (ABC/3TC[b] or TDF/FTC or AZT/3TC)	RPV[c] + AZT/3TC
PI-based	(ATV or ATV/r or DRV/r or FPV/r or LPV/r or SQV/r) + AZT/3TC	ATV + ABC/3TC[b]	SQV/r + (ABC/3TC[b] or TDF/FTC)
INSTI-based	RAL + AZT/3TC		
Entry inhibitor-based	MVC + (ABC/3TC[b] + TDF/FTC + AZT/3TC)		

[a] NVP-based regimens should be avoided in men with baseline CD4 count >400 cells/mm^3 and women with baseline CD4 count >250 cells/mm^3.

[b] ABC-based NRTI combination should be avoided in patients with presence of HLA-B5701 allele and used with caution in patients with HIV viral load >100 000 copies/mL.

[c] RPV-based regimens should be avoided in patients with HIV viral load >100 000 copies/mL.

respect to viral load suppression. The ACTG 5202 compared each of these NRTI backbones head-to-head in combination with both EFV and ATV/r (each separately). The ABC/3TC arm demonstrated higher cholesterol levels, more adverse effects (most likely from ABC hypersensitivity in the setting of HLA-B5701 positivity), and, most importantly, significantly higher virologic failure in patients with high initial viral loads (>100 000 copies/mL) compared to the TDF/FTC arm. The rate of virologic failure was so significant that this group of patients was unblinded and offered TDF/FTC as alternative therapy. This increased rate of virologic failure was not observed in a second randomized trial.

A large cohort review trial did show increased risk of myocardial infarction in patients using ABC over the prior 6 months, although follow-up studies have not clearly supported this finding.

Caution is generally recommended when considering ABC/3TC for patients at risk for vascular disease or viral load >100 000 copies/mL. The HLA-B5701 allele status of candidate patients should always be checked before administration, and therapy is absolutely contraindicated in positive patients.

The ABC/3TC combination may gain popularity in the near future, as a full single-pill regimen containing DTG/ABC/3TC has been proposed. Given the immense potential of DTG, this proposed coformulation may one day see extensive use.

SELECTION OF NNRTI

NNRTI-based regimens are frequently employed in treatment-naïve patients. EFV is generally considered the first-line medication in this class, with RPV being the primary alternative. As mentioned above, EFV is Pregnancy Category D and should not be initiated in pregnant patients (although it may be continued in patients already taking EFV when pregnancy is diagnosed). EFV is available in a single-pill, once-daily fixed-dose combination as EFV/TDF/FTC. RPV is also a popular choice since it has been made available in the single-pill combination of RPV/TDF/FTC (see Table 99.4 for complete formulation). However, it is considered less effective than EFV in patients with viral loads >100 000 copies/mL and is contraindicated in such patients as well as patients requiring proton-pump inhibitors for stomach acid suppression. ETV is not approved for treatment-naïve patients and is generally reserved for patients with MDR HIV.

SELECTION OF PI

PI-based regimens all generally make use of RTV boosting, as discussed above. ATV and DRV are considered preferred agents of this class because of their minimal toxicity, although lopinavir (LPV), fosamprenavir (FPV), and saquinavir (SQV) have all demonstrated noninferiority with respect to efficacy. DRV is the most robust agent in the face of multiple viral mutations. ATV has the least effect on lipids, although DRV is almost

equivalent. As mentioned previously, COBI may replace RTV as the boosting agent of choice in these regimens, although hopes it would have less adverse reactions compared to RTV have not necessarily been demonstrated.

If virologic failure occurs on an initial first-line regimen, a switch to a boosted PI-based regimen is often recommended. Again, the boosted PI is usually combined with two NRTIs. If PI mutations occur in addition to resistance to other classes, a boosted DRV- or TPV-based regimen is especially recommended.

SELECTION OF INSTI

RAL is currently the preferred medication of this class. EVG (as part of the EVG/COBI/TDF/FTC combination) is considered an alternative regimen for treatment-naïve patients, primarily due to increased potential for drug–drug interactions.

ART selection in patients with multidrug-resistant HIV

MDR HIV can frequently be seen in patients who have failed two or more standard ART regimens and occasionally in patients newly diagnosed with HIV. Treatment in these settings often requires a nonstandard regimen. At least two active drugs, and ideally three active drugs, should be administered, and potency of the drugs is considered a more important factor than the number of drugs administered. Typically, a boosted PI should be selected based on genotypic resistance testing (data exist indicating that DRV/r or TPV/r are most effective in this setting). Etravirine (ETR) has been studied in the setting of known NNRTI resistance in combination with DRV/r and NRTIs and was found to confer benefit. In settings where no documented RAL resistance exists, it should be added as well because there is evidence for significant efficacy in this setting (although special resistance testing to RAL may be needed, especially if RAL has been used in the past, as resistance attenuates benefit). MVC has shown effect in CCR5-tropic infections. NRTIs may continue to provide partial efficacy, even in the face of known mutations. ENF can be considered for salvage therapy, although it is poorly tolerated and rarely used because of the need for injections and significant injection site reactions.

As mentioned previously, DTG has demonstrated efficacy in patients with known INSTI mutations when administered twice daily in MDR HIV. DTG may therefore soon play a pivotal role in the treatment of such patients.

The presence of certain mutations to particular drugs may lend credence to their addition when these mutations decrease the fitness of the HIV virus. For instance, the M184V mutation may significantly reduce the action of FTC and 3TC, but this particular mutation confers a fitness disadvantage to the HIV virus and makes AZT highly effective, even in the presence of TAM mutations. Therefore, FTC or 3TC might be continued in the face of such a mutation.

ART selection in patients with comorbidities

CARDIOVASCULAR DISEASE

ABC, LPV/r, and FPV/r have been associated with some potential increased risk of cardiovascular disease, and alternatives should be considered in patients at high risk.

RENAL DISEASE

TDF, ATV/r, and LPV/r have been associated with decline in renal function in some cases. Renal function should be monitored while using these agents, and they should be avoided, if possible, in patients with baseline renal dysfunction. As mentioned previously, COBI, as well as RPV, may cause an artificial increase in serum creatinine that is not associated with true decline in GFR. Since COBI is frequently administered with TDF, it may be difficult to distinguish true renal failure from this artifact in patients who are treated with both drugs.

As mentioned previously, the investigational TDF-prodrug TAF could potentially minimize renal toxicity when substituted for TDF in a full ART regimen.

OSTEOPOROSIS

With respect to bone mineral density, HIV alone is considered an independent risk factor for bone loss. Decreased bone mineral density can generally be expected with all ART regimens during the first year of therapy. In particular, TDF has been shown to be a strong independent risk factor for bone density loss and fracture, and should potentially be avoided in postmenopausal women or those at high risk for osteoporosis.

As with effects on renal function, TAF is currently being investigated to determine if bone mineral density loss is minimized compared to TDF when used as a substitute for TDF.

PREGNANCY

Pregnancy is a level AIa indication for initiation of ART. Prevention of vertical transmission of HIV from mother to fetus is the primary goal. HIV testing should be performed on all pregnant female patients, and ART should be initiated as soon as possible, even if diagnosis is made immediately before delivery.

Pregnant female patients with HIV should be started on ART regardless of CD4 count. As with traditional ART, a two-drug NRTI backbone should generally be used in combination with a third active medication. Current guidelines list AZT/3TC as the preferred backbone in pregnancy, given that there exists the most historical data regarding the combination's use in pregnant patients. However, the known toxicities associated with AZT compared with newer agents make its choice less attractive, and in clinical practice less toxic regimens with newer ART medications are frequently employed (Table 99.9). Generally, all preferred and alternate NRTI backbones that are used in treatment-naïve patients can be considered in pregnancy.

Most boosted PI-based regimens are considered to be reasonably safe during pregnancy, although LPV/r and ATV are preferred.

With regard to NNRTI-based regimens, EFV is the only ART medication that is Pregnancy Category D, and its initiation in pregnancy should be avoided. Neural tube defects have been reported with the use of EFV during pregnancy, especially in the first trimester. However, the Antiretroviral Pregnancy Registry has recorded no increase in the rate of these congenital defects compared to the general population with EFV or any other ART medications (even with first-trimester exposure). Since most pregnancies are diagnosed after the first trimester, patients taking EFV at diagnosis may be continued on such therapy, provided they are virologically suppressed. NVP is considered the preferred NNRTI in pregnancy.

Insufficient data exist for the recommended use of INSTI-based regimens. RAL is considered a third-line agent for use in special circumstances.

The PACTG 076 trial demonstrated the benefit of intravenous AZT infusion starting 3 hours before delivery in HIV-positive mothers with viral load greater than 400 copies/mL, regardless of use of antenatal ART. Pregnant patients with a viral load >400 copies/mL near the time of delivery should therefore receive intravenous AZT at delivery. Intravenous AZT should also be administered in the same fashion to all mothers newly diagnosed with HIV immediately prior to delivery.

Cesarean section should be scheduled for pregnant HIV patients with a viral load of >1000 copies/mL near the time of delivery.

Infants of mothers with HIV should receive AZT for 6 weeks after delivery. Infants of mothers with HIV who were not taking ART during the antenatal period should be administered AZT for 6 weeks after birth in addition to three doses of NVP given at birth, 48 hours of life, and 96 hours of life. This AZT/NVP regimen has demonstrated efficacy and safety in such patients.

Table 99.9 ART medications and their pregnancy category

Drug	Recommendation
NRTI	
3TC	Preferred
AZT	Preferred
FTC	Alternative
TDF	Alternative
ABC	Alternative
ddI	Third-line
d4T	Third-line
NNRTI	
NVP	Preferred
EFV	Pregnancy category D. Do not initiate during pregnancy. Can continue if patient was taking prior to diagnosis of pregnancy and is virologically suppressed
ETR	Insufficient data
RVP	Insufficient data
PIs	
LPV	Preferred
RTV	Preferred (for boosting)
ATV	Preferred
DRV	Alternative
SQV	Alternative
IDV	Third-line
NFV	Third-line
FPV	Insufficient data
TPV	Insufficient data
INSTIs	
RAL	Third-line
Entry inhibitors	
ENF	Insufficient data
MVC	Insufficient data

MYCOBACTERIAL INFECTIONS

Patients concurrently taking rifamycin antibiotics for mycobacterial infections are particularly susceptible to drug–drug interactions. Guidelines exist for dose adjustments in such cases. An EFV-based regimen is generally preferred in patients taking a rifampin-based antimycobacterial regimen. Despite concern for a reduction in EFV levels in this setting, this result is not felt to be clinically significant. While package recommendations suggest the EFV dose should be increased to 800 mg/day in patients weighing more than 50 kg taking rifampin, the fixed-dose formulation of 600 mg of EFV in EFV/TDF/FTC has been shown to produce reliable treatment of HIV in coadministration with rifampin regardless of weight. If EFV cannot be used, rifampin should be switched to rifabutin and a PI-based regimen should be considered. PI-based regimens have been shown to increase the drug concentration of rifabutin, and therefore the dose of rifabutin should be reduced to 150 mg once daily.

RAL-based regimens have not been extensively studied in the setting of antimycobacterial treatment. RAL levels are decreased in the setting of rifampin, so either the dose of RAL should be increased to 800 mg twice daily, or rifabutin should be substituted for rifampin.

EVG is not recommended in combination with either rifampin or rifabutin due to decreased EVG levels. Therefore, an EVG-based regimen should be avoided when concern exists for mycobacterial coinfections such as tuberculosis.

A recently approved 3-month once-weekly regimen of isoniazid and rifapentine for the treatment of latent tuberculosis infection should not be used in patients on ART, and generally should be avoided in patients with HIV.

LIVER DISEASE

All ART medications have some degree of hepatic metabolism, and caution should be exercised with their use in patients with liver disease or cirrhosis (although patients with Pugh score A can still tolerate most medications). The NNRTI NVP is especially notorious with regard to hepatic failure and should be avoided if possible in this patient population.

CHRONIC HEPATITIS B VIRUS

Interferon-based hepatitis B virus (HBV)-treatment regimens have not been extensively studied in the setting of HIV. Therefore, an NRTI-based approach is generally employed. Usually, a typical three-drug HIV ART regimen is selected that includes an NRTI backbone with two active NRTIs against HBV and two active NRTIs against HIV. TDF combined with either FTC or 3TC is recommended, as all of these agents are active against both HBV and HIV.

NRTI backbones in which FTC or 3TC is the only active medication against HBV are not recommended. Therefore, in cases where significant contraindications to TDF exist, additional dedicated HBV drugs may need to be added to a full ART regimen.

Entecavir is an NRTI that is fully active against HBV, but only partially active against HIV and should therefore not be counted as a viable drug for HIV therapy. Coinfected patients taking entecavir for HBV should therefore still additionally receive a full ART regimen for HIV. Selection of HIV RT mutations such as the M184V might result due to entecavir if it is combined with only two other drugs that are fully active against HIV.

To illustrate, any three-drug ART regimen including TDF/FTC would have full activity versus both HIV and HBV. However, a three-drug ART regimen consisting of entecavir in addition to FTC or 3TC and a third HIV agent would cover HBV acceptably, but would be an incomplete HIV regimen and may lead to resistance.

CHRONIC HEPATITIS C VIRUS

Peginterferon alfa and ribavirin had classically been used for treatment of hepatitis C virus (HCV) in patients coinfected with HCV and HIV. The addition of the protease inhibitors telaprevir and boceprevir to peginterferon alfa and ribavirin has been demonstrated to improve treatment response in patients with lone HCV genotype 1 infection. Phase II and III trials suggest similar efficacy in patients with HCV/HIV coinfection as well. It should be noted that neither telaprevir nor boceprevir are considered to be active PIs against HIV.

Limited data exist regarding drug–drug interactions between telaprevir or boceprevir with current HIV ART medications. It is currently felt that RAL-based regimens may be safely used in combination with either telaprevir or boceprevir; however, EVG is contraindicated in combination with either of these medications.

ATV/r may be administered with telaprevir, but not boceprevir. All other HIV PIs are contraindicated with both telaprevir and boceprevir.

With regard to NNRTIs, EFV may be used with telaprevir (telaprevir must be dose-adjusted), but not boceprevir.

Table 99.10 Relevant labs and studies pre- and post-ART initiation in HIV patients

Test	At diagnosis	Before ART initiation	At ART initiation	ART follow-up	Virologic failure
CD4 count	+	+ (3-month intervals)	+ (and 2–8 weeks later)	+ (3-month intervals)	+
HIV viral load	+	+ (3-month intervals)	+ (and 2–8 weeks later)	+ (every 4–8 weeks until undetectable, then at 3-month intervals)	+
HIV genotype[a,b]	+	–	+	–	+
Complete blood count/ differential	+	+ (3-month intervals)	+	+ (3-month intervals)	–
Complete metabolic panel	+	+ (3-month intervals)	+	+ (3-month intervals)	–
Fasting lipid panel	+	+ (12-month intervals)	+	+ (12-month intervals)	–
Pregnancy test	–	–	+	–	–
Serologies for HAV, HBV, HCV[c]	+	–	–	–	–
ECG	–	–	+/– (if considering SQV or ATV)	–	–
HLA-B5701[d]	–	–	+/– (if considering ABC)	–	–
Urinalysis	+	+ (12-month intervals)	+	+ (12-month intervals)	–

[a] Genotypic testing on patients with virologic failure should preferably be performed while the patient is still taking the failing ART regimen.

[b] A minimum viral load of 1000 copies/mL is recommended to ensure accuracy of genotypic testing.

[c] HAV = hepatitis A virus, HBV = hepatitis B virus, HCV = hepatitis C virus.

[d] Patients positive for the HLA-B5701 allele should not be started on ABC therapy for concern of severe hypersensitivity reaction.

Coadministration of the NRTIs didanosine (ddI) or AZT should be avoided with ribavirin to avoid possible hepatic failure and hematologic toxicity.

Laboratory testing

With the expanded role of ART in patients with less advanced disease, a new diagnosis of HIV in any patient should prompt a panel of blood tests to evaluate the appropriateness of offering such therapy. Similarly, patients with a known diagnosis of HIV who are not taking ART should have studies performed at regular intervals to continuously re-evaluate disease status. If not performed recently, lab testing should be performed immediately prior to therapy initiation. Testing should continue at regular intervals during treatment to monitor for virologic failure, HIV-related or unrelated organ dysfunction, and medication side effects. Relevant lab tests to be performed before and after initiation of ART are listed in Table 99.10; this list does not include additional tests that may also be indicated to screen for chronic coinfections or malignancy (e.g., syphilis serology, cervical cancer screening, tuberculin skin test, etc.).

In general, a follow-up lab panel consisting of CD4 count, HIV viral load, complete blood count (CBC) with differential, and complete metabolic panel should be monitored every 3 months from the time of diagnosis with or without therapy. For a patient with reliable adherence to an ART regimen with CD4 $\geq$350 cells/mm^3 and undetectable viral load for greater than 1 year, it may be reasonable to extend this monitoring interval to every 6 months. Fasting lipids and urinalysis should be repeated every 12 months (unless significant abnormalities exist or there is concern for HIV-associated nephropathy, where biannual testing may be appropriate). CD4 count and HIV viral load should also be reassessed 2 to 8 weeks after initiation of a new ART regimen.

CD4 counts estimate an HIV patient's immune status. These counts are monitored prior to initiation of ART to ascertain the need to begin therapy and/or prophylaxis for opportunistic infections (OIs). They are also monitored after therapy initiation to roughly assess the immune response to ART and to re-evaluate need for prophylaxis for OIs. Generally, the CD4 count should increase by at least 50 to 150 cells/mm^3 in the first year of therapy and an additional

50 to 100 cells/mm^3 in the second year. A lower CD4 count at the time of therapy initiation correlates to a lower potential CD4 count ceiling once therapy stability has been achieved. Patients with CD4 counts less than 200 cells/mm^3 at ART initiation rarely achieve counts greater than 500 cells/mm^3 after 4 years of therapy. Immunologic failure is the inability to appropriately mount a CD4 response to ART treatment. There is currently no known benefit to changing therapy based on immunologic failure, however, and guidelines may relax recommendations on the frequency of CD4 monitoring in the future due to unclear benefit.

The HIV viral load is the gold-standard measurement of ART effectiveness. An undetectable HIV viral load is the major goal of treatment. The viral load should be expected to drop by a factor of $\log_{10}$ copies/mL after 4 weeks of initial therapy. The viral load should then reasonably be expected to become undetectable by 16 to 24 weeks of therapy. During this initial time frame, it is advisable to monitor HIV viral load every 4 to 8 weeks (instead of the usual 3- to 6-month follow-up interval) to assess for virologic failure. Virologic failure is the inability to achieve an appropriately undetectable viral load despite administration of ART.

Once a patient has achieved an undetectable viral load, an elevation in the viral load during repeat testing could represent one of two scenarios. A temporary increase in the viral load from undetectable to 50 to 1000 copies/mL likely represents a "blip." Blips do not represent virologic failure, and the patient should be continued on the current regimen without changes. Blips should prompt an assessment of patient compliance with ART, as omitted therapy may sometimes account for a blip. A blip should also be confirmed with repeat viral load testing in 2 to 4 weeks. As viral load testing has become more sensitive over the years, blips may become a more common phenomenon, increasingly leaving determination of relevance to the clinician.

True virologic failure represents a sustained elevation in the viral load in previously undetectable patients, or the inability to fully suppress the viral load at 24 to 48 weeks of ART treatment. Virologic failure should prompt HIV resistance testing and consideration of a different ART regimen.

Viral load monitoring should always be the true metric of ART treatment success. Judging success of an ART regimen by CD4 count or clinical outcome alone may mask subclinical incomplete viral suppression. This incomplete viral suppression can lead to significant viral resistance, as this implies that the virus may be replicating in the presence of drug. Clinicians who administer ART should be especially mindful of viral resistance in patients who were previously treated in the developing world, where frequent viral load monitoring may be unavailable or unaffordable.

A recommendation to check a patient's co-receptor status (CCR5 or CXCR4) with a tropism assay is not included in Table 99.10. In general, this test should only be performed when MVC therapy is being considered. As mentioned above, MVC is generally not a medication that is used to construct an ART regimen for treatment-naïve patients. There is little utility to checking this tropism assay at the time of HIV diagnosis, as a patient's co-receptor status can change over time. If MVC is being considered, an HIV viral load of at least 1000 copies/mL is recommended to ensure accuracy of most available tropism assays. Most patients will develop at least a small subpopulation of CXCR4-using viruses 5 years after initial diagnosis. As mentioned previously, MVC has not been shown to confer benefit to patients with CXCR4 viral populations.

POSTEXPOSURE PROPHYLAXIS

Percutaneous or mucous membrane exposure to HIV-contaminated bodily fluids does confer a 0.3% and 0.09% risk of infection, respectively. Exposures in the healthcare workplace are generally related to blood and are often caused by contact with sharp objects or accidental splashes to the facial area. Additional infectious fluids that could be encountered by healthcare workers include peritoneal fluid, cerebrospinal fluid, pleural fluid, synovial fluid, pericardial fluid, and amniotic fluid. Nonoccupational exposures generally occur through voluntary or forced sexual contact and intravenous drug use.

Expert consensus guides the usage of antiretroviral therapy for postexposure prophylaxis (PEP), as no randomized prospective trials have been conducted in this area. For occupational exposures, the HIV status of the reference patient and the severity of the exposure contribute to the risk of transmission. In general, inoculation of HIV-infected blood into a vein or artery, deep injury, hollow-bore needle injury, or exposure to fluids from patients with a high viral load increase the risk of infection to the exposed individual. Exposures involving a patient on

ART with an undetectable viral load do not completely eliminate the risk of transmission. Mucous membrane exposure, such as eye splashes, has also been implicated in HIV occupational transmissions.

When treatment is indicated, it should ideally be initiated within 4 hours of exposure. Duration of therapy should be 28 days. Initiation of PEP is generally not recommended beyond 72 hours of exposure, although no definitive human studies exist to define the true interval in which PEP initiation might be effective at preventing infection.

Prior PEP guidelines from 2005 for occupational exposures recommended a risk assessment of the exposure. Based on a determination of low or high risk, an ART regimen of either two or three drugs was recommended. To avoid ambiguity, updated 2013 guidelines recommend a full three-drug (or more) ART regimen for PEP for all healthcare workers with an HIV exposure, especially with newer, better-tolerated medications available. In general, two NRTIs in combination with an NNRTI, a PI, or an INSTI is indicated, although special considerations must be made regarding resistance of the infected patient's virus, drug–drug interactions, pregnancy status, etc. While there is minimal data to suggest ART administered to nursing mothers for 28 days confers toxicity to infants who are breastfeeding, this potential risk along with risk for HIV transmission via breast milk make it reasonable to advise mothers to abstain from breastfeeding during a course of PEP.

Side effects of ART are major barriers to completion of the full 28 days of therapy by healthcare workers. Anecdotal reports from HIV providers indicate that noninfected healthcare workers taking ART for PEP seem to tolerate these medications poorly compared to patients infected with HIV. Therefore, selection of a PEP regimen should emphasize tolerability. Many experts recommend TDF/FTC in combination with RAL due to its tolerability (as well as the theoretical benefit of rapidly dropping the viral load as discussed previously).

Of special note, NVP should never be administered as PEP, as severe hepatotoxicity may occur.

If a reference patient's HIV status is unknown after an occupational exposure, testing should be offered to the reference patient, and PEP for the healthcare worker should be discontinued if the reference patient is found to be negative for HIV. While a concern, no documented transmissions have occurred during the "window" period of acute infection when a patient has a detectable viral RNA level, but has not yet developed a positive HIV antibody.

Table 99.11 Recommendations for nPEP regimens (2005 Guidelines)[2]

Recommendation	Regimen
Preferred	EFV + (TDF or AZT)/(FTC or 3TC)
Preferred	LPV/r + AZT/(FTC or 3TC)
Alternative	EFV + (ABC or ddI or d4T) + (FTC or 3TC)
Alternative	ATV + (FTC or 3TC) + [(AZT or d4T or ABC) or (TDF/r)]
Alternative	FPV + (FTC or 3TC) + [(AZT or d4T) or (ABC or TDF or ddI)]
Alternative	FPV/r + (FTC or 3TC) + (TDF or ABC or ddI or d4T)
Alternative	IDV/r + (FTC or 3TC) + (TDF or ABC or ddI or d4T)
Alternative	LPV/r + (FTC or 3TC) + (TDF or ABC or ddI or d4T)
Alternative	NFV + (FTC or 3TC) + (TDF or AZT or ddI or d4T)
Alternative	SQV/r + (FTC or 3TC) + (TDF or ABC or AZT or ddI or d4T)
Third-line	ABC + 3TC + AZT

PEP in the setting of a nonoccupational exposure (nPEP) is recommended within 72 hours of exposure to bodily fluids such as blood, semen, vaginal or rectal secretions, or breast milk from a known HIV-positive contact. It may also be indicated on a case-by-case basis when the HIV status of the assailant is unknown, such as for victims of sexual assault. Again, treatment should begin promptly and continue for a 28-day course. A three-drug regimen is used for nPEP. Guidelines for nPEP have not been updated since 2005, and currently the preferred regimens are EFV- or LPV/r-based. See Table 99.11 for recommended regimens for nPEP.

PRE-EXPOSURE PROPHYLAXIS

Pre-exposure prophylaxis (PrEP) is the administration of ART to an HIV-negative patient who is at high risk for acquiring HIV infection. In general, these patients are sexually active with a known HIV-positive partner or with partners at high risk for HIV disease. While minimizing the viral load in the HIV-positive patient is protective, patients with undetectable plasma HIV RNA levels may still harbor viral RNA in significant quantity in the genital region. Compared to the plasma viral load, the genital viral RNA concentration is a more important risk factor for

transmission, yet testing for this metric is not widely available. Therefore, PrEP has been considered as an adjunct to condom use to minimize HIV transmission to the uninfected patient who partakes in high-risk sexual situations, even in cases where an infected partner may have an undetectable serum viral load.

Several clinical trials have evaluated the use of PrEP in both heterosexual and homosexual patients. These studies employed either daily single-drug TDF or a TDF/FTC oral combination and/or the use of a topical TDF gel. In general, patient compliance in these trials was not ideal; however, patients who adhered to their medication appeared to significantly reduce their risk of infection.

iPrEx studied TDF/FTC in men who have sex with men. Partners PrEP examined both TDF and TDF/FTC in HIV-discordant heterosexual couples, and TDF2 examined TDF/FTC in heterosexual men and women as well. These studies used TDF blood level examinations to confirm adherence, and each demonstrated benefit for patients who took their medications.

Fem-PrEP and VOICE, two PrEP trials of heterosexual women in Africa, each failed to demonstrate benefit of TDF or TDF/FTC. Overall patient compliance in these trials was poor.

Updated 2013 guidelines now recommend consideration of PrEP in patients at risk for HIV through the use of intravenous drugs as well. A trial from Bangkok demonstrated benefit using TDF. Again, patients that were compliant with their medications had the greatest level of protection.

Major concerns do exist with PrEP, especially in those patients who might still become infected with HIV despite taking PrEP. As mentioned, the PrEP regimen is not a full three-drug ART treatment regimen, and therefore viral resistance may quickly develop to the PrEP drugs should infection occur. A negative HIV status must be confirmed prior to PrEP initiation and should be monitored frequently throughout therapy, as a new positive result should prompt immediate full three-drug ART therapy. Patients who are unwilling or unable to undergo frequent monitoring may pose a risk to themselves (potential for development of a resistant HIV virus) and to the community (potential to transmit a resistant HIV infection).

As mentioned previously, compliance was not ideal in virtually all PrEP trials. Such results likely imply a general impracticality in the expectation that healthy, at-risk patients will take PrEP reliably. The benefit appears to be highest in extremely motivated patients who will take PrEP faithfully as prescribed. Predicting which patients these may be will be a significant challenge to practitioners.

Other considerations must be made prior to starting PrEP as well. A patient's HBV status should be assessed. Willingness of patients to undergo interval lab testing should be evaluated. Females taking PrEP who may become or recently became pregnant should have risks and benefits to the fetus clearly discussed. Ideally, uninfected females taking PrEP who become pregnant should abstain from further high-risk sexual contact to fully minimize their risk of contracting HIV during their pregnancy. Since TDF is a primary medication in this regimen, PrEP should not be offered to patients with renal dysfunction. There are no data available for the use of PrEP in the setting where a monogamous HIV-positive partner is currently taking ART therapy.

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

HIV-positive patients who are initiated on ART at a low baseline CD4 count (usually less than 100 cells/mm^3) may be at risk for immune reconstitution inflammatory syndrome (IRIS). In this patient population, hosts may be unable to mount an appropriate immune inflammatory defense response, and OIs may exist in the absence of significant symptoms. As the immune system is restored with ART treatment, these subclinical infections can stimulate an aggressive inflammatory reaction. This reaction usually involves infected organ systems, and is generally more common and profound in patients with disseminated OIs and high titers of pathogen. Autoimmune IRIS reactions that are unrelated to a known OI have also been described.

IRIS is a clinical diagnosis that may be difficult to discern from a true new infection or drug reaction. Once IRIS is considered the most likely possibility, nonsteroidal anti-inflammatory or corticosteroid medications may be considered depending on severity.

Some controversy exists with regard to the timing of ART initiation in newly diagnosed AIDS patients with active OIs. A concern has been that starting ART in the setting of a known OI might provoke an IRIS response that could compromise the health of the patient. Limited data suggest that ART therapy should be initiated earlier rather

Table 99.12 Amino acid abbreviations

Alanine	A
Arginine	R
Asparagine	N
Aspartic acid	D
Cysteine	C
Glutamic acid	E
Glutamine	Q
Glycine	G
Histidine	H
Isoleucine	I
Leucine	L
Lysine	K
Methionine	M
Phenylalanine	F
Proline	P
Serine	S
Threonine	T
Tryptophan	W
Tyrosine	Y
Valine	V

Table 99.13 Strength of recommendations

A	Strong support
B	Moderate support
C	Limited support

Table 99.14 Quality of recommendations

Ia	Evidence from one or more randomized controlled clinical trials published in the peer-reviewed literature
Ib	Evidence from one or more randomized controlled clinical trials presented in abstract form at peer-reviewed scientific meetings
IIa	Evidence from nonrandomized clinical trials or cohort or case–control studies published in the peer-reviewed literature
IIb	Evidence from nonrandomized clinical trials or cohort or case–control studies presented in abstract form at peer-reviewed scientific meetings
III	Recommendation based on the panel's analysis of the accumulated available evidence

than later in these patients (Table 99.5), although care should be taken in certain special situations. For example, caution should be taken with patients with cryptococcal meningitis. A randomized clinical trial from Zimbabwe in patients with cryptococcal meningitis compared ART administration in a group 72 hours after diagnosis and in a second group after 10 weeks of fluconazole administration. The early-treatment group had over 2.5 times the risk of death. Therefore, the general recommendation is to delay ART for patients with cryptococcal meningitis until they have received at least 2 to 10 weeks of antifungal therapy.

Patients with most OIs or active tuberculosis with a CD4 count <50 cells/mm^3 should be started on ART within 2 weeks of OI diagnosis and/or initiation of anti-tuberculosis treatment. Patients with active tuberculosis infection with a CD4 count ≥ 50 cells/mm^3 should be started on ART within 8 to 10 weeks of anti-tuberculosis treatment initiation. Timing of ART initiation in patients with tuberculosis meningitis is less certain. A Vietnamese study demonstrated no significant outcome improvement and more adverse effects in patients started on immediate ART in this setting versus patients started on 2-month delayed ART (tuberculosis treatment was started immediately in both groups). However, because of a sense of better patient monitoring in the United States, a grade CIII recommendation exists to initiate patients with tuberculosis meningitis and HIV on ART immediately (Tables 99.12, 99.13 and 99.14).

SUGGESTED READING

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100. Immune reconstitution inflammatory syndrome (IRIS)

Suzaan Marais and Graeme Meintjes

INTRODUCTION

In the majority of patients with advanced human immunodeficiency virus (HIV) disease, treatment with antiretroviral therapy (ART) results in a decreased HIV viral load, increased CD4 count, improved immunologic function, and subsequently, reduced opportunistic infections (OIs) and mortality. During the early stages of immune recovery on ART, up to 25% of patients experience clinical deterioration due to the immune reconstitution inflammatory syndrome (IRIS). IRIS typically occurs during the initial 3 months of ART (when there is rapid reversal of the immunosuppressed state) as the result of a dysregulated immune response directed at infective or, less commonly, noninfective antigens. The majority of IRIS cases are associated with mycobacterial, fungal, or viral infections. However, IRIS may also be associated with other diseases (Table 100.1). Selected significant IRIS manifestations are discussed in further sections. Cutaneous IRIS manifestations are common and are highlighted in Table 100.1.

Two forms of infective IRIS are recognized: (1) paradoxical IRIS (p-IRIS), in which an OI is diagnosed and treated appropriately prior to starting ART with the subsequent development of recurrent, worsening or new symptoms and signs after starting ART and (2) unmasking IRIS (u-IRIS), in which a previously present but clinically undetected and therefore untreated OI becomes apparent after starting ART, typically with an unusually exaggerated inflammatory presentation (Figure 100.1). In both scenarios the spectrum of IRIS manifestations vary considerably; these may be localized or involve multiple organ systems and systemic inflammatory signs may be prominent. IRIS may be mild and self-limiting lasting days to weeks, or persist for years. In a small proportion of cases IRIS may be life-threatening or fatal, particularly in forms that involve the central nervous system (CNS) and those that result in airway compromise, organ failure, or organ rupture (Table 100.2). Risk factors associated with IRIS include a low CD4 count (particularly <50 cells/mm^3), high HIV viral load (5 $\log_{10}$), high pathogen load related to the OI, a rapid decline in HIV viral load and/or rise in CD4 count on ART, and short interval between initiation of OI treatment and ART. As no confirmatory tests exist, the diagnosis of p-IRIS relies on identifying the characteristic sequence of clinical events and exclusion of other possible causes for clinical deterioration such as drug reaction or toxicity, failure of treatment for the OI (due to poor adherence, drug malabsorption or antimicrobial drug resistance), or an alternative/additional infection or malignancy. U-IRIS is diagnosed using standard diagnostic tests for the underlying infection.

GENERAL PRINCIPLES IN INFECTIVE IRIS PREVENTION AND MANAGEMENT

Prior to starting ART, thorough screening for OIs and when diagnosed initiation of appropriate treatment will prevent some cases of u-IRIS. A short interval between OI treatment and ART initiation is a strong risk factor for p-IRIS. However, delaying ART comes at the cost of remaining vulnerable to HIV disease progression, additional OIs, and mortality, particularly in severely immunosuppressed patients. The optimal time for starting ART depends on the underlying OI and will be discussed in relevant sections below.

A key component of management is optimal therapy of the OI. Anti-inflammatory therapy should be considered to alleviate symptoms and reduce inflammation particularly in more severe cases. Nonsteroidal anti-inflammatory drugs (NSAIDs) may provide symptomatic relief in patients with mild IRIS manifestations. Corticosteroids are the most frequently used anti-inflammatory drugs, particularly in severe cases, and it is the only treatment modality for

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Table 100.1 Infectious causes and noninfective manifestations of IRIS

Infections	Other conditions
Mycobacteria	**Autoimmune**
Tuberculosis	Systemic lupus erythematosus (SLE), lupus-like disease
Nontuberculous mycobacteria, especially *Mycobacterium avium* complex	Thyroid disease
Leprosy	Rheumatoid arthritis
Bacille Calmette–Guérin	Guillain–Barré syndrome
Fungi	Reiter's syndrome
Cryptococcus	Polymyositis
Pneumocystis	Relapsing polychondritis
Histoplasma	Alopecia
Candida	Cerebral vasculitis
Trichophyton rubrum	Idiopathic thrombocytopenic purpura
Penicillium marneffei	Poststreptococcal glomerulonephritis
Coccidioides	Vitiligo
Viruses	Nephrotic syndrome
Herpes simplex virus[a]	Auto-immune hepatitis
Herpes zoster virus[a]	Thrombotic thrombocytopenic purpura
Cytomegalovirus	**Other inflammatory conditions**
JC polyomavirus	Sarcoidosis
Hepatitis B and C virus	Foreign-body reaction
Molluscum contagiosum[a]	Folliculitis[a]
Human papilloma virus[a]	Lymphoid interstitial pneumonitis
Polyoma BK virus	Photodermatitis
HIV encephalitis	Peyronie's disease
Parvovirus B19	Dermatofibromata
Human T lymphotropic virus type-2	Dyshidrosis
Epstein–Barr virus	Gouty arthritis
Protozoa	**Malignancy**
Toxoplasma	Kaposi's sarcoma
Microsporidia	
Leishmania	
Cryptosporidia	
Helminths	
Schistosoma	
Strongyloides	
Bacteria	
Bartonella	
Proprionibacteria[a]	
Klebsiella	
Arthropods	
Sarcoptes scabiei	

[a] Common causes and manifestations of cutaneous IRIS.

which supportive clinical trial data exist. However, corticosteroids should generally only be considered when the diagnosis of IRIS has been made with certainty, having excluded alternative causes for clinical deterioration. Corticosteroids should normally not be used in patients with Kaposi's sarcoma and chronic hepatitis B (HBV) infection as they may worsen these conditions. There are isolated case reports of clinical response when other immunomodulatory drugs such as thalidomide and adalimumab were used to treat IRIS, but such approaches remain experimental. ART should not be interrupted in IRIS cases as this may increase vulnerability to other OIs and predispose to ART drug resistance. IRIS may also recur after ART reinitiation. ART interruption may be considered, however, as a last resort for patients with life-threatening IRIS, particularly those nonresponsive to corticosteroid therapy.

PATHOGEN-SPECIFIC IRIS MANIFESTATIONS

Tuberculosis (TB)

TB-IRIS is one of the most frequent forms of IRIS in countries where TB/HIV coinfection rates are high. P-TB-IRIS occurs in 8% to 54% of patients who start ART while on TB treatment, typically 1 to 3 weeks, but up to 3 months, after starting ART. Presenting features relate to inflammation at previously recognized and/or new TB disease sites. Common symptoms and signs include fever, cough, tachycardia, lymphadenitis, pulmonary infiltrates (Figure 100.2), serous effusions, and tender hepatomegaly. Other manifestations include abscesses and osteitis. Neurologic TB-IRIS occurs in a substantial proportion of p-TB-IRIS cases (12% in one series) and presents as meningitis (Figure 100.3), intracranial tuberculomata, radiculomyelitis, spinal epidural abscesses, or brain abscesses. Although p-TB-IRIS is usually a self-limiting condition with a reported mortality of 3.2%, neurologic forms are frequently fatal. The average symptom duration for p-TB-IRIS is 2 to 3 months, but in a minority TB-IRIS is prolonged, lasting for months to years. Of particular importance in making the diagnosis

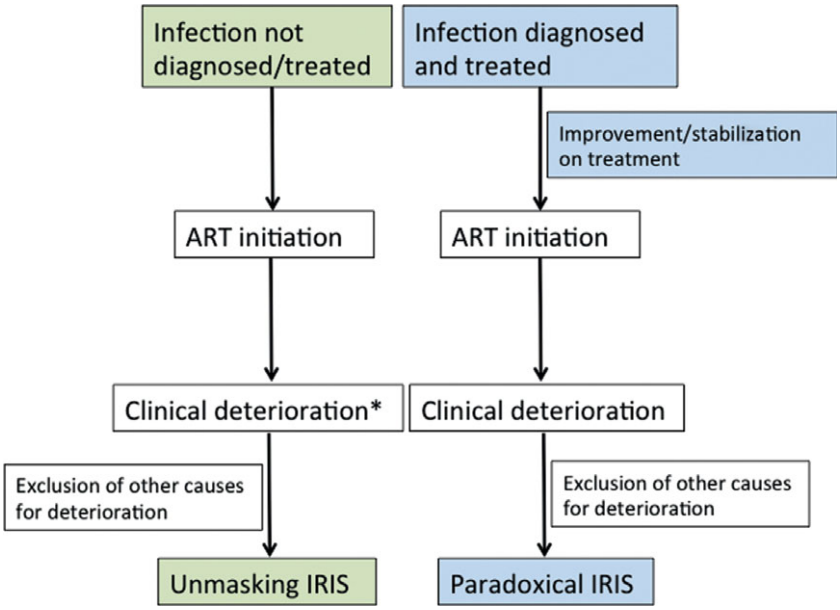

Figure 100.1 Schematic representation of the typical sequence of events associated with the two forms of infective IRIS: unmasking (green) and paradoxical (blue). * = Characterized by heightened inflammatory features; ART = antiretroviral therapy.

is the exclusion of drug-resistant TB, which may present indistinguishable from p-TB-IRIS associated with drug-susceptible TB. Superficial and fluctuant lymph nodes can be aspirated and large deep collections such as psoas abscesses may be drained under ultrasound guidance, to provide symptomatic relief and to obtain a specimen to rule out drug-resistant TB. The use of anti-inflammatory drug treatment depends on disease severity. Corticosteroid treatment (at a starting dose of 1 to 2 mg/kg/day of prednisone, or its equivalent, for 2 to 4 weeks and thereafter tapered based on individual clinical response) is indicated for life-threatening forms and may provide symptomatic relief for other cases with significant symptoms. The only randomized controlled trial (RCT) to assess treatment for any form of IRIS compared prednisone with placebo for the treatment of p-TB-IRIS, excluding patients with immediately life-threatening TB-IRIS. Patients in the prednisone arm received 1.5 mg/kg/day for 2 weeks followed by 0.75 mg/kg/day for a further 2 weeks. Prednisone was associated with a significant reduction in number of days hospitalized and also resulted in more rapid symptom and radiologic improvement.

Evidence from three RCTs suggests that the optimal time to start ART in severely immunosuppressed TB patients (CD4 <50 cells/mm^3) is 2 to 4 weeks after TB treatment initiation. Starting ART at this time point (compared with 8 to 12 weeks) was associated with a survival benefit in one trial and a reduction in AIDS progression and mortality as a combined end point in the others, even though earlier ART increased the incidence of TB-IRIS 2- to 5-fold. Thus ART cannot be deferred for IRIS prevention in patients with very low CD4 counts. TB meningitis (TBM) patients are at higher risk of developing life-threatening neurologic TB-IRIS and early ART was associated with more severe adverse events in an RCT of ART timing in TBM patients. Hence certain guidelines recommend deferring ART until 4 to 6 weeks after TB treatment initiation in TBM patients.

U-TB-IRIS is diagnosed in patients who present with unusually inflammatory or accelerated features of TB during the first 3 months of ART. Examples include unmasking pulmonary TB-IRIS presenting with rapid onset of respiratory symptoms and respiratory distress, mimicking bacterial pneumonia, and suppurative lymphadenitis. A high index of suspicion for TB should be maintained in TB endemic settings in all patients who present with clinical deterioration after starting ART. When diagnosed, standard TB treatment should be initiated.

Cryptococcosis

Cryptococcal IRIS most commonly presents with meningitis which is a major cause of death during early ART in resource-poor settings. Paradoxical cryptococcal meningitis (p-CM)-IRIS occurs in up to 30% of CM patients who commence ART.

Table 100.2. Causes and manifestations of IRIS reported that are potentially life-threatening

Causes	Manifestations
Neurologic manifestations	
Tuberculosis	Meningitis, intracerebral space-occupying lesions, spinal epidural abscess
Nontuberculous mycobacteria	Meningoencephalitis, brain abscess
JC virus	Progressive multifocal leukoencephalopathy
Cytomegalovirus	Encephalitis, vasculitis, ventriculitis
Herpes simplex virus	Encephalitis
Herpes zoster virus	Meningoencephalitis, vasculitis
Candida	Meningitis, vasculitis
Parvovirus B19	Encephalitis
BK virus	Meningoencephalitis
Toxoplasma	Encephalitis
Auto-immune reaction	Demyelinating central nervous system disease, cerebral vasculitis, Guillain–Barré syndrome
HIV itself the target of IRIS	Meningoencephalitis
Cryptococcus	Meningitis, intracerebral space-occupying lesions, cerebellitis
Coccidioides	Meningitis
Extraneural manifestations	
Kaposi's sarcoma	Pneumonitis, airway and gastrointestinal tract involvement
Tuberculosis	Splenic rupture, bowel perforation, airway compression by lymph nodes, pericardial effusion, and acute renal failure
Nontuberculous mycobacteria	Airway compression by lymph nodes, alveolitis
Hepatitis B and C virus	Fulminant liver failure, progression of liver cirrhosis
Bacille Calmette–Guérin	Disseminated disease
Pneumocystis	Pneumonitis

Other CNS manifestations include intracranial cryptococcomas or abscesses, cerebellitis, and spinal cord abscesses. Extra-CNS manifestations such as fever, lymphadenitis, soft-tissue and skin lesions, cavitating or nodular pulmonary disease, choreoretinitis, and disseminated disease have also been described. The majority of cases present 1 to 2 months after ART initiation, although a minority may present after more than a year on ART. P-CM-IRIS is associated with raised intracranial pressure (ICP) in up to 75% of cases and an increased inflammatory response with higher protein and white cell concentrations in cerebrospinal fluid (CSF), when compared to those from the pre-ART CM event. Diagnostic workup for p-CM-IRIS is directed at excluding other neuroinflammatory etiologies and cryptococcal relapse as causes for deterioration by CSF analysis. A cryptococcal relapse is indicated by a positive cryptococcal CSF culture after more than 3 months of antifungal therapy or an increase in quantitative culture from pre-ART results. Amphotericin B plus flucytosine (where available) or fluconazole (induction phase doses of 800 mg/day) should be restarted pending fungal culture results in patients with severe deterioration. If the CSF is sterile, maintenance doses of fluconazole could be resumed. Aggressive management of raised ICP with daily lumbar puncture, where required, is critical in the management of p-CM-IRIS. Although no clinical trial data exist, prednisone (1 mg/kg/day, or equivalent, tapered over 2 to 6 weeks) should be considered in patients with ongoing symptoms or life-threatening neurologic impairment, but ideally only after cryptococcal relapse has been excluded.

Starting ART early (within 1 to 2 weeks from CM diagnosis versus 4 to 5 weeks) is associated with increased mortality in CM patients and ART should be deferred until 4 to 6 weeks of antifungal treatment have been received.

Unmasking cryptococcal IRIS presents during the initial months of ART with manifestations such as meningitis with a particularly high CSF white cell count (for example >50 cells $\times 10^6$/L) or a raised opening pressure refractory to treatment, suppurative lymphadenitis, rapidly expanding CNS lesions (cryptococcomas), and cavitating or necrotic pneumonitis. A clear distinction between CM cases first diagnosed after ART that are related to immune reconstitution and those that are related to persistent immunosuppression may be difficult; therefore, these two groups are collectively referred to as "ART-associated CM." In resource-limited settings currently at least a third of all new CM cases are diagnosed in patients on ART. An important preventative strategy for ART-associated CM in high-burden settings involves screening patients with CD4 counts <100 cells/mm^3 for subclinical cryptococcal infection prior to ART using blood cryptococcal antigen test. A positive test is highly predictive of subsequent ART-associated CM and such patients should have meningitis excluded. If no meningitis is diagnosed they should be treated pre-emptively with fluconazole at a starting dose of 800 mg daily.

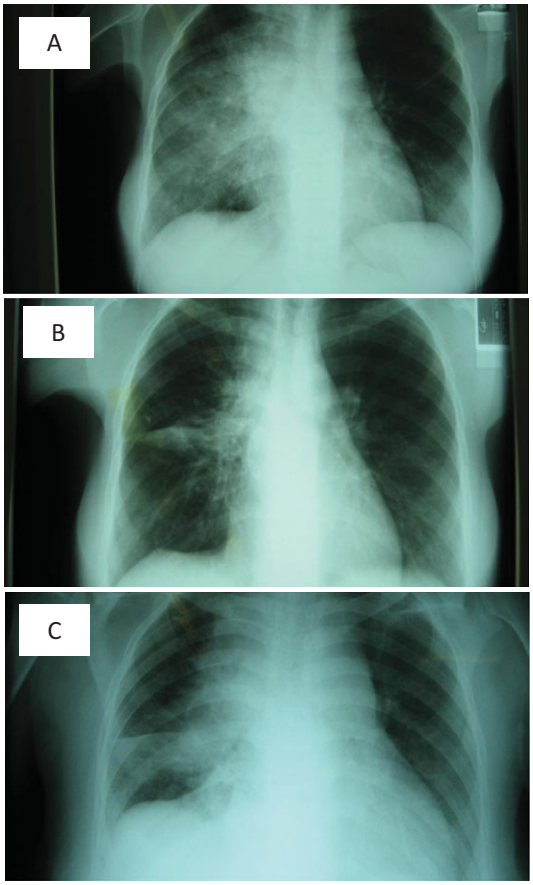

Figure 100.2 Chest radiograph sequence in a patient with paradoxical TB-IRIS: (A) at time of TB diagnosis, (B) improvement on TB treatment prior to ART, (C) worsening of pulmonary infiltrate and mediastinal lymph node enlargement at the time of IRIS presentation.

JC virus

Reactivation of the JC virus results in progressive multifocal leukoencephalopathy (PML), a demyelinating disease of the brain, usually diagnosed in patients with CD4 counts <100 cells/mm^3. Both u-PML-IRIS and p-PML-IRIS are described and both are associated with a significant mortality. The majority of cases present within 3 months of ART initiation, but u-PML-IRIS may develop after more than 6 months on ART. Clinical deterioration during PML-IRIS is usually acute and may be transient, unlike the course of PML in patients not on ART. In more than 50% of PML-IRIS cases there is gadolinium enhancement on magnetic resonance imaging (MRI), which is not observed outside the context of IRIS. The diagnosis cannot rely on detecting JC virus from CSF by PCR as partial containment of viral replication by the recovering immune system can result in negative results, which is found in ~40% of PML cases receiving ART compared to ~5% of ART-naïve PML cases. Brain biopsy may be required to exclude other causes for deterioration (e.g., lymphoma). The treatment of PML-IRIS is particularly difficult, as no effective antiviral therapy for JC virus exists. Interruption of ART for 2 to 3 weeks has been associated with favorable outcome in isolated cases, but this is associated with risks and PML-IRIS may recur when ART is resumed. The role of corticosteroids is controversial, given that there is no specific treatment for the underlying JC virus infection, but may be indicated in patients with severe neurologic deterioration and those with edema on brain imaging.

Cytomegalovirus (CMV)

CMV-IRIS usually presents with eye involvement. This can manifest as a first episode of retinitis after starting ART. More commonly though, CMV-IRIS presents as immune recovery uveitis (IRU), which usually occurs in patients diagnosed with CMV retinitis prior to ART who subsequently experience an increase in CD4 count on ART. IRU can also be unmasked by ART. Rarely, CMV-IRIS may affect other organs such as the colon, esophagus, or brain. The cumulative incidence of p-CMV-IRU is 38% and patients with the greatest retinal involvement (>30% of the retinal surface) during the pre-ART retinitis episode are at highest risk for IRU. CMV-IRU is distinguished clinically from typical CMV retinitis by the abundance of intraocular inflammatory cells, and inactive CMV retinitis in the former. The spectrum of IRU inflammation ranges from asymptomatic vitritis to persistent uveitis with cystoid macular edema (CME) and epiretinal membrane formation. Worsening retinitis due to active CMV infection, and persistent visual symptoms due to vitreous debri relating to previous CMV retinitis as well as new OIs should be considered in the differential diagnosis. The treatment of CMV-IRU varies according to disease severity. Cases with mild CME and visual acuity more than 20/30 can be observed without treatment. In more severe cases, periorbital or intravitreal corticosteroid injections usually result in decreased inflammation, but these treatments are not always associated with improved vision.

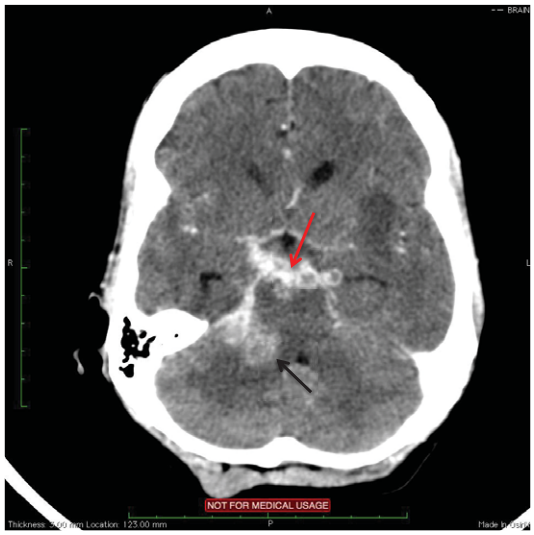

Figure 100.3 Computed tomography brain findings in a patient who developed TB meningitis-IRIS. Post-contrast imaging shows marked basal meningeal enhancement (red arrow) and multiple ring-enhancing lesions (red and black arrow) at IRIS presentation.

Hepatitis B and C viruses

ART initiation is frequently complicated by liver enzyme elevation (LEE). Patients coinfected with HBV or hepatitis C virus (HCV) are at increased risk, because they are predisposed to drug-induced liver injury but also because of enhanced immune responses directed at the hepatitis virus. Hepatitis-IRIS is poorly defined, but significant LEE (rise of alanine aminotransferase [ALT] $>$ 5 $\times$ upper limit of normal, or $>$ 3 $\times$ of baseline if abnormal prior to ART), particularly within 3 months of starting ART, should prompt consideration of the diagnosis. Rarely, hepatitis-IRIS has been associated with severe hepatic dysfunction resulting in fulminant hepatic failure or life-threatening progression of cirrhosis. The diagnosis of hepatitis-IRIS is challenging as the most important differential diagnosis is drug-induced liver injury. Risk factors for hepatic flares on ART in HBV coinfection include high HBV DNA and ALT levels before ART. There are no evidence-based guidelines for managing hepatitis-IRIS. It has been suggested that HBV or HCV should be treated prior to ART initiation to minimize the risk of hepatitis-IRIS in high-risk cases (e.g., those with underlying liver cirrhosis). A pragmatic approach to a patient with chronic viral hepatitis with significant LEE on ART includes the following: (1) stop hepatotoxic non-ART drugs, (2) exclude alternative causes, as far as possible, (3) alter ART (if necessary) to exclude drugs with the highest risk for hepatotoxicity (especially nevirapine) and maintain patients coinfected with HBV on an effective ART regimen that contains two drugs also active against HBV (e.g., tenofovir and either lamivudine or emtricitabine), (4) monitor liver function tests and clinical status closely and consider liver biopsy if no improvement, (5) interrupt ART if hepatic failure occurs and restart once liver enzymes are normalizing. In HBV coinfected patients, an HBV active drug should be continued during ART interruption to prevent viral rebound. None of the HIV drugs is effective against HCV and treatment with anti-HCV therapy should be considered during ART interruption in affected patients. Corticosteroids and other immunosuppressive drugs should be avoided in hepatitis-IRIS as they may result in increased viral replication and hepatic deterioration.

Kaposi's sarcoma

Kaposi's sarcoma (KS) is caused by the Kaposi's sarcoma-associated herpesvirus (KSHV) and is the most common malignancy in HIV-infected persons. Although starting ART is associated with the resolution or improvement of KS lesions in most patients, p-KS-IRIS occurs in approximately 14% of patients with KS at a median time of 7 weeks on ART. U-KS-IRIS has also been reported. KS-IRIS cases present with new lesions, or inflammation or enlargement of existing skin lesions. Lymphedema, oral, gastrointestinal, airway, and lung involvement are other manifestations. KS-IRIS is frequently fatal in settings with limited access to chemotherapy, with mortality of 48% reported for p-KS-IRIS in an African cohort. Pre-ART risk factors for p-KS-IRIS include more extensive KS disease, high plasma HIV-1 viral load ($>5\log_{10}$), detectable plasma KSHV DNA, and not receiving KS treatment (chemotherapy). P-KS-IRIS might be prevented by administering chemotherapy, particularly in severe cases, prior to ART. Treatment of KS-IRIS similarly includes systemic chemotherapy and/or localized radiotherapy. Corticosteroids may result in rapid progression of existing, or new, KS lesions and are therefore not used for KS-IRIS.

IRIS UNRELATED TO HIV INFECTION

IRIS is best described in the context of ART treatment of HIV infection, but it is also recognized in persons recovering from other causes of immune

suppression, such as patients who are postpartum or who interrupt immune suppressive drugs (e.g., tumor necrosis factor [TNF] inhibitors, natalizumab, and drugs used in solid organ/stem cell transplants). Further discussion is beyond the scope of this chapter and the reader is referred to the review by Sun *et al*. (see suggested reading).

IRIS PATHOGENESIS

Central to the pathogenesis of most forms of ART-related IRIS is the rapid recovery of immune function in the presence of large amounts of infective antigen. Several components of the immune system have been implicated including activated antigen-specific CD4 and CD8 T lymphocytes, macrophages and monocytes, neutrophils, natural killer (NK) cells, and pro-inflammatory cytokines and chemokines. The hallmark of the tissue pathology associated with mycobacterial and fungal IRIS is granuloma formation sometimes with suppuration. Viral forms of IRIS are characterized by CD8 T-cell infiltrates.

CONCLUSION

IRIS may complicate ART initiation in up to 25% of patients. The major underlying determinant of IRIS is progression to advanced HIV disease that places individuals at risk of OIs. In resource-poor settings many patients still enter HIV care with advanced HIV and remain at risk for IRIS. Because there is no confirmatory test for IRIS it is a clinical diagnosis and other causes of deterioration should be excluded. In most cases ART is continued, treatment for the underlying infection should be optimized, and for mycobacterial and fungal forms of IRIS corticosteroids can be considered when symptoms are significant. There is RCT evidence to support the use of steroids in p-TB-IRIS but in other forms of IRIS their use is based on anecdotal evidence of benefit.

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101. Differential diagnosis and management of HIV-associated opportunistic infections

Anthony Ogedegbe and Marshall J. Glesby

Timely recognition and treatment of human immunodeficiency virus (HIV)-associated opportunistic infections (OIs) remains an important skill for practicing physicians worldwide. Whereas the overall incidence of these infections has fallen sharply since the advent of highly active antiretroviral therapy (HAART), OIs remain the single most serious threat to well-being and survival amongst HIV-infected individuals. Despite improved access to testing globally, all too often the first indication of underlying HIV infection is *not* routine screening but rather overt stigmata of one or more OIs. Lack of familiarity with these disorders delays key HIV interventions – such as safe sex counseling and antiretroviral therapy – and leads to worse clinical as well as public health outcomes.

With most OIs, the likelihood of active disease rises sharply at specific CD4-count thresholds (Figure 101.1). Periodic CD4 measurements are therefore an integral part of both OI treatment and prevention. This chapter offers a systems-based overview of presenting signs and symptoms of the most commonly encountered OIs. Current concepts and approaches to management are also discussed.

MUCOCUTANEOUS INFECTIONS

Thrush and angular cheilitis are the major manifestations of oropharyngeal candidal infection in HIV-infected patients. Thrush is particularly common and often heralds the presence of other more serious OIs (Figure 101.1). It typically presents as asymptomatic, white, loosely adherent deposits on the dorsum of the tongue but frequently extends posteriorly to involve the palate and oropharynx. Severe cases are

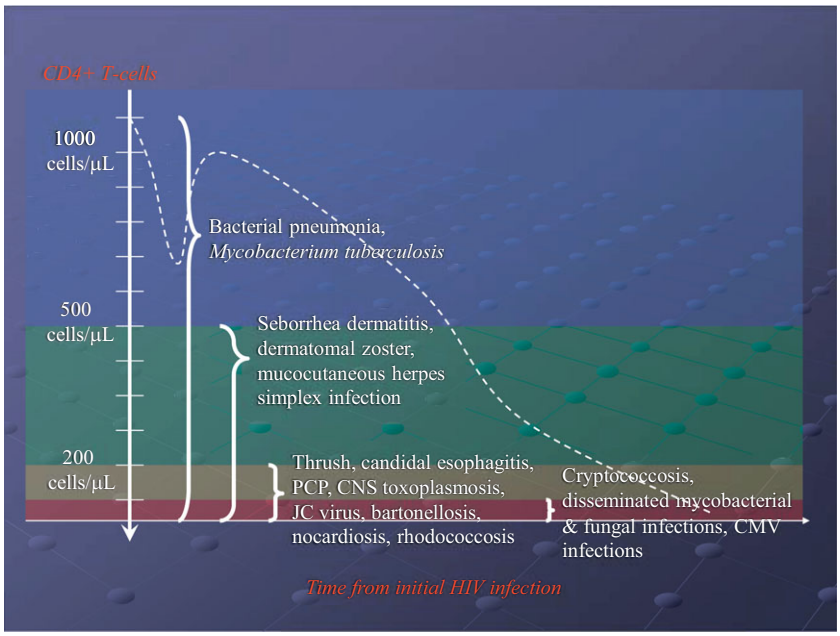

Figure 101.1 Spectrum of opportunistic infections in untreated HIV infection and the CD4-T-cell-count ranges in which they manifest. CMV = cytomegalovirus; CNS = central nervous system; PCP = *Pneumocystis jirovecii* pneumonia.

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Table 101.1 Management of mucocutaneous opportunistic infections

Condition/pathogen	First-line treatment	Notes
Thrush or candidal angular cheilitis	Clotrimazole troches, 10 mg PO 5 × daily; nystatin solution, swish and swallow QID; or fluconazole, 100–200 mg PO qd for 7–14 days	In the event of azole resistance: amphotericin B suspension, 100 mg/mL PO QID; amphotericin B deoxycholate, 0.3–0.7 mg/kg IV qd; liposomal or lipid complex amphotericin, 3–5 mg/kg; voriconazole, 200 mg PO qd; or caspofungin 50 mg IV qd for 7–14 days
Seborrhea dermatitis	Face: imidazole cream (ketoconazole 2% or clotrimazole 1%) plus hydrocortisone 1.0%–2.5% or desonide 0.05% cream BID Scalp/body: antidandruff shampoo (e.g., Selsun Blue or Head and Shoulders) plus triamcinolone 0.1% cream (body) or solution (scalp)	Severe cases may require addition of oral ketoconazole, 200–400 mg qd for 2–4 weeks
Varicella-zoster virus	Acyclovir, 800 mg PO 5 × daily; famciclovir, 500 mg PO TID; or valacyclovir, 1000 mg PO TID for 7–10 days	(1) Trigeminal or disseminated cutaneous zoster; attendant meningoencephalitis; or evidence of visceral involvement (i.e., elevated transaminases and/or pancreatic enzymes) all merit IV acyclovir, 10 mg/kg q8h, until clinical resolution (minimum 14–21 days). (2) In the event of acyclovir resistance: foscarnet, 40–60 mg/kg IV q8h, or cidofovir plus IV hydration and oral probenecid to mitigate renal toxicity
Herpes simplex virus	Acyclovir, 400 mg PO TID; famciclovir, 500 mg PO BID; or valacyclovir, 1000 mg PO BID for 7–14 days	In the event of acyclovir resistance: foscarnet, 40–60 mg/kg IV q8h, or cidofovir plus IV hydration and oral probenecid to mitigate renal toxicity
Molluscum contagiosum	Laser, cryotherapy, and curettage plus HAART	
Oral hairy leukoplakia (OHL)	HAART	(1) OHL is pathognomonic of underlying HIV infection. (2) Rarely warrants specific therapy; but oral acyclovir 800 mg PO 5 × daily and podophyllin have been used with variable success in severe cases

Abbreviations: PO = orally; QID = four times per day; qd = every day; BID = twice per day; TID = three times per day; HAART = highly active antiretroviral treatment; IV = intravenously.

associated with oral discomfort, dysgeusia, and nausea. Angular cheilitis is rarer and presents as painful, sometimes bleeding sores at the corners of the mouth. Treatment of both conditions consists of topical or oral antifungal therapy (Table 101.1).

Seborrhea dermatitis is a greasy, flaky, and faintly erythematous rash with a predilection for the face. Areas rich in sebaceous glands – the hairline, eyebrows, nose, and nasolabial folds – are primary targets. The role of *Malazesia furfur* infection in pathogenesis remains uncertain. Topical antifungal and corticosteroid agents are used to treat this condition (Table 101.1).

Recurrent or multidermatomal cutaneous herpes zoster infections are sometimes the only outward indication of waning cell-mediated immunity in HIV-infected adults. Lancinating pain and paresthesias in the soon-to-be involved dermatome are followed days later by the sudden outcropping of a vesicular rash on an erythematous base. Use of oral acyclovir or related agents (valacyclovir or famciclovir) within 72 hours improves symptoms, speeds up crusting, and may reduce the risk of post-herpetic neuralgia (Table 101.1).

Mucocutaneous herpes simplex virus (HSV) infections are more frequent at CD4 counts $\leq$500 cells/mm^3. These primarily manifest as painful vesicles in the genital and perirectal areas. Oral acyclovir, valacyclovir, and famciclovir are all effective in reducing the severity and duration of symptoms. They are also effective prophylactically (Table 101.1).

Molluscum contagiosum is a poxvirus that causes characteristically firm, umbilicated, and sometimes pedunculated skin lesions (Figure 101.2). Intertriginous areas of the body, namely the axillae, perineum, antecubital, and popliteal fossae, are disproportionately involved. Transmission requires intimate physical contact with an infected person. No specific chemotherapy exists; however, effective antiretroviral therapy can hasten lesion regression. Alternatively, lesions can be removed by cryotherapy, curettage, or laser cautery (Table 101.1).

Table 101.2 Etiologic correlates of radiologic findings in HIV-infected patients with pneumonia

Chest x-ray or computed tomography findings	Common pathogens
(1) Focal/lobar asymmetric consolidation *without* intrathoracic lymphadenopathy	*Streptococcus pneumoniae, Moraxella catarrhalis, Haemophilus influenzae; Mycobacterium tuberculosis* in individuals with primary infection or CD4 counts >350 cells/mm^3
(2) Diffuse interstitial or alveolar infiltrates *without* intrathoracic lymphadenopathy	*Pneumocystis jirovecii*, respiratory viruses (e.g., influenza virus and respiratory syncytial virus), *Mycoplasma pneumoniae*
(3) Reticulonodular and/or cavitating nodular infiltrates *without* intrathoracic lymphadenopathy (*acute presentations*)	*Mycoplasma pneumoniae, Staphylococcus aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa*
Reticulonodular and/or cavitating nodular infiltrates *plus* intrathoracic lymphadenopathy (*indolent presentations*)	*Mycobacterium tuberculosis, Norcardia asteroides, Aspergillus fumigatus, Rhodococcus equi*

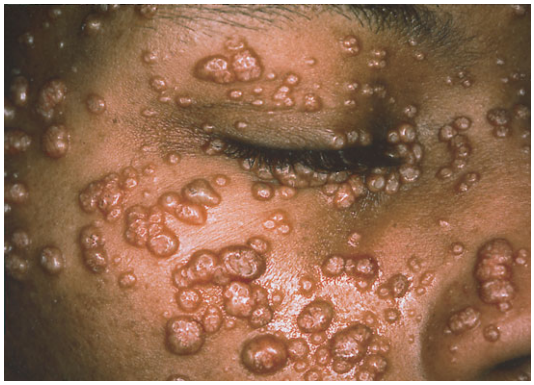

Figure 101.2 Molluscum contagiosum. Numerous flesh-colored umbilicated papules appeared on the face of a 33-year-old man with a three-year history of the acquired immunodeficiency syndrome and a CD4 cell count of 60 cells/μL. Prominent lesions along the margin of the eyelids prevented him from closing his eyes completely. Reproduced with permission from Stephanie Cotell. Cotell SL, Roholt NS. *N Engl J Med*. 1998 Mar 26;338(13):888. Northwestern University, Chicago, IL 60611, USA.

Oral hairy leukoplakia is virtually pathognomonic of underlying HIV infection. These characteristically painless, white, tightly adherent vertical ridges on the lateral aspect of the tongue are outward manifestations of Epstein–Barr virus infection of lingual squamous epithelium. Robust immune recovery through HAART is the most effective treatment for this condition (Table 101.1).

PULMONARY INFECTIONS

Three elements govern the initial evaluation and management of lower respiratory infections in HIV-positive patients: (1) prompt administration of empiric antibiotics against community-acquired or healthcare-associated pneumonia pathogens; (2) immediate respiratory isolation for individuals presenting with either symptoms or chest imaging findings concerning for pulmonary tuberculosis; and (3) early administration of empiric treatments for *Pneumocystis jirovecii* (*carinii*) pneumonia (PCP) in individuals presenting with evidence of advanced HIV disease *plus* either acute respiratory failure and/or radiographic findings suspicious for PCP (discussed below).

Computed tomography (CT) scans, given their increased sensitivity and superior image resolution over chest roentgenograms (CXR), are frequently necessary in evaluating patients with AIDS. This is particularly true in cases where the CXR shows either nodular/cavitary infiltrates or suggests the presence of mediastinal or hilar lymphadenopathy. The vast array of diagnostic possibilities in such cases (including noninfectious causes such as metastases from cancer) makes devising empiric therapeutic regimens unwieldy (Table 101.2). Thus, CT imaging is often helpful in refining and paring down empiric chemotherapeutic choices pending definitive results from sputa, bronchoscopy or lung biopsy.

Pneumocystis jirovecii pneumonia

Low-grade fever, dry cough, and progressive dyspnea are the cardinal symptoms of *Pneumocystis jirovecii* pneumonia (aka PCP). PCP is the most frequently identified cause of lower respiratory infection in HIV-infected patients. Risk factors include CD4 counts ≤ 200 cells/mm^3, CD4 percentage ≤ 14, prior PCP, and thrush. Radiographically, PCP usually presents as symmetric, perihilar interstitial or alveolar infiltrates (Figure 101.3). However, excluding PCP purely on the basis of CXR findings can be hazardous.

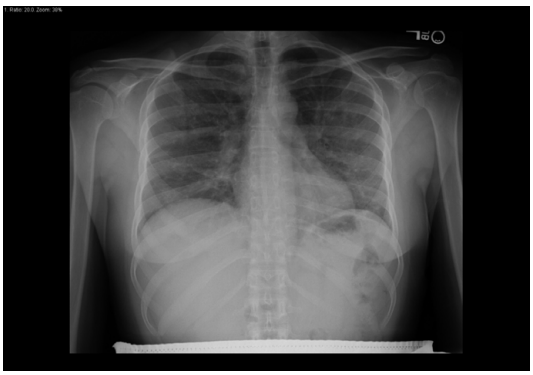

Figure 101.3 *Pneumocystis jirovecii* pneumonia (PCP). Bilateral interstitial infiltrates on chest x-ray in a 39-year-old woman with AIDS and CD4 count of 33 cells/mm^3.

For example, follow-up CTs sometimes uncover classic PCP findings where prior CXRs had either been clear or suggestive of a bacterial process. Secondly, a number of "atypical" radiographic findings – including cystic, apical, nodular, and cavitary infiltrates – have also been described in cytologically proven cases of PCP.

Intravenous trimethoprim–sulfamethoxazole (TMP–SMX) is the first-line agent for treating *severe* PCP (Table 101.3). In patients with sulfa allergies, intravenous pentamidine should be used instead. Pentamidine-related toxicities – acute pancreatitis, hypoglycemia, and renal failure – are, however, common and should be aggressively sought when using this drug. Adjunctive steroids have been shown to improve survival in individuals presenting with a PaO_2 $\leq$70 mm Hg or alveolar–arterial (A-a) gradients $>$30 mm Hg. Nonetheless, overall mortality rates, even in the post-HAART era, approach 30% and remain as high as 60% to 80% in ventilated patients.

In *mild-to-moderate* PCP, double-strength *oral* TMP–SMX is the drug of choice. Other effective oral regimens are available for individuals with sulfa allergies, including clindamycin plus primaquine, dapsone plus trimethoprim, and atovaquone (Table 101.3).

Clinical improvement in severe cases is typically protracted and can take as long as a week. Only patients failing to show improvement beyond this time period are deemed treatment failures. We advocate the following approach to such cases: (1) starting adjunctive corticosteroid therapy in situations where the initial PaO_2 or A-a gradient had suggested otherwise; (2) switching to *intravenous* TMP–SMX (or intravenous pentamidine in patients allergic to sulfa) if either *oral* TMP–SMX or a second-line agent had been used initially; and/or (3) repeating bronchoscopy and bronchoalveolar lavage to identify non-PCP respiratory co-pathogens that may have been missed during the initial diagnostic evaluation.

Mycobacterial infections

Unlike PCP, the risk of active *Mycobacterium tuberculosis* (MTB) infection in HIV-infected individuals is high even at normal CD4 counts. However, lower lobe, noncavitary, and extrapulmonary disease are more frequent at CD4 counts $\leq$350 cells/mm^3. Chemotherapy recommendations are identical to seronegative patients with pulmonary MTB except clinicians have to be mindful of higher rates of treatment failure and drug resistance in HIV-positive patients. Furthermore, dose adjustments of HAART and/or antituberculous agents are frequently necessary to avoid adverse drug interactions in patients being treated for both infections concurrently (Table 101.3).

The leading nontuberculous mycobacterial pulmonary pathogen in HIV-positive patients is *Mycobacterium avium* complex (MAC). Such cases are distinct from *disseminated* MAC (discussed below) in which severe CD4 lymphopenia and mycobacteremia are the rule. In the post-HAART era, the majority of cases of pulmonary MAC manifest within weeks of initiating HAART, leading some to posit an immunologic mechanism. Combination therapy comprising clarithromycin or azithromycin, ethambutol, and rifabutin is the treatment regimen of choice (Table 101.3).

Rarer mycobacterial causes of pneumonia in HIV-infected patients are *Mycobacterium kansasii* and the so-called "rapid-grower" mycobacteria, namely *Mycobacterium abscessus, Mycobacterium fortuitum*, and *Mycobacterium chelonae*. *M. kansasii* lung infections often mimic pulmonary MTB clinically as well as radiographically (see Table 101.3 for treatment recommendations).

Endemic mycoses

Pulmonary coccidioidomycosis, histoplasmosis, and blastomycosis primarily affect individuals with CD4 counts $\leq$250 cells/mm^3. Rates of infection are higher in endemic areas, namely the San Joaquin valley and Ohio as well as Mississippi river basins for coccidioidomycosis and histoplasmosis, respectively, and the Southeastern and

Table 101.3 Management of pulmonary opportunistic infections

Pathogen	First-line treatment	Notes
Pneumocystis jirovecii	Mild to moderate disease: TMP–SMX-DS, 2 tabs PO TID; dapsone, 100 mg PO qd, plus TMP, 5 mg/kg PO q8h; clindamycin, 450 mg PO or 600 mg IV q8h, plus primaquine, 15 mg qd; or atovaquone, 1500 mg qd for 21 d Severe disease: TMP–SMX, 15 mg/kg IV (TMP component) qd in 3–4 divided doses, or, in patients with sulfa allergy, pentamidine, 4 mg/kg IV qd, plus prednisone (40 mg BID × 5 d; 20 mg BID × 5 d; 20 mg qd × 11 d) for 21 d	(1) Caution must be taken with the use of primaquine or dapsone in patients at risk for G6PD deficiency because of the risk of hemolytic anemia. Such individuals should be tested for the latter in anticipation of exposure to these drugs. (2) May discontinue *secondary* prophylaxis after CD4 >200 cells/mm^3 for >3 mo
M. tuberculosis	Isoniazid, 5 mg/kg/d, plus rifampin, 600 mg PO qd, plus pyrazinamide, 15–30 mg/kg PO qd, plus ethambutol, 15–25 mg/kg/d as initial therapy	If patient is taking a protease inhibitor, replace rifampin with rifabutin, 150–300 mg PO qd, because rifampin significantly lowers serum levels of protease inhibitors
M. avium complex	Clarithromycin, 500 mg PO BID, or azithromycin, 600 mg qd, plus ethambutol, 15–25 mg/kg/d, plus rifabutin, 300 mg PO qd for a minimum of 12 mo	In patients on efavirenz, azithromycin is preferred over clarithromycin as part of the 3-drug regimen because efavirenz lowers the serum levels of the latter
M. kansasii	Isoniazid, 5 mg/kg/d, plus rifampin, 600 mg PO qd, plus ethambutol, 25 mg/kg/d (× 2 months then 15 mg/kg) for 15–18 mo	If patient is taking a protease inhibitor, replace rifampin with rifabutin, 150–300 mg PO qd, because rifampin significantly lowers serum levels of protease inhibitors
M. abscessus	Amikacin plus either cefoxitin or imipenem plus macrolide for 4–8 wk, followed by macrolide plus second agent for 6–12 mo	Monitor for inducible macrolide resistance
M. fortuitum	Amikacin or tobramycin plus 2 of cefoxitin or imipenem or levofloxacin for 2–6 wk followed by 2 oral agents for 12 mo	
Histoplasma capsulatum (pulmonary and non-CNS disseminated disease)	Mild-to-moderate disease: itraconazole, 200 mg PO TID for 3 d, followed by itraconazole, 200 mg BID for 12 wk Severe illness: amphotericin B deoxycholate, 0.7 mg/kg IV qd, or liposomal or lipid complex amphotericin, 3–5 mg/kg, until clinically improved followed by itraconazole, 200 mg q12h for 12 wk	
Coccidioides immitis (pulmonary and non-CNS disseminated disease)	Mild-to-moderate disease: fluconazole, 400–800 mg PO qd Severe illness: amphotericin B deoxycholate, 0.5–1.0 mg/kg IV qd, followed by fluconazole, 400–800 mg PO qd	Lifelong suppression with fluconazole, 400 mg PO qd, is recommended, even with CD4 >200 cells/mm^3 HAART
Blastomycosis dermatitidis (pulmonary and non-CNS disseminated disease)	Amphotericin B deoxycholate, 0.7–1.0 mg/kg IV qd, or liposomal amphotericin, 3–5 mg/kg, until clinically improved, followed by itraconazole, 200 mg for 12 wk	
Aspergillus fumigatus (pulmonary and non-CNS disseminated disease)	Voriconazole, 6 mg/kg IV × 1, followed by either 4 mg/kg IV or 100–200 mg PO BID for 2–3 wk; oral voriconazole for suppression	(1) Alternatives to voriconazole: amphotericin B deoxycholate; liposomal or lipid complex amphotericin 3–5 mg/kg; or caspofungin +/− voriconazole (2) Also note: when using voriconazole with efavirenz, voriconazole dose should be increased to 400 mg q12h and decrease the efavirenz to 300 mg QD
Nocardia asteroides (pulmonary and non-CNS disseminated disease)	TMP–SMX (15 mg/kg/d TMP; 75 mg/kg/d SMX) × 3 wk followed by 10 mg/kg/d TMP component PO	In severe cases: add amikacin or imipenem or third-generation cephalosporin when limited by aminoglycoside toxicity
Rhodococcus equi (pulmonary and *non-CNS* disseminated disease)	Erythromycin or imipenem, 0.5 g IV q6h, plus rifampin, 600 mg PO qd for 2 wk, followed by oral clarithromycin or azithromycin plus rifampin for suppression	Alternative agents: ciprofloxacin or linezolid

Abbreviations: TMP–SMX = trimethroprim-sulfamethoxazole; DS = double strength; PO = orally; TID = three times a day; IV = intravenously; qd = every day; BID = twice a day; CNS = central nervous system; G6PD = glucose-6-phosphate dehydrogenase; HAART = highly active antiretroviral therapy.

Midwestern United States in the case of blastomycosis. Previous residence in these regions is the main risk factor for all of these infections. In patients with higher CD4 counts, focal alveolar or nodular/cavitary infiltrates with or without intrathoracic lymphadenopathy is the common radiographic finding. Diffuse reticulonodular infiltrates, indicative of hematogenous dissemination, are, however, more common in individuals with very advanced immunodeficiency (i.e., CD4 counts $\leq$100 cells/mm^3). Life-threatening infections require induction chemotherapy with amphotericin-B-based drugs followed by maintenance treatment with oral triazoles (Table 101.3).

Pulmonary aspergillosis

Severe CD4 lymphopenia is one of several risk factors that are associated with pulmonary aspergillosis, others include neutropenia, recent exposure to corticosteroids, and even marijuana use. Two distinct clinical syndromes have been described: isolated tracheobronchitis and pneumonitis. Symptoms in both cases include fever, productive cough, chest pain, and hemoptysis. Wheezing is more indicative of tracheobronchial involvement. Bronchoscopy in such cases reveals airway-obstructing mycelia and mucous balls. However, airway invasion can also occur, resulting in the formation of pseudomembranes and ulcerations. Radiographically, a variety of patterns have been observed with parenchymal disease, including subpleural focal opacities, diffuse reticulonodular infiltrates, and cavitary apical lesions. Treatment comprises voriconazole and/or amphotericin B-based drugs (Table 101.3).

Filamentous bacteria

Pulmonary nocardiosis and rhodococcosis are rare complications of AIDS in the post-HAART era. Nocardia and rhodococcus are gram-positive, weakly acid-fast, filamentous bacteria. Both are associated with indolent to subacute lower respiratory infections. Radiographic features include nodular/cavitary pulmonary infiltrates with or without abscess formation. Concurrent mediastinal lymphadenopathy is also common. Disseminated disease with a predilection for brain and skin lesions has been observed with these organisms. Unlike nocardia where blood cultures rarely turn positive, the yield of standard blood cultures approaches 50% in rhodococcal infections. The diagnosis of pulmonary nocardiosis, on the other hand, typically requires detection of branching, filamentous, acid-fast organisms either in sputa, bronchoalveolar lavage, or lung biopsy specimens. Chemotherapy is protracted in both diseases and relapse common in the absence of durable immune recovery from HAART (Table 101.3).

GASTROINTESTINAL INFECTIONS

Infections of the esophagus

Candidal esophagitis is a very common AIDS-defining OI. It manifests at CD4 counts $\leq$200 cells/mm^3 and presents primarily as dysphagia and/or odynophagia. These symptoms are sometimes accompanied by chest pain or fever. In rare instances esophageal perforation can occur, usually as a complication of delayed or inadequate treatment. Triazoles are the mainstay of therapy (Table 101.4). Azole resistance may occur particularly with recurrent episodes and in patients with very advanced HIV disease. In such cases, amphotericin-B-based therapies or echinocandins are usually effective (Table 101.4).

Rarely, herpes simplex virus (HSV) or cytomegalovirus (CMV) may infect the esophagus, causing symptoms indistinguishable from those encountered with candidal disease. Patients with the former are, however, usually more immunodeficient (i.e., CD4 counts $\leq$100 cells/mm^3). In patients presenting with esophageal symptoms but without evidence of thrush, it is customary to institute empiric candidal treatment and only pursue alternate causes (through endoscopically guided biopsy) with treatment failures (Table 101.4).

Diarrheal illness

Patients on HAART, particularly protease inhibitor-containing regimens, often experience treatment-related diarrhea. However, protracted symptoms or evidence of intestinal inflammation or invasion (i.e., fever, hematochezia, or abdominal pain) mandates an infectious workup.

Common community-acquired enteric pathogens, such as norovirus, salmonella, campylobacter, shigella, yersinia, and giardia, are the usual culprits in individuals with CD4 counts >200 cells/mm^3. Invasive salmonellosis, campylobacteriosis, and shigellosis are, however, more frequent relative to the general population. Consequently, antibiotic treatment for these

Table 101.4 Management of opportunistic infections of the digestive tract

Condition/ pathogen	First-line treatment	Notes
Candidal esophagitis	Fluconazole, 200–400 mg PO qd for 14–21 d	In the event of azole resistance: amphotericin B suspension, 100 mg/mL PO QID; amphotericin B deoxycholate, 0.3–0.7 mg/kg IV qd; liposomal or lipid complex amphotericin, 3–5 mg/kg; voriconazole, 200 mg PO BID; or caspofungin, 50 mg IV qd, micafungin 150 mg IV qd, or anidulafungin 100 mg IV x 1 then 50 mg IV qd for 14–21 d
Herpes simplex esophagitis	Acyclovir, 5 mg/kg IV, followed by acyclovir, 400 mg PO TID; famciclovir, 500 mg PO BID; or valacyclovir, 1000 mg PO BID for 7–14 d once patient is tolerating oral therapy	In the event of acyclovir resistance: foscarnet, 40–60 mg/kg IV q8h, or cidofovir, IV plus IV hydration, and oral probenecid to mitigate renal toxicity
Cytomegalovirus esophagitis	Ganciclovir, 5–6 mg/kg/d IV, or valganciclovir, 900 mg PO BID, once patient tolerating oral therapy, for 2–3 wk followed by half-dose valganciclovir for chronic suppression	In the event of ganciclovir resistance: foscarnet, 90 mg/kg IV q12h, or cidofovir, IV plus IV hydration, and oral probenecid to mitigate renal toxicity
Salmonellosis	Ciprofloxacin, 500–750 mg BID, or levofloxacin, 500 mg qd for 7–14 d	(1) Relapse is common and may necessitate chronic suppression; therefore, treat for 4–6 weeks in patients with CD4 count $\leq$200 cells/mm^3 or bacteremia. (2) Fluoroquinolone resistance is increasing, in which case azithromycin should be used
Shigellosis	Ciprofloxacin, 500 mg BID, or levofloxacin, 500 mg qd for 3 d	(1) Treat for up to 14 d in patients with CD4 count $\leq$200 cells/mm^3 or bacteremia. (2) Alternative agent: azithromycin
Campylobacteriosis	Ciprofloxacin, 500 mg BID, or azithromycin, 500 mg qd for 3 d	(1) Treat for up to 14 d in patients with CD4 count $\leq$200 cells/mm^3 or bacteremia. (2) Fluoroquinolone resistance is increasing rapidly, particularly in Southeast Asia
Cryptosporidiosis	HAART *plus* antispasmodic +/− nitazoxanide 500 mg PO q12h for 14 d	
Microsporidiosis	Albendazole, 400 mg q12h for 3 wk	The most common cause of diarrheal illness, *Enterocytozoon bieneusi*, is the least susceptible species to albendazole
Cyclosporidiosis	TMP–SMX-DS q6h for 10 d then 1 tab 3×/wk	Alternative agent: ciprofloxacin
Isosporiosis	TMP–SMX-DS q6h for 10 d then 1 tab 3×/wk	Alternative agents: ciprofloxacin, pyrimethamine plus folinic acid

Abbreviations: PO = orally; qd = every day; QID = four times a day; IV = intravenously; BID = twice a day; TID = three times a day; HAART = highly active antiretroviral therapy; TMP–SMX-DS = trimethoprim–sulfamethoxazole-double strength.

infections, whereas discretionary in otherwise healthy, HIV-seronegative persons, is recommended when these infections occur in the context of HIV disease (Table 101.4).

Patients with CD4 $\leq$100 cells/mm^3 may experience severe, protracted watery diarrhea as a result of cryptosporidium, microsporidia, cyclospora, or isospora intestinal infections. Although much less frequent in the post-HAART era, effective chemotherapeutic agents against these organisms (with the exception of isospora and cyclospora) are sorely lacking. Antispasmodics and immune reconstitution via HAART are the mainstays of management (Table 101.4).

Symptomatic gastrointestinal CMV infections present most often in the large bowel. CMV colitis typically occurs at CD4 counts $\leq$100 cells/mm^3 and presents as fever, bloody diarrhea, and abdominal pain. Treatment comprises 2 to 3 weeks of induction therapy with IV ganciclovir or oral valganciclovir with half the induction dose as maintenance therapy thereafter (Table 101.4).

HIV cholangiopathy

Some intestinal pathogens (primarily *Cryptosporidium parvum* but also microsporidia, CMV, and cyclospora) are also able to infect the biliary tract, giving rise to a syndrome known collectively as HIV cholangiopathy. Typically a complication of very advanced HIV disease (CD4 counts $\leq$100 cells/mm^3), HIV cholangiopathy presents as right upper quadrant discomfort (rarely accompanied by fever or jaundice) and serum alkaline phosphatase elevation. Endoscopic retrograde cholangiopancreatography (ERCP) findings include

papillary stenosis, biliary stricture, and/or biliary obstruction. Symptoms, while usually refractory to antimicrobial therapy, are often relieved by biliary stenting and sphincterotomy. Ursodeoxycholic acid (300 mg orally three times daily) is effective for symptom relief in patients with lesions not amenable to endoscopic intervention.

NEUROLOGIC INFECTIONS

Meningitis

Cryptococcus neoformans is the most commonly identified cause of meningitis amongst HIV-infected patients. Patients present subacutely with headache, fever, and lethargy. Other manifestations of increasing intracranial pressure (the most feared complication of this disease) include nausea, emesis, blindness, obtundation, and coma. Delays in therapy can be fatal. Management is three-pronged: (1) prompt initiation of induction antifungal therapy with an amphotericin-B-based drug *plus* 5-flucytosine for 14 days (Table 101.5); (2) serial lumbar punctures to alleviate excess intracranial pressure; and (3) consolidation as well as maintenance therapy with oral fluconazole. Similar clinical presentations, including a propensity for elevated intracranial pressure, are seen with MTB, histoplasma, and coccidioides meningitis (see Table 101.5 for treatment recommendations).

Encephalitis

Progressive multifocal leukoencephalopathy (PML) is caused by reactivation of previously latent JC virus infection within the brain parenchyma. Although much less frequent in the post-HAART era, PML remains one of the most disheartening complications of advanced HIV disease (i.e., CD4 counts $\leq$200 cells/mm^3). No effective antiviral therapies have been identified for this highly debilitating and often lethal disorder. Immune recovery through HAART remains the only recourse. Patients present with nonenhancing, periventricular, subcortical white matter lesions devoid of mass effect or surrounding edema. Lesions are more likely to enhance in patients who develop symptoms in the context of HAART, i.e., as part of an immune recovery inflammatory syndrome (IRIS). Symptoms in either case include progressive focal motorsensory deficits; visual field cuts; cerebellar findings such as ataxia, dysmetria, and vertigo; and seizures.

CMV meningoencephalitis is a marker of very advanced HIV immunodeficiency ($\leq$100 cells/mm^3). Rapid cognitive deterioration marked by fever and headache is the usual presentation. The classic, almost pathognomonic, finding on MRI is a symmetric, T2-bright ventriculitis with extension to the adjacent periventricular white matter. However, nonspecific white matter changes are more common. Progressive cognitive decline in the face of antiviral treatment is common. Combination therapy comprising intravenous ganciclovir and foscarnet may improve outcomes (Table 101.5).

Varicella-zoster virus (VZV) brain infections are typically observed at CD4 counts $\leq$200 cells/mm^3. Several variants have been described including focal as well as diffuse meningoencephalitis, cerebritis, and CNS vasculitis. Patients present with fever, encephalopathy, and/or focal motorsensory deficits that typically follow, but may also precede, a dermatomal zoster outbreak. Treatment comprises intravenous acyclovir for a minimum of 2 to 3 weeks (Table 101.5).

Brain abscess

The most common cause of space-occupying brain lesions in HIV-infected patients with CD4 counts $\leq$200 cells/mm^3 is toxoplasmosis (Figure 101.4). Patients present with headache, fever, confusion, and sometimes seizure. CNS toxoplasmosis is rare in toxoplasma-seronegative patients. In cases where primary CNS lymphoma is deemed less likely (i.e., patients seropositive for toxoplasma with multiple ring-enhancing brain lesions on MRI), an empiric trial of toxoplasma antibiotics (Table 101.5) is instituted in lieu of brain biopsy. Individuals who fail to improve after 10 to 14 days of treatment are subjected to stereotactic brain biopsy for a definitive histopathologic diagnosis.

Rarer causes of brain abscess in HIV-positive individuals include MTB, cryptococcus, aspergillus, the endemic mycoses, nocardia, and rhodococcus infections (see Table 101.5 for treatment recommendations). Concomitant pulmonary involvement, whereas rare with toxoplasma brain infections, is a frequent finding with all these other pathogens.

Retinitis

Acute blurry vision, photopsia, and/or scotomata in a patient with $\leq$100 cells/mm^3 merits emergent evaluation for CMV retinitis. Left untreated,

Table 101.5 Management of neurologic opportunistic infections

Pathogen/condition	First-line treatment	Notes
Cryptococcus neoformans	Amphotericin B, 0.7 mg/kg IV qd, plus 5-flucytosine (5-FC), 25 mg/kg q6h, or liposomal or lipid complex amphotericin, 4 mg/kg, plus 5-flucytosine, 25 mg/kg q6h for 2 wk, followed by 10 wk of fluconazole, 400 mg PO qd, followed by chronic suppression with fluconazole, 200 mg PO qd	Note: monitor 5-FC serum levels – peak and trough levels >80 mg/L and 40 mg/L, respectively, are associated with significant bone marrow toxicity
M. tuberculosis	Isoniazid, 5 mg/kg/d, plus rifampin, 600 mg PO qd, plus pyrazinamide, 15–30 mg/kg PO qd, plus ethambutol 15–25 mg/kg/d for a minimum of 12 mo	If patient is taking a protease inhibitor, replace rifampin with rifabutin, 150–300 mg PO qd, because rifampin significantly lowers serum levels of protease inhibitors
Histoplasma capsulatum meningoencephalitis	Amphotericin B deoxycholate, 0.7 mg/kg IV qd; liposomal or lipid complex amphotericin, 3–5 mg/kg, until clinically improved followed by itraconazole, 200 mg for 12–16 wk. Chronic suppression with 200 mg qd thereafter	Blood cultures, and even DuPont fungal isolators, are often negative in systemic histoplasma infections. However, a urinary histoplasma antigen-based test is >90% sensitive in patients with AIDS
Coccidioides immitis meningoencephalitis	Fluconazole 400–800 mg IV or PO qd	Lifelong suppression with fluconazole, 400 mg PO qd, is recommended, even with CD4 >200 cells/mm^3 on HAART
Blastomycosis dermatitidis meningoencephalitis	Amphotericin B deoxycholate, 0.7–1.0 mg/kg IV qd, or liposomal amphotericin, 3–5 mg/kg, until clinically improved, followed by itraconazole, 200 mg for 12 wk	
JC virus (progressive multifocal leukoencephalopathy)	HAART	
Varicella-zoster virus	Meningoencephalitis: acyclovir, 10 mg/kg IV for 14–21 d Acute retinal necrosis: intravenous acyclovir as above followed by chronic suppression with valacyclovir or famciclovir	In the event of acyclovir resistance: foscarnet 40–60 mg/kg IV q8h or cidofovir IV plus IV hydration and oral probenecid to mitigate renal toxicity
Cytomegalovirus	Meningoencephalitis/polyradiculitis: ganciclovir, 5–6 mg/kg/d IV, or valganciclovir, 900 mg PO BID, +/– IV foscarnet, 90–120 mg/kg/d, until clinical improvement Retinitis: as above plus sustained-release ganciclovir intraocular implant q6–9 mo	(1) Lifelong chronic suppression with valganciclovir is recommended. (2) Under supervision of a qualified ophthalmologist, may discontinue maintenance therapy after maximal improvement and CD4 count has been >150 cells/mm^3 for >6 mo
Toxoplasma gondii brain abscess	Pyrimethamine, 200 mg PO 1×, then 50–75 mg qd plus sulfadiazine, 1.0–1.5 g PO QID, plus folinic acid, 10–20 mg PO qd for 6 wk, followed by half-dose of all 3 drugs as chronic suppression	(1) Primary CNS lymphoma is the other leading cause of brain mass in this population but is more often unifocal, >4 cm, and distinguishable from cerebral toxoplasmosis on single-photon emission computed tomography and positron emission tomography. (2) In patients with sulfa allergy: replace sulfadiazine with clindamycin, dapsone, or atovaquone
Aspergillus fumigatus	Voriconazole, 6 mg/kg IV 1×, followed by either 4 mg/kg IV or 100–200 mg PO BID for 2–3 wk; oral voriconazole for suppression	Less preferred agents: (1) amphotericin B deoxycholate; (2) liposomal or lipid complex amphotericin, 3–5 mg/kg; or (3) caspofungin +/– voriconazole
Nocardia asteroides	TMP–SMX (15 mg/kg/d TMP; 75 mg/kg/d SMX) plus ceftriaxone, 2 g IV qd × 6 wk, followed by reduced doses of both drugs IV for 6–12 mo	In sulfa-allergic patients: substitute TMP–SMX with amikacin
Rhodococcus equi	Erythromycin, 0.5 g IV q6h, plus imipenem, 0.5 g IV q6h, plus rifampin, 600 mg PO qd for 2 wk, followed by oral clarithromycin or azithromycin plus rifampin for suppression	Alternative agents: ciprofloxacin and linezolid

symptoms quickly progress to blindness within days to weeks. Mechanisms for decreased visual acuity in CMV retinitis include retinal detachment (a consequence of large, peripheral lesions), involvement of the macula, and extension of lesions to the optic nerve. Fundoscopically, CMV retinitis appears as multiple pale yellow exudates against a red background. Retinal hemorrhages are also a common finding. Ganciclovir-impregnated retinal implants combined with oral valganciclovir is first-line therapy (Table 101.5).

Table 101.6 Management of disseminated infections

Pathogen/ condition	First-line treatment	Notes
M. avium complex	Clarithromycin, 500 mg PO BID, or azithromycin, 600 mg qd, plus ethambutol, 15–25 mg/kg/d, plus rifampin, 600 mg PO qd, for a minimum of 12 mo	(1) In patients on efavirenz, azithromycin is preferred over clarithromycin as part of the 3-drug regimen; because efavirenz lowers drug levels of the latter. (2) If patient is taking a protease inhibitor, replace rifampin with rifabutin, 150–300 mg PO qd, because rifampin significantly lowers serum levels of protease inhibitors
Histoplasma capsulatum	Mild to moderate disease: itraconazole, 200 mg PO TID for 3 d, followed by itraconazole, 200 mg BID for 12 wk Severe illness: amphotericin B deoxycholate, 0.7 mg/kg IV qd; amphotericin liposomal or lipid complex, 3–5 mg/kg, until clinically improved followed by itraconazole, 200 mg for 12 wk	
Penicilliosis	Amphotericin B deoxycholate, 0.6 mg/kg IV qd for 2 wk, followed by itraconazole, 200 mg q12h for 10 wk and then 100 mg PO q12h for suppression	
Bartonellosis	Erythromycin, 500 mg PO q6h for 12 wk minimum and until CD4 count >200 cells/mm^3	(1) Doxycycline with or without rifampin is preferred for CNS involvement. (2) Alternative agents for non-CNS disease: clarithromycin, 500 mg PO BID; azithromycin, 600 mg PO qd; or ciprofloxacin, 500 mg PO BID

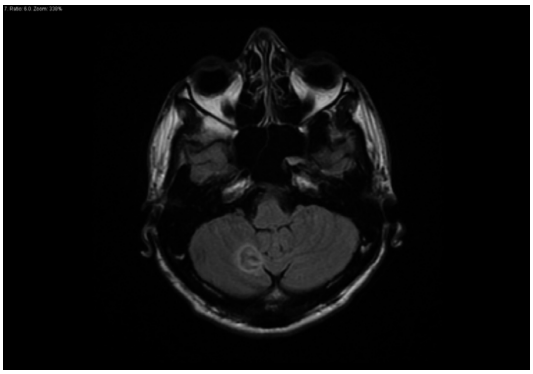

Figure 101.4 Cerebral toxoplasmosis. Magnetic resonance imaging reveals a 2.5 cm ring-enhancing lesion in the right cerebellar hemisphere.

VZV is a less common cause of acute retinal necrosis (ARN) in patients with HIV. Like CMV retinitis, permanent visual loss rapidly ensues if left untreated. Unlike the latter, however, VZV-related ARN can occur at any CD4 count. Progressive outer retinal necrosis (PORN), on the other hand, is a variant of VZV retinitis that targets individuals with very low CD4 counts, typically $\leq$100 cells/mm^3. (More recently, HSV and CMV have been implicated in isolated cases of PORN; however, VZV is generally thought to be the culprit in the majority of cases.) The lesions expand and coalesce in the periphery of the retina; thus, visual loss in VZV-related PORN occurs primarily as a result of retinal detachment. Treatment for VZV-related ARN consists of intravenous acyclovir for 2 to 3 weeks followed by oral valacyclovir (Table 101.5). VZV-related PORN, however, carries a worse prognosis primarily because it is more often refractory to antiviral therapy. One approach has been to administer ganciclovir and foscarnet intravenously along with intravitreal injections of ganciclovir and/or foscarnet.

DISSEMINATED INFECTIONS

Mycobacterium avium complex

Patients with disseminated MAC characteristically present with high, spiking fevers, progressive weight loss, and sometimes diarrhea. Elevated alkaline phosphatase levels – present in approximately 50% of cases – and enlarged para-aortic lymph nodes are also observed. Treatment consists of clarithromycin (or azithromycin), weight-based ethambutol, and rifabutin (Table 101.6).

Histoplasmosis

Disseminated histoplasmosis is a rare but potentially lethal complication of HIV infection. Presentations vary from indolent (progressive fever, weight loss, and pancytopenia) to fulminant. The latter is marked by fever, septic shock, acute

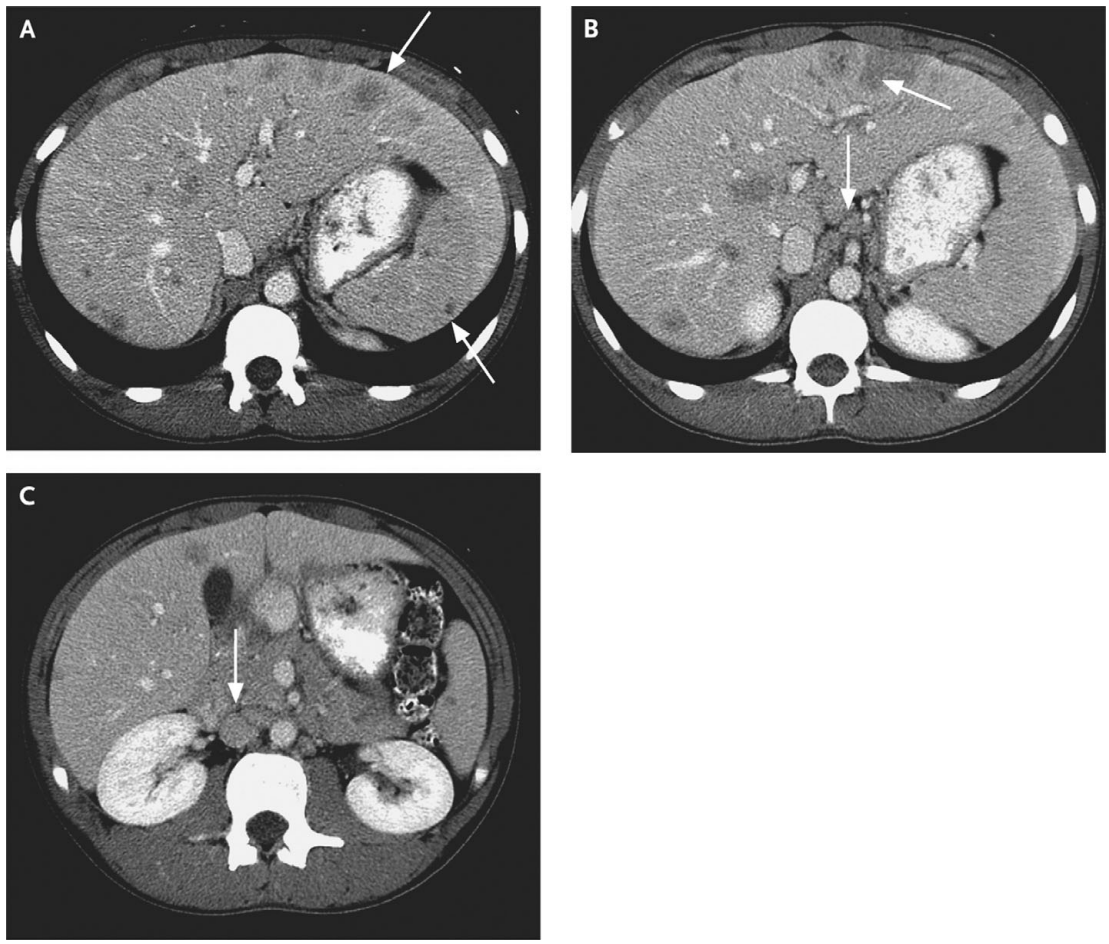

Figure 101.5 *Bartonella henselae* hepatosplenic peliosis. Computed tomography of the abdomen with intravenous contrast reveals multiple low-density lesions with central septations and surrounding halos (arrows) in the liver and spleen. An image obtained slightly below the image shown in Panel A (Panel B) shows larger lesions, as well as lymphadenopathy around the celiac axis (arrows). An image obtained below the image shown in Panel B (Panel C) shows additional lymphadenopathy in the peri-pancreatic and periportal regions (arrow). Reproduced with permission from Stephen Pelton, MD. Pelton SI, Kim JY, Kradin RL. Case records of the Massachusetts General Hospital. *Case 27–2006*. Department of Pediatric Infectious Disease, Boston Medical Center, Massachusetts General Hospital and Harvard Medical School, Boston, USA.

respiratory distress syndrome, and adrenal insufficiency resulting from bilateral adrenal infiltration by histoplasmosis organisms. Treatment comprises amphotericin B-based chemotherapy followed by chronic suppression with oral itraconazole (Table 101.6).

Penicilliosis

Penicillium marneffei is a dimorphic fungal pathogen that converts to a yeast at human body temperature. Disseminated penicilliosis is the third most common OI (after cryptococcal and MTB infection) in HIV-infected patients residing in Southeast Asia. Patients at highest risk have CD4 counts $\leq$50 cells/mm^3. Usual symptoms include fever, weight loss, dry cough, lymphadenopathy, hepatosplenomegaly, and a rash similar to the umbilicated lesions of molluscum contagiosum. Serum alkaline phosphatase levels are often elevated. Blood cultures turn positive within 5 to 7 days of incubation. Treatment is similar to that of disseminated histoplasmosis (Table 101.6).

Bartonellosis

Patients present with fever, rash, abdominal and/or bone pain. Risk factors include CD4 count $\leq$200 cells/mm^3 and prior cat contact (*Bartonella henselae*) or louse infestation (*Bartonella quintana*). Mucocutaneous manifestations, known as bacillary angiomatosis, are variable in appearance but classically present as enlarging violaceous plaques or nodules that mimic Kaposi's sarcoma. Bartonella osteomyelitis, a complication of *B. quintana* infection, is rare and involves the long bones and sometimes underlies cellulitic plaques.

Bartonella henselae infections are uniquely associated with hepatosplenic peliosis which comprises cystic blood-filled, endothelium-lined spaces that appear as focal, hypodense lesions on CT (Figure 101.5). Application of Warthin–Starry stain to tissue specimens reveals pleomorphic microorganisms. In the absence of diagnostic tissue samples, confirmation of bartonellosis rests on culture and serology. Blood cultures and subsequent chocolate or heart infusion agar subcultures, however, have to be held for a minimum of 21 days. Prolonged treatment with an oral macrolide is the treatment of choice (Table 101.6).

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102. Prophylaxis of opportunistic infections in HIV disease

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Prior to the introduction of antiretroviral therapy (ART), treatment and prevention of opportunistic infections (OIs) were the main-stays of reducing morbidity and mortality in people living with human immunodeficiency virus (HIV). While the widespread use of ART has greatly decreased the frequency of OIs, a sizeable number of HIV-infected individuals are either not taking ART or do not have an adequate immune response to ART. Thus OIs continue to cause a significant burden of disease in people living with HIV, and prophylaxis against OIs remains a major component in the management of HIV. The guidelines for OI prophylaxis in HIV-infected individuals are published by the Centers for Disease Control and Prevention, National Institutes of Health, and HIV Medicine Association of the Infectious Disease Society of America. The newest version of the guidelines was published in 2013 and includes revisions on the vaccination strategies for HIV-infected people.

Primary prophylaxis refers to treatment given to prevent development of infection. The most influential example of primary prophylaxis in HIV is the use of trimethoprim–sulfamethoxazole (TMP–SMX) in immune compromised individuals to prevent development of *Pneumocystis jirovecii* (*carinii*) pneumonia (PCP).

Secondary prophylaxis refers to continued treatment given after the acute course of treatment is complete in order to decrease the risk of relapse. Depending on the infection, secondary prophylaxis is sometimes referred to as maintenance or chronic suppressive therapy for difficult-to-treat OIs. The timing of primary prophylaxis and recommended vaccinations is summarized in Table 102.1. The preferred and alternative agents and dosages for primary and secondary prophylaxis are summarized in Tables 102.2 and 102.3.

PNEUMOCYSTIS PNEUMONIA

Primary and secondary prophylaxis

Use of TMP–SMX has decreased the frequency of PCP infection from 70% to 80% of patients with acquired immunodeficiency syndrome (AIDS) to less than one case per 100 person-years in the United States and Western Europe. All patients with a CD4 T-cell count below 200 cells/mm^3 or a history of oral candidiasis regardless of CD4 count should be offered primary PCP prophylaxis, including patients on ART. Individuals with a CD4 percentage of below 14% or a history of an AIDS-defining illness should also be considered for primary prophylaxis against PCP, as should patients with a CD4 count between 200 and 250 cells/mm^3 when it is impossible or unlikely that regular CD4 count monitoring will occur. TMP–SMX is the recommended agent for both primary and secondary PCP prophylaxis. The preferred regimen is one double-strength (DS) tablet daily; however, one single-strength (SS) tablet daily is an option for patients unable to tolerate the higher-strength dose. One DS TMP–SMX tablet three times a week is also an alternative. TMP–SMX has the added benefit of being effective as prophylaxis against *Toxoplasma gondii* and a variety of bacterial infections.

Common adverse effects of TMP–SMX include rash, gastrointestinal upset, and fever. It is recommended that patients with mild adverse reaction to TMP–SMX continue to be treated if possible. Reintroduction of TMP–SMX, potentially at a lower dose, should be considered after non-life-threatening adverse reactions resolve. A majority of patients with mild adverse reactions to TMP–SMX will tolerate the medication if it is given at a lower dose or reduced frequency. Desensitization to TMP–SMX can also be considered. In people who develop severe adverse reactions including

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Table 102.1 Timing of primary prophylaxis and vaccination schedule for HIV-infected adults

CD4 count level	Recommended primary prophylaxis and vaccinations
All patients regardless of CD4 count	TB prophylaxis if indicated Influenza vaccination annually Pneumococcal vaccination[a] PPSV23 – 1 dose then 2nd booster ≥5 years after previous dose. Can give 3rd booster at ≥65 years and ≥5 years after previous dose. PCV13 – 1 dose Td booster every 10 years (substitute 1-time dose of Tdap for Td booster) Hepatitis A (HAV) vaccination if HAV susceptible Hepatitis B (HBV) vaccination if HBV susceptible HPV vaccination if ≤26 years of age (women and men) PCP prophylaxis if indicated (see Table 102.2 for indications)
CD4 <250 cell/mm^3	Coccidioidomycosis prophylaxis if indicated (see Table 102.2)
CD4 <200 cell/mm^3	PCP prophylaxis
CD4 <150 cell/mm^3	*Histoplasma* prophylaxis if indicated (see Table 102.2)
CD4 <100 cell/mm^3	*Toxoplasma* prophylaxis if indicated (see Table 102.2)
CD4 <50 cell/mm^3	*Mycobacterium avium* complex prophylaxis Fundoscopic exam for CMV

Abbreviations: TB = tuberculosis; PPSV23 = pneumococcal polysaccharide 23 vaccine; PCV13 = pneumococcal conjugate 13-valent vaccine, Td = tetanus-diphtheria vaccine; Tdap = combined tetanus, diphtheria, pertussis vaccines; HPV, human papillomavirus; PCP = *Pneumocystis jirovecii* pneumonia; CMV = cytomegalovirus.

[a] If no prior pneumococcal vaccination, give PCV13 first then give PPSV23 ≥8 weeks later. If previously vaccinated with PPSV23, give PCV13 ≥12 months later.

possible or definite Stevens–Johnson syndrome or toxic epidermal necrolysis (TEN), TMP–SMX should be permanently discontinued.

If TMP–SMX cannot be given, recommended alternative regimens for primary and secondary PCP prophylaxis include dapsone with or without pyrimethamine and leucovorin; aerosolized pentamidine; and atovaquone with or without pyrimethamine and leucovorin. Adverse effects of dapsone include rash, anemia, methemoglobinemia, agranulocytosis, and hepatic dysfunction. The majority of individuals with an allergy to TMP–SMX tolerate dapsone; however, dapsone should not be given to patients with a history of a severe TMP–SMX reaction. In addition, patients should be tested for glucose-6-phosphate dehydrogenase deficiency prior to receiving dapsone. While dapsone and atovaquone are similar in efficacy, atovaquone is much more expensive compared to the other alternative regimens, may cause gastrointestinal upset, and only comes in a liquid formulation. Although similarly effective to dapsone and atovaquone, aerosolized pentamidine via Respirgard II nebulizer is less frequently used for PCP prophylaxis because of cost and inconvenience of administration. In addition, aerosolized pentamidine has no efficacy for prophylaxis against toxoplasmosis, and cases of extrapulmonary PCP have been reported in patients using aerosolized pentamidine for PCP prophylaxis. For individuals who are seropositive for *Toxoplasma gondii*, the recommended alternatives to TMP–SMX which cover both PCP and toxoplasmosis include dapsone plus pyrimethamine plus leucovorin or atovaquone with or without pyrimethamine plus leucovorin.

Both primary and secondary PCP prophylaxis should be continued until patients on ART have a CD4 count of at least 200 cells/mm^3 for more than 3 months; and should be restarted if the CD4 count decreases below 200 cell/mm^3. People with a CD4 count above 200 cells/mm^3 at the time of PCP diagnosis should be considered for life-long PCP prophylaxis. A CD4 percentage of 14% is roughly equivalent to a CD4 count of 200 cells/mm^3; thus for individuals with discordance between the absolute CD4 count and percentage, primary and/or secondary prophylaxis should likely be continued until the CD4 percentage is at least 14%.

TOXOPLASMA GONDII ENCEPHALITIS

Primary prophylaxis

Before ART was routinely used, about one-third of those with advanced immunosuppression and positive *Toxoplasma* serology developed toxoplasmosis. HIV-infected individuals should be tested for immunoglobulin (IgG) antibodies to *Toxoplasma* at the time of HIV diagnosis. The seroprevalence of *Toxoplasma* antibodies varies from about 11% in the United States to more than 50% in some parts of Europe, Latin America, and Africa. People living with HIV should avoiding eating raw or undercooked meats or shellfish and should wash their hands after contact with raw meats or soil. Uncooked fruits and vegetables should be washed before consumption. HIV-infected individuals who are seronegative for *Toxoplasma* should be counseled on thorough hand washing after changing cat litter boxes or to avoid changing litter boxes if possible.

Table 102.2 Preferred and alternative agents for primary prophylaxis

Infection	Indication	Drug/dosage
Pneumocystis jirovecii pneumonia (PCP)	1. CD4 T-cell count <200 cells/mm^3 2. History of oral candidiasis 3. CD4 percentage $<14\%$ 4. History of an AIDS-defining illness 5. CD4 count between 200 and 250 cells/mm^3 when unlikely that the CD4 count will be monitored regularly	**Preferred**:[a] • Trimethoprim–sulfamethoxazole (TMP–SMX) 1 DS (160/800 mg) tablet PO daily • TMP–SMX 1 SS (80/400 mg) tablet PO daily **Alternative**: • TMP–SMX 1 DS (160/800 mg) tablet PO 3 times a week • Dapsone 100 mg PO daily or 50 mg PO twice daily • Dapsone 50 mg PO daily plus pyrimethamine 50 mg and leucovorin 25 mg PO weekly • Dapsone 200 mg and pyrimethamine 75 mg and leucovorin 25 mg PO weekly • Aerosolized pentamidine 300 mg via Respirgard II nebulizer (Marquest; Englewood, Colorado) monthly • Atovaquone 1500 mg PO daily • Atovaquone 1500 mg and pyrimethamine 25 mg and leucovorin 10 mg daily
Toxoplasmosis	• CD4 count <100 cells/mm^3 and *Toxoplasma* IgG seropositive	**Preferred**: • TMP–SMX 1 DS tablet PO daily **Alternative**: • TMP–SMX 1 DS table PO 3 times weekly • TMP–SMX 1 SS tablet PO daily • Dapsone 50 mg PO daily plus pyrimethamine 50 mg PO weekly and leucovorin 25 mg PO weekly • Dapsone 200 mg and pyrimethamine 75 mg and leucovorin 25 mg PO weekly • Atovaquone 1500 mg PO daily • Atovaquone 1500 mg PO and pyrimethamine 25 mg and leucovorin 10 mg PO daily
Histoplasmosis	• Individuals with a CD4 count <150 cells/mm^3 with increased risk of *Histoplasma* exposure	• Itraconazole 200 mg PO daily
Coccidioidomycosis	• Individuals with a CD4 count <250 cells/mm^3 and newly positive IgM or IgG *Coccidioides* serology	• Fluconazole 400 mg PO daily
Tuberculosis (TB)	1. Positive tuberculin skin test (TST) of ≥ 5 mm induration at 48–72 hours 2. Positive interferon-gamma release assay (IGRA) result 3. Recent exposure to active TB	**Preferred**: • Isoniazid 300 mg and pyridoxine 25 mg PO daily $\times$ 9 months • Isoniazid 900 mg PO twice weekly plus pyridoxine 25 mg PO daily $\times$ 9 months **Alternative**: • Isoniazid 15 mg/kg and rifapentine 900 mg PO weekly given as directly observed therapy $\times$ 3 months (if not on ART) • Rifampin 600 mg PO daily $\times$ 4 months (if not on a protease inhibitor or non-nucleoside reverse transcriptase inhibitor) • Rifabutin – dosage based on ART used $\times$ 4 months
Disseminated *Mycobacterium avium* complex disease	• CD4 count <50 cells/mm^3 and no evidence of disseminated disease	**Preferred**: • Azithromycin 1200 mg PO weekly • Azithromycin 600 mg PO twice weekly • Clarithromycin 500 mg PO BID **Alternative**: • Rifabutin 300 mg PO daily (dose adjusted for ART)
Cytomegalovirus (CMV)	• CD4 ≤ 50 cells/mm^3 and CMV IgG antibody positive	• Fundoscopic monitoring

[a] Per Centers for Disease Control "Treatment of Opportunistic Infection Guidelines." See text for timing of discontinuation of prophylaxis.
Abbreviations: CD4 = CD4 T-cell count; DS = double-strength; PO = by mouth; SS = single-strength; AIDS = acquired immunodeficiency syndrome; IgG, immunoglobulin G; BID, twice daily; ART = antiretroviral therapy.

Table 102.3 Preferred and alternative agents for secondary prophylaxis

Infection		Drug/dosage
Pneumocystis jirovecii pneumonia (PCP)		Same as primary prophylaxis
Toxoplasmosis		**Preferred**:[a] • Pyrimethamine 25–50 mg PO daily plus sulfadiazine 2000–4000 mg PO daily (in 2–4 divided doses) plus leucovorin 10–25 mg PO daily **Alternative**: • Clindamycin 600 mg PO q8h plus pyrimethamine 25–50 mg PO daily plus leucovorin 10–25 mg PO daily (requires additional agent to prevent PCP) • TMP–SMX 1 DS PO BID • Atovaquone 750–1500 mg PO BID • Atovaquone 750–1500 mg PO BID plus pyrimethamine 25 mg and leucovorin 10 mg PO daily • Atovaquone 750–1500 mg PO BID plus sulfadiazine 2000–4000 mg PO daily (in 2–4 divided doses)
Oropharyngeal, esophageal or vulvovaginal candidiasis	Only if frequent or severe recurrences	Oropharyngeal: • Fluconazole 100 mg PO daily • Fluconazole 100 mg PO 3 times weekly Esophageal: • Fluconazole 100–200 mg PO daily • Posaconazole 400 mg PO BID Vulvovaginal: • Fluconazole 150 mg PO weekly
Cryptococcosis		• Fluconazole 200 mg PO daily
Histoplasmosis		• Itraconazole 200 mg TID × 3 days, then 200 mg BID
Coccidioidomycosis		**Preferred**: • Fluconazole 400 mg PO daily • Itraconazole 200 mg PO BID **Alternative**: • Posaconazole 200 mg PO BID • Voriconazole 200 mg PO BID
Disseminated *Mycobacterium avium* complex disease		**Preferred**: • Clarithromycin 500 mg PO BID plus ethambutol 15 mg/kg PO daily • Azithromycin 500–600 mg PO daily plus ethambutol 15 mg/kg PO daily (if drug interactions or intolerance preclude clarithromycin use) **Alternative**: Third or fourth drug should be considered for patients with CD4 $<$50 cells/mm^3, high mycobacterial loads ($>$2 log CFU/mL of blood), or in the absence of effective ART Third or fourth drug options: • Rifabutin 300 mg PO daily (dose adjusted for ART) • An aminoglycoside: amikacin 10–15 mg/kg IV daily or streptomycin 1 g IV or IM daily • A fluoroquinolone: levofloxacin 500 mg PO daily or moxifloxacin 400 mg PO daily
Cytomegalovirus (CMV)		**Preferred**: • Valganciclovir 900 mg PO daily plus ganciclovir intraocular implant (if sight-threatening retinitis present) • Valganciclovir 900 mg PO daily (if retinal lesions are small and peripheral) **Alternative**: • Ganciclovir 5 mg/kg IV 5–7 times weekly • Foscarnet 90–120 mg/kg IV daily • Cidofovir 5 mg/kg IV every other week with saline hydration before and after treatment plus probenecid 2 g PO 3 hours prior to cidofovir, then 1 g PO 2 hours after cidofovir and 1 g PO 8 hours after cidofovir (4 g total of probenecid)

Table 102.3 *(continued)*

Infection		Drug/dosage
Herpes simplex	Only for frequent or severe recurrences	• Valacyclovir 500 mg PO BID • Famciclovir 500 mg PO BID • Acyclovir 400 mg PO BID
Salmonella bacteremia	Long-term role of secondary prophylaxis unclear	**Preferred**: • Ciprofloxacin, 500 mg PO BID **Alternative**: • TMP–SMX 1 DS PO BID

[a] Per Centers for Disease Control "Treatment of Opportunistic Infection Guidelines." See text for timing of discontinuation of prophylaxis.
Abbreviations: PO = by mouth; TMP–SMX = trimethoprim–sulfamethoxazole; DS = double-strength; BID = twice daily; TID = three times daily; CD4 = CD4 T-cell count; CFU = colony-forming unit; ART = antiretroviral therapy; IV = intravenous; IM = intramuscular.

HIV-infected patients should keep their cats inside and avoid contact with stray cats.

HIV-infected patients with a CD4 count below 100 cells/mm^3 who are *Toxoplasma* seropositive should receive primary prophylaxis against toxoplasmosis. One DS TMP–SMX daily is the recommended agent for primary prophylaxis against toxoplasmosis; however, TMP–SMX DS three times weekly or SS daily are also likely to be effective. If TMP–SMX cannot be given, dapsone plus pyrimethamine and leucovorin or atovaquone with or without pyrimethamine and leucovorin are alternatives. If *Toxoplasma* seronegative individuals are on a PCP prophylaxis regimen that is not effective against toxoplasmosis, their *Toxoplasma* IgG antibody level should be rechecked if their CD4 count declines below 100 cells/mm^3. Primary prophylaxis against toxoplasmosis can be discontinued for HIV-infected patients on ART when the CD4 count increases to above 200 cells/mm^3 for more than 3 months. Primary prophylaxis in *Toxoplasma* seropositive individuals should be restarted if the CD4 count declines below 200 cells/mm^3.

Secondary prophylaxis

Patients diagnosed with *Toxoplasma* encephalitis should continue treatment with suppressive therapy with chronic maintenance therapy (or secondary prophylaxis) after initial treatment has been completed until they have been on ART with a CD4 count above 200 cells/mm^3 for more than 6 months.

The recommended regimen for secondary prophylaxis for toxoplasmosis is pyrimethamine and sulfadiazine plus leucovorin daily, which also protects against PCP. While sulfadiazine is generally dosed four times daily for treatment, it appears that twice-daily dosing for secondary prophylaxis is effective. Pyrimethamine and clindamycin plus leucovorin is an alternative option for patients who are unable to tolerate sulfadiazine; however, an additional agent must be given for PCP prophylaxis when this regimen is used. The high dose of clindamycin (600 mg every 8 hours) recommended may cause gastrointestinal intolerance in some patients. Atovaquone with or without pyrimethamine (plus leucovorin) or sulfadiazine is an additional option for secondary prophylaxis of toxoplasmosis with efficacy against PCP. It is possible that TMP–SMX could be used for secondary prophylaxis; however, data for this option are limited. As in primary prophylaxis, secondary prophylaxis should be restarted if the CD4 count declines below 200 cells/mm^3.

FUNGAL INFECTIONS

Primary and secondary prophylaxis

CANDIDIASIS

While prophylaxis with fluconazole has been shown to decrease the risk of development of mucosal candidiasis in HIV-infected individuals with low CD4 counts, routine primary prophylaxis is not recommended due to the cost, concerns for development of resistant candida infections, drug–drug interactions, and low morbidity and mortality caused by mucosal candida infections. Fluconazole can be considered for severe or frequent recurrent oropharyngeal, esophageal, or vulvovaginal candidal infections and posaconazole is an alternative for secondary prophylaxis of esophageal candidiasis. If secondary prophylaxis is elected, the optimal timing of discontinuation is unknown; however, discontinuation should be considered once the CD4 count is above 200 cells/mm^3 on ART.

CRYPTOCOCCOSIS

Primary prophylaxis against cryptococcal disease in the United States is not recommended for

HIV-infected individuals because of the low prevalence, the potential for drug–drug interactions and antifungal resistance, and the lack of proven benefit in mortality. HIV-infected patients diagnosed with cryptococcosis should complete at least 2 weeks of induction treatment, followed by at least 8 weeks of consolidation treatment. Once consolidation treatment is complete, HIV-infected people with cryptococcal disease should receive chronic maintenance treatment (or secondary prophylaxis) with fluconazole in order to prevent relapse. The discontinuation of secondary prophylaxis can be considered in individuals who have been treated with chronic maintenance therapy for at least 1 year and have achieved a CD4 count above 100 cells/mm^3 on at least 3 months on ART. Secondary prophylaxis against cryptococcal disease should be restarted if the CD4 count decreases below 100 cells/mm^3.

HISTOPLASMOSIS

HIV-infected individuals with a CD4 count below 150 cells/mm^3 who live in or travel to endemic areas should avoid exposures associated with increased histoplasmosis risk such as soil, chicken coops, bat and bird droppings, caves, and working on old buildings. Primary prophylaxis with itraconazole is effective at reducing frequency of histoplasmosis infections for people living with HIV with a CD4 count below 150 cells/mm^3 at high risk due to occupational exposure or residence in a community with a hyperendemic rate of histoplasmosis. Itraconazole must be dose-adjusted for ART and serum itraconazole levels. Primary prophylaxis should be discontinued for people on ART with a CD4 count of at least 150 cells/mm^3 for at least 6 months; and should be restarted for high-risk individuals if the CD4 count declines below 150 cells/mm^3.

Secondary prophylaxis of histoplasmosis with itraconazole can be discontinued in those with negative fungal blood cultures and a serum *Histoplasma* antigen below 2 enzyme immunoassay (EIA) units who have been treated with itraconazole for more than 1 year and have a CD4 count of at least 150 cells/mm^3 on ART for at least 6 months. Prophylaxis should be resumed if the CD4 count decreases below 150 cells/mm^3.

COCCIDIOIDOMYCOSIS

HIV-infected individuals living or traveling to areas endemic for *Coccidioides* should avoid disturbing soil and stay inside during dust storms. There is no proven benefit to primary prophylaxis of *Coccidioides*; however, it is reasonable to consider yearly *Coccidioides* IgM and IgG serologies for HIV-infected people living in endemic areas. Primary prophylaxis with fluconazole should be initiated for patients with a CD4 count below 250 cells/mm^3 and a newly positive IgM or IgG *Coccidioides* serology.

After treatment of coccidioidomycosis, suppressive therapy with fluconazole or itraconazole should be continued in HIV-infected patients. Posaconazole and voriconazole are alternative secondary prophylaxis options. HIV-infected individuals with focal coccidioidal pneumonia should be treated for at least 12 months, and then antifungal treatment can be discontinued if the CD4 count rises above 250 cells/mm^3 on ART. Patients with focal pneumonia should have continued monitoring with chest x-rays and coccidioidal serology after discontinuing prophylaxis. HIV-infected people with a history of diffuse pulmonary or nonmeningeal disseminated coccidioidomycosis are at risk for relapse despite CD4 counts $\geq$250 cells/mm^3 and use of ART. Therefore, consideration should be given for lifelong secondary prophylaxis for these individuals. Patients with coccidioidal meningitis are at high-risk for relapse and therefore should receive lifelong secondary prophylaxis.

MYCOBACTERIAL INFECTIONS

Primary prophylaxis

MYCOBACTERIUM TUBERCULOSIS

The annual risk of active tuberculosis (TB) infection in HIV-infected individuals with latent tuberculosis infection (LTBI) who are not on ART is 3% to 16% compared to a 5% lifetime risk in those without HIV. HIV-infected people should be tested for LTBI at the time of HIV diagnosis. Those with a CD4 cell count below 200 cells/mm^3 should be retested for LTBI once they have initiated ART and have a CD4 count $\geq$200 cells/mm^3. People at high risk for TB exposure should undergo annual LTBI testing. HIV-infected individuals should be counseled on the risks of working in or traveling to areas with a high prevalence of TB and should be evaluated for LTBI after return from international travel.

LTBI is defined by no clinical or radiographic evidence of TB and either: (1) the presence of a positive tuberculin skin test (TST) of $\geq$5 mm induration at 48 to 72 hours, or (2) a positive interferon-gamma release assay (IGRA) result. TST requires a second visit to read the result, is less specific for LTBI in individuals who have

received the bacille Calmette Guérin (BCG) vaccination, and is less sensitive in individuals with advanced HIV. IGRAs are also less sensitive in advanced HIV; however, they are more specific than TST and have less cross-reactivity to BCG vaccination and nontuberculous mycobacteria. Either TST or IGRA can be utilized for LTBI screening; however, routine use of both is not recommended. HIV-infected individuals in close contact with someone with infectious TB should also receive primary prophylaxis regardless of LTBI screening test results.

The recommended primary prophylaxis regimen for people diagnosed with LTBI is a 9-month course of isoniazid (INH) with pyridoxine daily. A preferred alternative option for LTBI treatment is INH twice weekly by directly observed therapy plus pyridoxine daily for 9 months. A 3-month course of INH and rifapentine given by weekly directly observed therapy is equally effective as 9 months of daily INH, but is not recommended for HIV-infected patients on ART because of the risk of drug interactions between rifapentine and some ART agents. Acceptable alternatives include rifampin or rifabutin for 4 months; however, these agents have considerably more interactions with ART compared to INH and must be dose-adjusted.

Individuals receiving LTBI treatment should be assessed at baseline and monthly thereafter with liver function tests including serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin. Those coinfected with HIV and viral hepatitis are at higher risk of INH-related hepatic toxicity and require closer follow-up. Liver enzymes typically increase in the first 3 months of INH therapy and then return to normal. LTBI treatment should be stopped in asymptomatic individuals with a greater than 5-fold increase in AST above the upper limit of normal, symptomatic individuals with a greater than 3-fold increase above the upper limit of normal, and individuals with baseline abnormal liver enzymes with a greater than 2-fold increase above baseline AST level.

DISSEMINATED *MYCOBACTERIUM AVIUM* COMPLEX DISEASE

Twenty percent to 40% of people living with HIV with advanced immunosuppression and no ART or primary prophylaxis will develop disseminated *Mycobacterium avium* complex (MAC) disease. However, with routine ART use the incidence of disseminated MAC has decreased 10-fold. HIV-infected individuals with a CD4 count below 50 cells/mm^3 should be clinically evaluated for active MAC disease with MAC isolator blood cultures and appropriate tissue biopsies obtained as indicated. If active disease is not present, these patients should receive primary prophylaxis against MAC with azithromycin and clarithromycin being the recommended agents. Rifabutin is an alternative prophylactic agent for individuals with no evidence of TB. Primary MAC prophylaxis should be discontinued in people on ART with a CD4 count above 100 cells/mm^3 for at least 3 months, and restarted if the CD4 count declines below 50 cells/mm^3.

Secondary prophylaxis

HIV-infected individuals diagnosed with disseminated MAC should continue secondary prophylaxis until they are asymptomatic, have completed at least 12 months of MAC treatment, and have had an increase in their CD4 count to above 100 cells/mm^3 sustained for at least 6 months after starting ART. Secondary prophylaxis should be restarted if the CD4 count declines below 100 cells/mm^3.

VIRAL INFECTIONS

Primary and secondary prophylaxis

CYTOMEGALOVIRUS DISEASE

Prior to ART, about 30% of people with AIDS developed Cytomegalovirus (CMV) retinitis prior to death. The incidence of CMV disease has decreased by 75% to 80% with widespread use of ART. Although oral valganciclovir was shown to prevent occurrence of CMV disease in individuals with a CD4 count below 100 cell/mm^3 prior to widespread use of ART, it is not recommended for primary prophylaxis because of cost, toxicity, and number needed to treat to significantly prevent occurrence of disease. In addition, oral ganciclovir is no longer available in the United States. People with CD4 counts below 50 cells/mm^3 should be evaluated with a yearly fundoscopic exam to recognize early disease.

The preferred regimens for chronic maintenance therapy or secondary prophylaxis of CMV retinitis after induction therapy is completed are valganciclovir plus ganciclovir intraocular implant (if sight-threatening retinitis present) or valganciclovir daily (if retinal lesions are small and peripheral). Alternative agents for secondary prophylaxis include ganciclovir, foscarnet, or cidofovir plus probenecid. Secondary prophylaxis

for CMV retinitis should be continued for at least 3 to 6 months until the lesions are inactive and the CD4 count has increased above 100 cells/mm^3 after at least 3 to 6 months of ART. Relapse is possible and ophthalmologic monitoring should occur at least every 3 months until immune reconstitution, and then annually thereafter, with the timing of discontinuation of secondary prophylaxis for CMV retinitis decided in consultation with an ophthalmologist. Secondary prophylaxis should be reinitiated if the CD4 count declines below 100 cells/mm^3.

Individuals with CMV gastrointestinal disease, pneumonitis, or central nervous system disease should receive ART and do not routinely require secondary prophylaxis after resolution of the acute CMV infection unless the patient has concurrent retinitis or prior relapse.

HERPES SIMPLEX VIRUS DISEASE

Consistent condom use reduces the risk of *Herpes simplex* virus (HSV)-2 transmission and HIV-infected HSV-2 seronegative individuals should consider asking their partners to undergo HSV type-specific antibody testing and should avoid sexual contact when their partner is having an outbreak. Primary prophylaxis of HSV is not recommended. Chronic suppressive HSV therapy is recommended for patients with severe recurrences or for individuals who want to limit the frequency of their recurrences. Oral valacyclovir, famciclovir, or acyclovir are all options for suppressive HSV therapy and can be continued indefinitely.

VARICELLA-ZOSTER VIRUS DISEASES

HIV-infected patients seronegative for *Varicella-zoster* virus (VZV) should avoid exposure to individuals with varicella or herpes zoster infection. VZV susceptible HIV-infected individuals with a known or suspected exposure to VZV should receive postexposure prophylaxis with varicella-zoster immune globulin (VariZIG), as soon as possible, but within 10 days, after exposure. Postexposure prophylaxis with acyclovir or valacyclovir can be considered; but has not been studied in this population.

Although the varicella vaccine is a live attenuated vaccine, it has been safely used in HIV-infected children with CD4 percentage of at least 15% and can be considered for VZV seronegative HIV-infected adults with a CD4 count of at least 200 cells/mm^3. There is increased risk of infection from vaccination in patients with advanced immunosuppression. Herpes zoster vaccine is US Food and Drug Administration (FDA) approved for immunocompetent individuals, but can be considered for off-label use in HIV-infected people aged 60 or older with a CD4 count of at least 200 cells/mm^3.

BACTERIAL INFECTIONS

Primary and secondary prophylaxis

The Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices recommends that HIV-infected individuals be vaccinated with both the pneumococcal polysaccharide (PPSV23) vaccine and the pneumococcal conjugate 13-valent (PCV13) vaccine. For those without prior pneumonia vaccination, the PCV13 should be given initially followed by the PPV23 at least 8 weeks later. If the PPV23 has already been given, the PCV13 should be deferred until at least 1 year after PPV23 vaccination. Consideration should be given to defer the PPV23 vaccine until the CD4 count is at least 200 cells/mm^3 to increase efficacy. The PPV23 vaccine should be repeated at least 5 years after the initial PPV23 vaccination in adults 64 years of age or younger. A third PPV23 dose is recommended for adults aged 65 years or older if at least 5 years has elapsed since the prior dose. Inactivated influenza vaccine is recommended annually in HIV-infected individuals and can reduce the risk of bacterial pneumonia as a complication of influenza. PCP prophylaxis with TMP–SMX and MAC prophylaxis with azithromycin or clarithromycin may reduce the risk of bacterial respiratory infection. However, these agents should not be used solely for prevention of bacterial infections due to the risks of developing drug resistant organisms.

HIV-infected individuals with recurrent *Salmonella* bacteremia can be considered for prophylaxis with an agent active against salmonella. However, the benefit of secondary prophylaxis for salmonella has not been well established and should be weighed against the risks of long-term antibiotic use. If secondary prophylaxis is utilized, it is likely that it can be stopped after response to ART with a CD4 above 200 cells/mm^3.

SUGGESTED READING

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PART XIII

Nosocomial infection

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103. Prevention of healthcare-associated infections in staff and patients

Karen Beydoun and Gonzalo Bearman

Healthcare-associated infections (HAIs) are defined as an infection acquired during the course of hospitalization and exclude infections that were either present or incubating at the time of admission. HAIs are a leading cause of death in hospitalized populations and are associated with an increased length of stay and high cost.

It is estimated that HAIs affect over 2 million patients per year with an approximate cost of over $4.5 billion annually in the United States.

There are multiple factors influencing HAIs. These include microbial agents and virulence, patient susceptibility, environmental factors, and bacterial resistance.

Evidence-based guidelines for infection control and prevention were created with the intention to decrease rates of HAIs and assure maximal adherence to these guidelines by healthcare workers (HCWs).

This chapter highlights infection prevention strategies and interventions that reduce rates of HAIs in modern healthcare settings.

HORIZONTAL VERSUS VERTICAL INFECTION CONTROL STRATEGIES

In the last decade, a significant paradigm shift in infection prevention has occurred. First, although all infections are not preventable by the current state of science, there is a growing emphasis on implementation of evidence-based infection interventions. There are currently two major infection control strategies, horizontal versus vertical infection control interventions.

A horizontal infection control strategy is defined as interventions attempting to decrease the rates of all infections produced by pathogens similarly transmitted. This approach is broad based and favors multipotent, common sense evidence-based infection prevention interventions such as robust hand hygiene (HH) practices, chlorhexidine (CHG) patient bathing, CHG impregnated central line dressings, central line checklists, and head of bed elevation in ventilated patients.

A vertical infection control strategy focuses on specific organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA) or vancomycin-resistant *Enterococcus* (VRE). This is considered a narrow infection prevention approach and may not impact the rates of all infections produced by pathogens similarly transmitted.

Notwithstanding some overlap between the two strategies, financial and personnel constraints prohibit full-scale implementation of all components of vertical and horizontal strategies broadly and simultaneously. Consequently, a horizontal infection prevention strategy may be the more effective approach. Wenzel *et al*. suggested that outcomes of horizontal programs outweigh those of programs with a vertical focus in terms of reduced mortality, years of life lost, and cost. Under this paradigm, a vertical, or pathogen-based, focus should be adopted only when the approach demonstrates a significant, incremental benefit atop a horizontal infection prevention strategy.

THE USE OF BUNDLES FOR INFECTION PREVENTION

The Institute for Healthcare Improvement (IHI) defines bundles as a "small straightforward set of practices," generally three to five interventions, that when performed collectively and reliably, have been demonstrated to improve patient outcomes. Bundles are a relatively new approach for the implementation of evidence-based clinical practice guidelines. Bundles are most effective when implemented with concurrent educational sessions on their purpose and methodology.

Important infection prevention bundles are targeted at ventilator-associated pneumonias (VAP), central line-associated bloodstream infections (CLABSIs), and urinary tract infections (UTIs) (Table 103.1).

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Table 103.1. Infecton prevention bundles

Ventilator-associated pneumonia (VAP)	– Elevation of the head of the bed to 30–45 degrees – Daily "sedation vacation" – Daily assessment for extubation – Peptic ulcer disease prophylaxis – Deep venous thrombosis prophylaxis
Urinary tract infection	– Evaluate daily the need for indwelling catheter – Maintain sterile technique for catheter insertion – Maintain a sterile closed drainage system – Secure the indwelling catheter to prevent migration of the catheter – Assure daily catheter care hygiene measures
Central venous line	– Hand hygiene – Maximal barrier precautions – Use of chlorhexidine as a skin antiseptic – Optimal catheter site selection – Daily assessment of line necessity – Prompt removal of central lines when indicated

Ventilator-associated pneumonia bundle

VAP is defined as pneumonia developing 48 hours or longer after mechanical intubation. Ventilator-associated pneumonias are associated with the highest mortality of all HAIs. Additionally, VAP is associated with excess antibiotic use, frequently caused by multidrug-resistant organisms (MDROs), and results in a significant increase in mortality, hospital length of stay, and cost.

Bereholtz *et al*. demonstrated a substantial (up to 71%) and sustained (up to 2.5 years) decrease in rates of VAP following the implementation of a VAP bundle. This bundle consists of four components: elevation of the head of the bed to 30–45 degrees, daily "sedation vacation," daily assessment for extubation, and peptic ulcer disease and deep venous thrombosis prophylaxis. In some institutions, the addition of CHG as an oral antiseptic was demonstrated as an effective VAP prevention strategy and should be included in the bundle.

Urinary tract infection bundle

Urinary catheters are utilized in more than 5 million patients in acute care hospitals and extended care facilities. Most catheter-associated UTIs are from the patient's own flora. A significant risk factor associated with UTIs is the prolonged and unnecessary use of urinary catheters.

This bundle includes daily evaluation of the need for the indwelling catheter, the use of a sterile technique for a catheter insertion, the consistent use of a sterile closed drainage system, the utilization of a secure system to prevent migration of the catheter, and daily compliant measures with catheter care hygiene.

Central venous line bundle

A CLABSI is defined as bacteremia or fungemia recovered in peripheral blood cultures in a patient with a central intravascular device and with no apparent source of infection at another anatomic site. Five evidence-based interventions constitute the central line bundle checklist, which when consistently implemented result in safer care and improved outcomes. This bundle includes HH, the use of maximal barrier precautions, the implementation of CHG as a skin antiseptic, optimal catheter site selection with avoidance, if possible, of the femoral vein, and daily assessment of line necessity with prompt removal when indicated. During the process of catheter insertion, the bedside nurse is empowered to stop the procedure in the event that any checklist items are missed.

HAND HYGIENE: NEW TECHNOLOGIES AND COMPLIANCE OBSERVATION STRATEGIES

HH is essential for the prevention of HAIs and remains the most effective method limiting the spread of pathogens in the hospital setting. Despite ongoing calls for HH, compliance among HCWs remains below 40%.

Recent advances in HH are worth highlighting. To boost compliance, products, including an alcohol-based hand-rub formulation or medicated soap, water, and drying agents, such as disposable paper or cloth towels, must be conveniently available and within 3 ft (1 m) of a patient's room. HH should be practiced by HCWs before and after all patient contact.

There are two accepted HH techniques. The first consists of hand rubbing with an alcohol-based hand-rub formulation. The procedure should take 20 to 30 seconds. The other technique is hand washing with soap and water. This procedure should take at least 15 to 30 seconds.

Alcohol-based HH formulations have certain advantages such as increased availability, higher antimicrobial efficacy, ease of use, and better skin tolerability. However, there are specific indications for the use of soap and water, such as when hands are visibly contaminated with blood, body fluids, or proteinaceous material and following exposure to spore-forming organisms such as *Clostridium difficile* or *Bacillus anthracis*.

Observation of HH is helpful to determine compliance and for feedback on methodology. Methods employed for HH observation include direct observation, self-reporting by HCWs, observation by patients, measurement of product usage, and electronic systems utilizing hand sensor technologies.

Although imperfect, direct observation obtained by trained observers remains the gold standard for HH measurement and the only method to evaluate HCWs during all potential types of HH opportunities. However, this method has limitations such as being time-consuming, costly, and laborious, particularly if attempts to document all HH opportunities at the bedside are made. Consequently, most HH observations focus on adherence by HCWs entering and leaving a patient room. The observation of HH is subject to the Hawthorne effect, resulting in improved HH compliance as a result of increased attention by superiors and colleagues. Self-reported HH adherence by HCWs and patient observation is generally unreliable.

New technologies may enhance HH practice. Electronic monitoring systems evaluate the rate of HH compliance by measuring the amount of product used at the level of a dispenser. Other promising electronic methods include the use of sensor badges detecting the presence of alcohol vapors on HCW hands after the application of waterless HH products. These badges are typically carried adjacent to HCW nametags. When coupled with electronic technologies that track HCWs entry and exit of patient rooms, blinking sensor badges are effective reminders of HH. Video technology has also been employed to enhance HH observation and adherence tracking. Newer technologies can improve HH adherence; however, cost is a barrier to widespread implementation.

CONTACT PRECAUTIONS

Contact precautions are frequently employed by healthcare systems to control MDROs and other pathogens. Contact precautions include the use of gowns, gloves, personal stethoscopes, and strict isolation of the patient.

Contact precautions are applied in both endemic and outbreak settings. Unlike in outbreak situations, the incremental benefits of contact precaution over standard precautions for pathogens in endemic settings are marginally beneficial. Additionally, a growing body of literature now reports adverse effects associated with contact precautions. Contact precautions are associated with increased medical errors; fewer patient visits by HCWs; delays in care; pressure ulcers; and increased patient anxiety, depression, and dissatisfaction with care.

Endemic pathogens such as MRSA or VRE may be controlled without the conventional use of contact precautions provided that multi-potent, horizontal, evidence-based infection prevention practices are consistently employed. Necessary elements for a less restrictive, noncontact precautions approach include a hospital-wide surveillance program for device-related infections and MDROs, a high compliance rate with HH program, adherence with infection prevention "bundles," the use of CHG impregnated central line dressings, and CHG bathing. Other relevant factors include a highly functional disinfection and sterilization program, the maximal use of private rooms, the implementation of an antimicrobial stewardship program, and staff education to improve compliance with infection prevention strategies. Surveillance and feedback measures should be implemented to ensure ongoing, sustained adherence to infection prevention best practices.

Contact precautions should be employed, as specified by the Centers for Disease Control and Prevention (CDC), for certain conditions including multidrug-resistant gram-negative rods, infectious diarrheas, viral infections, ectoparasitic disease, viral hemorrhagic infections, staphylococcal and streptococcal scalded skin syndromes, and novel respiratory pathogens.

Under this framework, contact precautions for the control of endemic pathogens, such as MRSA or VRE, may be of marginal benefit when robust and horizontal infection prevention efforts are maximally employed.

CHLORHEXIDINE BATHING AND CHLORHEXIDINE-IMPREGNATED SPONGE DRESSINGS (CHGIS)

The use of CHG in hospitals results in significant decreases in HAIs. Recent studies suggest that

CHG bathing and CHGIS can significantly reduce the rates of CLABSIs and colonization with MRSA, VRE, and gram-negative organisms. As an antiseptic, CHG has broad-spectrum antimicrobial activity with relatively low toxicity.

A total of 250 000 cases of CLABSI are estimated to occur annually in the United States with an associated mortality rate of up to 25% with an estimated cost of $34 000 to $56 000 per infection.

CHG bathing of hospitalized patients results in fewer BSIs. Multiple studies have demonstrated that daily CHG baths in critically ill patients reduce the colonization of patients with MRSA and VRE. A recent study in a general medical population resulted in 64% reduced risk of MRSA and VRE infections, demonstrating that daily CHG bathing is a beneficial infection control intervention for patients not only in the intensive care unit, but also in the general medical floor.

CHG now has multiple indications including oropharyngeal antisepsis to prevent VAP, presurgical skin preparation, impregnation of devices and dressings, and HCW hand disinfection. There are few adverse effects of bathing with CHG baths, most of them secondary to contact dermatitis or skin irritation that resolved after product use discontinuation.

The CHGIS is a recent advance in infection prevention. Its use is intended to reduce bacterial colonization at the catheter exit site with a resultant decrease in CLABSI rates. A recent study demonstrated that the use of CHGIS dressings resulted in lower rates of CLABSI (0.4 infections versus 1.3/1000 infections per catheter days) when compared to the standard dressings (0.4 infections versus 1.3/1000 infections per catheter days). This difference was observed atop an already low CLABSI rate following the successful introduction of a central line checklist.

In 2011, the use of CHGIS dressings to prevent CLABSI was designated by the CDC a Category 1B recommendation (Strongly recommended for implementation and supported by some experimental, clinical, or epidemiologic studies, and a strong theoretical rationale). The use of CHGIS dressings for central lines is now commonplace in modern healthcare centers.

COMPREHENSIVE UNIT SAFETY PROGRAM (CUSP) (TABLE 103.2)

The Comprehensive Unit Safety Program (CUSP) is a six-step program designed to improve awareness and implement strategies to enhance patient safety. By working as a team, CUSP can motivate HCWs to assume greater responsibility for patient safety.

Table 103.2 Elements of Comprehensive Unit Safety Program (CUSP)

- Staff education on safety
- Identification of hazards
- Senior executive partnership/safety rounds
- Understand the science of safety
- Tools to improve teamwork, communication, and the culture of safety
- Ongoing measurement, feedback, and improvement

First applied in 2003 known as a "The Keystone Project," it included over 100 intensive care units in Michigan. Within 18 months there was a two-third decrease in the rate of CLABSI, saving more than 1500 lives and nearly $200 million.

This method is currently in practice in several hospitals around the country and continues to demonstrate a dramatic decrease in HAIs.

The "key elements of CUSP" include:

Education on the basic science of safety: staff should be educated on all relevant patient safety matters.

Identification of hazards: team members utilize resources to identify potential hazards, including incident reporting system, liability claims, sentinel events, and morbidity and mortality. Staff members should ask daily about possible ways the next patient can be harmed and therefore attempt to fix the problem before it occurs.

Senior executive partnership/safety rounds: a hospital executive is assigned to work with the staff to prioritize safety improvement efforts and provide resources supporting these efforts. The partnership will also help the executive department facilitate a system-level perspective on quality and safety challenges existing at the unit level.

Understand the science of safety: aid HCWs to analyze patient safety as a science, with the goal of providing patient-centered care on hospital units.

Tools to improve teamwork, communication, and the culture of safety: the implementation of a variety of tools to support the practice of teamwork in a safe environment and reduce the patient harm potential. Tools include a daily goals checklist, morning briefing, shadowing another profession, and observing rounds.

Ongoing measurement, feedback, and improvement: results should be shared periodically to discuss potential hazards and evaluate ways for risk reduction.

CONCLUSION

HAIs are significant causes of morbidity, mortality, and excess cost. The prevention of HAIs requires implementation and ongoing assessment of evidence-based best practices through education, surveillance, feedback, checklists, and bundles. In addition, contact precautions must be used judiciously and appropriately to maximize benefit and minimize harm. Recent data suggest that CUSPs decrease adverse events and should be considered as part of a broader infection prevention strategy.

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104. Percutaneous injury: risks and prevention

David T. Kuhar

Healthcare personnel (HCP) are at risk of occupational exposure to bloodborne pathogens such as hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) from needlesticks and injuries from sharp objects. Risk factors for transmission of bloodborne pathogens as a result of occupational exposure are related to the source patient (e.g., titer and infectivity of the virus in his/her blood or body fluid), the injury (e.g., quantity of blood or body fluid transferred during the exposure), and the recipient individual (e.g., immunologic status).

Percutaneous exposures are the most common mechanism for transmission of bloodborne pathogens in healthcare settings. Hospital-based HCP in the United States are estimated to sustain an average of 384 325 (range: 311 091 to 463 922) percutaneous injuries annually. Data from several surveillance systems have demonstrated that the majority of reported injuries occur in the acute care setting, particularly medical floors, operating rooms, and intensive care units.

Prevention of bloodborne pathogen transmission through exposure prevention requires a diversified approach, including the development of improved engineering controls (e.g., safer medical devices), work practices (e.g., technique changes to reduce handling of sharp objects), and infection control measures, including use of personal protective equipment. Another important pre-exposure strategy to prevent infection includes HBV immunization.

Although preventing exposures is the primary means of preventing bloodborne pathogen infection, appropriate postexposure management is an important element of workplace safety. Healthcare organizations should have a system that includes written protocols for prompt confidential reporting, evaluation, counseling, treatment, and follow-up of any occupational exposures that may place HCP at risk for acquiring bloodborne infection. Each incident of occupational exposure to blood or body fluid that may contain HBV, HCV, or HIV should be evaluated as rapidly as possible and should include testing of the source patient for the appropriate bloodborne pathogens, testing of the exposed person for prior infection, and prompt administration of prophylactic agents when indicated.

INITIAL EXPOSURE MANAGEMENT AND EVALUATION

Wounds should be washed with soap and water. There is no evidence that the use of antiseptics for wound care or expressing fluid by squeezing the wound further reduces the risk of bloodborne pathogen transmission. However, the use of antiseptics is not contraindicated. The exposure should be evaluated for potential to transmit HBV, HCV, and HIV based on the type of potentially contaminated source body substance involved and the route and severity of the exposure. Blood, fluid containing visible blood, or other potentially infectious fluid (including semen; vaginal secretions; and cerebrospinal, synovial, pleural, peritoneal, pericardial, and amniotic fluids) or tissue can be infectious for bloodborne viruses.

The person whose blood or body fluid is the source of a percutaneous injury should be evaluated for HBV, HCV, and HIV infection. Information available in the medical record at the time of exposure (e.g., laboratory test results, admitting diagnosis, or past medical history) or from the source individual may help determine the likelihood of bloodborne virus infection. If the HBV, HCV, and/or HIV infection status of the source is unknown, the source person should be informed of the incident and tested for serologic evidence of bloodborne virus infection as soon as possible. Procedures should be followed for testing source persons, including obtaining informed consent, in accordance with applicable state and local laws. If the exposure source's infectious status cannot be determined (e.g., unknown source patient), decisions about postexposure management should be made on a case-by-case basis, after considering

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the type of exposure and the clinical and/or epidemiologic likelihood of infection with HBV, HCV, or HIV.

BLOODBORNE PATHOGENS

Hepatitis B virus infection

HBV infection is a well-recognized occupational risk for HCP. The risk of HBV infection is primarily related to the degree of contact with blood and also to the hepatitis B e antigen (HBeAg) status of the source patient. In studies of HCP who sustained injuries from needles contaminated with blood containing HBV, the risk of developing clinical hepatitis from exposure to hepatitis B surface antigen (HBsAg)- and HBeAg-positive blood was 22% to 31%, and the risk of developing serologic evidence of HBV infection, 37% to 62%. By comparison, the risk of developing clinical hepatitis from a needle contaminated with HBsAg-positive, HBeAg-negative blood was 1% to 6%, and the risk of developing serologic evidence of HBV infection, 23% to 37%.

All HCP at risk for contact with contaminated blood or body fluids should be vaccinated against HBV. Pre-vaccination serologic testing for previous infection is not performed for the majority of persons being vaccinated because of occupational risk unless the hospital or healthcare organization considers testing cost-effective. Regardless of vaccination history, testing is cost-effective for high-risk HCP populations including those born in geographic regions with high (≥8%) and intermediate (2%–7%) HBsAg prevalence, unvaccinated US-born HCP whose parents were born in regions of high HBsAg prevalence, HIV-positive HCP, HCP who have disclosed having engaged or currently engaging in high-risk substance abuse or sexual behaviors, and HCP who require immunosuppressive therapy or who are on hemodialysis. These HCP should be tested for HBsAg and anti-HBc/anti-HBs to determine infection status. Hepatitis B vaccine can be administered at the same time as other vaccines. If the vaccination series of the three recommended doses, given at time zero, 1 month, and 6 months, is interrupted after the first dose, the second dose should be administered as soon as possible. The second and third doses should be separated by at least 2 months. If only the third dose is delayed, it should be administered when convenient. To determine the need for revaccination and to guide postexposure prophylaxis, postvaccination serologic testing should be performed for all HCP at high risk for occupational exposure to blood or body fluids 1 to 2 months after completion of the three-dose vaccination series for a protective concentration of anti-HBs (≥10 mIU/mL). Persons who do not respond to the primary vaccine series should complete a second three-dose vaccine series or be evaluated to determine if they are HBsAg positive. Revaccinated persons should be retested at the completion of the second vaccine series.

HCP with previous documentation of a complete, ≥3-dose HepB vaccine series, but no documentation of anti-HBs ≥10 mIU/mL, may be at risk for HBV infection. Some experts suggest that they undergo anti-HBs testing upon hire or matriculation. Completely vaccinated HCP with anti-HBs <10 mIU/mL could receive an additional dose of HepB vaccine, followed by anti-HBs testing 1 to 2 months later. HCP whose anti-HBs remains <10 mIU/mL could receive two additional vaccine doses (to complete a second vaccine series), followed by repeat anti-HBs testing 1 to 2 months after the last dose.

Primary nonresponders to vaccination who are HBsAg negative should be considered susceptible to HBV infection and counseled regarding the need to obtain hepatitis B immunoglobulin (HBIG) prophylaxis for any known or probable exposure to HBsAg-positive blood (Table 104.1). Any blood or body fluid exposure of an unvaccinated susceptible person should lead to initiation of the hepatitis B vaccine series.

For percutaneous exposures to HBV-infected blood, the decision to provide prophylaxis must take into account several factors, including the HBsAg status of the source and the hepatitis B vaccination and vaccine-response status of the exposed person. The hepatitis B vaccination status and the vaccine-response status (if known) of the exposed person should be reviewed. Table 104.1 summarizes prophylaxis recommendations for percutaneous exposure to blood according to the HBsAg status of the exposure source and the vaccination and vaccine-response status of the exposed person. When HBIG is indicated, it should be administered as soon as possible after exposure (preferably within 24 hours). The effectiveness of HBIG when administered >7 days after exposure is unknown. Hepatitis B vaccine, when indicated, should also be given as soon as possible (preferably within 24 hours) and can be given simultaneously with HBIG (though it should be administered intramuscularly at a separate site, with vaccine always given in the deltoid muscle). For exposed persons who are in the process of being vaccinated, but have not completed the vaccination series, vaccination should be completed as

Table 104.1 Recommended postexposure prophylaxis for percutaneous exposure to hepatitis B virus (HBV), United States

Vaccination and antibody response status of exposed person[a]	Treatment when source is found to be:		
	HBsAg[b] positive	HBsAg negative	Source not tested or status unknown
Unvaccinated	HBIG[c] × 1; and initiate HB vaccine series[d]	Initiate HB vaccine series	Initiate HB vaccine series
Previously vaccinated			
Known responder[e]	No treatment	No treatment	No treatment
Known nonresponder[e]			
After 3 doses	HBIG × 1 and initiate revaccination	No treatment	If known high-risk source, treat as if source were HBsAg positive
After 6 doses	HBIG × 2 (separated by 1 month)	No treatment	If known high-risk source, treat as if source were HBsAg positive
Antibody response unknown	Test exposed person for anti-HBs[f] 1. If adequate,[e] no treatment 2. If inadequate,[e] HBIG × 1 and vaccine booster	No treatment	Test exposed for anti-HBs: 1. If adequate, no treatment 2. If inadequate, initiate revaccination

[a] Persons who have previously been infected with HBV are immune to reinfection and do not require postexposure prophylaxis.

[b] Hepatitis B surface antigen.

[c] Hepatitis B immunoglobulin; dose 0.06 mL/kg intramuscularly.

[d] Hepatitis B vaccine series. Healthcare personnel should be tested 1 to 2 months after completion of the vaccination series for anti-HBs.

[e] A seroprotective (adequate) level of anti-HBs after completion of a vaccination series is defined as anti-HBs $\geq$10 mIU/mL; a response $<$10 mIU/mL is inadequate and is not a reliable indicator of protection.

[f] Antibody to HBsAg.

scheduled and HBIG added. HBV testing should be performed on any exposed person who has an illness compatible with hepatitis.

Hepatitis C virus infection

HCV is not transmitted efficiently through occupational exposures to blood. The average incidence of anti-HCV seroconversion after accidental percutaneous exposure from an HCV-positive source is 1.8% (range, 0% to 7%). The risk for transmission after exposure to fluids or tissues other than HCV-infected blood has not been quantified but is thought to be low.

Healthcare professionals who provide care to persons exposed to HCV in the occupational setting should be knowledgeable regarding the risk for HCV infection and appropriate counseling, testing, and medical follow-up. Immunoglobulin and antiviral agents are not recommended for postexposure prophylaxis (PEP) after exposure to HCV. For the person exposed to a source with HCV viremia, testing for anti-HCV and alanine aminotransferase (ALT) activity should be performed at baseline. Follow-up testing for anti-HCV and ALT at 4 to 6 months is recommended and will identify those who were infected. However, follow-up testing only at 4 to 6 months postexposure will not allow for early detection of HCV infection. As the treatment response rate is higher in persons with acute, rather than chronic, HCV infection, more frequent monitoring with early treatment of acute HCV infection is favored by some experts.

One follow-up strategy advocated by some authorities involves periodic monitoring (e.g., every 4 to 6 weeks postexposure) of exposed HCP by polymerase chain reaction (PCR) for HCV RNA, following those who develop viremia over time to see if chronic infection develops, and then treating only individuals who remain positive for HCV RNA by PCR and have elevated ALT levels 12 weeks into the course of their infections. By this strategy, infected individuals have an opportunity to spontaneously clear their infections and be spared the toxicities and expense of interferon therapy. Other authorities suggest monitoring exposed HCP more frequently and implementing treatment sooner among those who develop HCV infection. These strategies represent reasonable approaches to the management of occupational HCV exposures based on the currently available information. HCV testing should be performed on any exposed person who has an illness compatible with hepatitis.

Human immunodeficiency virus infection

Prospective studies of HCP have estimated that the average risk of HIV transmission after a

percutaneous exposure to HIV-infected blood is approximately 0.3% (95% confidence interval [CI] = 0.2%–0.5%). Epidemiologic and laboratory studies suggest that a variety of factors may affect the risk of HIV transmission after an occupational exposure. In a retrospective case–control study of HCP who had percutaneous exposure to HIV, the risk for HIV infection was found to be increased with exposure to a larger quantity of blood from the source patient as indicated by (1) a device visibly contaminated with the patient's blood, (2) a procedure that involved a needle placed directly in a vein or artery, or (3) a deep injury. The risk was also increased for exposure to blood from source patients with terminal illness, probably reflecting the higher titer of HIV in blood late in the course of acquired immunodeficiency syndrome (AIDS). Taken together, these factors suggest a direct inoculum effect (i.e., the larger the viral inoculum, the higher the risk for infection).

HCP exposed to HIV should be evaluated as soon as possible (within hours) after their exposure and should be tested for HIV at baseline (i.e., to establish infection status at the time of exposure). Whenever possible, the HIV status of the exposure source patient should be determined to guide appropriate use of HIV PEP. Administration of PEP should not be delayed while waiting for test results. If the source patient is determined to be HIV negative, PEP should be discontinued and no follow-up HIV testing for the exposed provider is indicated.

Table 104.2 Recommended HIV postexposure prophylaxis regimens

Preferred HIV PEP regimen	
Raltegravir (Isentress®; RAL) 400 mg PO twice daily Plus Truvada™,1 PO once daily (Tenofovir DF [Viread®; TDF] 300 mg + emtricitabine [Emtriva™; FTC] 200 mg)	
Alternative regimens **(May combine one drug or drug pair from the left column with one pair of nucleoside/nucleotide reverse transcriptase inhibitors from the right column. Prescribers unfamiliar with these agents/regimens should consult physicians familiar with the agents and their toxicities.)**[a]	
Raltegravir (Isentress®; RAL)	Tenofovir DF (Viread®; TDF) + emtricitabine (Emtriva™; FTC); available as Truvada™
Darunavir (Prezista®; DRV) + ritonavir (Norvir®; RTV)	Tenofovir DF (Viread®; TDF) + lamivudine (Epivir®; 3TC)
Etravirine (Intelence®; ETR)	Zidovudine (Retrovir™; ZDV; AZT) + lamivudine (Epivir®; 3TC); available as Combivir®
Rilpivirine (Edurant™; RPV)	Zidovudine (Retrovir®; ZDV; AZT) + emtricitabine (Emtriva™; FTC)
Atazanavir (Reyataz®; ATV) + ritonavir (Norvir®; RTV)	
Lopinavir/ritonavir (Kaletra®; LPV/RTV)	
The following alternative is a complete fixed-dose combination regimen and no additional antiretrovirals are needed: Stribild™ (elvitegravir, cobicistat, tenofovir DF, emtricitabine)	
Alternative antiretroviral agents for use as PEP only with expert consultation	
Abacavir (Ziagen®; ABC)	
Efavirenz (Sustiva®; EFV)	
Enfuvirtide (Fuzeon™; T20)	
Fosamprenavir (Lexiva®; FOSAPV)	
Maraviroc (Selzentry®; MVC)	
Saquinavir (Invirase®; SQV)	
Stavudine (Zerit®; d4T)	
Antiretroviral agents generally not recommended for use as PEP	
Didanosine (Videx EC®; ddI)	
Nelfinavir (Viracept®; NFV)	
Tipranavir (Aptivus®; TPV)	
Antiretroviral agents contraindicated as PEP	
Nevirapine (Viramune®; NVP)	

[a] The alternative regimens are listed in order of preference; however, other alternatives may be reasonable based upon patient and clinician preference.

After exposure to HIV, PEP should be initiated as soon as possible. PEP should be administered for 4 weeks, if tolerated. The drug regimen selected for HIV PEP should have a favorable side effect profile, as well as a convenient dosing schedule to facilitate both adherence to the regimen and completion of 4 weeks of PEP. Given the complexity of choosing and administering HIV PEP, whenever possible, consultation with an infectious diseases specialist or another physician who is an expert in the administration of antiretroviral agents is recommended. Such consultation should not, however, delay timely initiation of PEP.

Table 104.2 lists the preferred regimen for HIV PEP, alternative regimens, medications to be used only in consultation with an expert, and medications that are not recommended for use as PEP. A regimen containing three (or more) antiretroviral drugs is now recommended routinely for all occupational exposures to HIV. Tenofovir (TDF) plus emtricitabine (FTC) plus raltegravir (RAL) is recommended as the preferred regimen for occupational exposures to HIV. This regimen is tolerable, potent, conveniently administered, and has been associated with minimal drug interactions. When prescribing PEP, anticipating and

Table 104.3 Practice recommendations for healthcare facilities (HCFs) implementing guidance for management of occupational exposures to bloodborne pathogens (BBPs)

Practice recommendation	Implementation checklist
Establish a BBP management policy	All institutions where HCP may experience exposures should have a written policy for management of exposures The policy should be based on the US Public Health Service (PHS) guidelines The policy should be reviewed periodically to ensure it is consistent with current PHS recommendations
Implement management policies	HCFs should provide appropriate training to all personnel on the prevention of and response to occupational exposures HCFs should establish hepatitis B vaccination programs HCFs should establish exposure-reporting systems HCFs should have personnel who can manage an exposure readily available at all hours of the day HCFs should have ready access to PEP for use by exposed personnel as necessary
Establish laboratory capacity for BBP testing	HCFs should provide prompt processing of specimens from exposed and source persons to guide management of occupational exposures Testing should be performed with appropriate counseling and consent
Select and use appropriate postexposure prophylaxis (PEP) regimens	HCFs should develop a policy for the selection and use of PEP antiretroviral regimens for HIV exposures within their institution Hepatitis B vaccine and hepatitis B immunoglobulin (HBIG) should be available for timely administration HCFs should have access to resources with expertise in the selection and use of PEP
Provide access to counseling for exposed healthcare personnel (HCP)	HCFs should provide counseling for HCP who may need help to deal with the emotional impact of an exposure and who should be instructed to use precautions to prevent secondary transmission during the follow-up period HCFs should provide medication adherence counseling to assist HCP complete human immunodeficiency virus (HIV) PEP as necessary
Monitor for adverse effects of PEP	HCP taking antiretroviral PEP should be monitored periodically for adverse events through clinical evaluation, including blood testing, at baseline and 2 weeks postexposure
Monitor for seroconversion	HCF should develop a system to encourage exposed HCP to return for follow-up testing Exposed HCP should be tested for hepatitis C virus (HCV) and HIV
Monitor exposure management programs	HCFs should develop a system to monitor reporting and management of occupational exposures to ensure timely and appropriate response Evaluate: Exposure reports for completeness and accuracy Access to care (i.e., the time of exposure to the time of evaluation) Laboratory result reporting time Review: Exposures to ensure that HCP exposed to sources not infected with BBPs do not receive PEP or PEP is stopped Monitor: Completion rates of HBV vaccination and HIV PEP Completion of exposure follow-up

pre-emptively treating side effects (e.g., nausea, diarrhea, etc.) commonly associated with taking antiretroviral agents is encouraged.

Re-evaluation of the exposed person should be performed within 72 hours postexposure, especially as additional information about the exposure or source person becomes available. HCP with occupational exposure to HIV should receive follow-up counseling regarding precautions to prevent secondary transmission during the follow-up period, postexposure testing, and medical evaluation regardless of whether they receive PEP. HIV testing should be performed for 6 months postexposure (e.g., at 6 weeks, 12 weeks, and 6 months). Use of fourth-generation combination HIV p24 antigen–HIV antibody immunoassays allow for earlier detection of HIV infection. If the clinician is certain that a fourth-generation combination HIV p24 antigen–HIV antibody test is being utilized, then HIV testing could be performed at baseline, 6 weeks, and concluded at 4 months postexposure. If PEP is used, the HCP should be monitored for drug toxicity by medical evaluation and by checking, at a minimum, complete blood counts, and renal and hepatic function tests at baseline and again 2 weeks after starting PEP. The scope of postexposure blood testing should be based on medical conditions in the exposed person and the anticipated toxicities of the drugs included in the PEP regimen. Further testing may be indicated if abnormalities were detected. HIV testing should be performed on any exposed person who has an illness compatible with HIV seroconversion.

GUIDANCE FOR HEALTHCARE FACILITIES

In Table 104.3, specific practice recommendations for the management of occupational bloodborne pathogen exposures are outlined to assist healthcare institutions with the implementation of established exposure management guidelines. All recommendations given are valid as of August 2013. Please see http://www.cdc.gov/hai/ for any updates.

DISCLAIMER

The findings and conclusions in this report are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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105. Hospital-acquired fever

Susan K. Seo and Arthur E. Brown

Fever is a common clinical problem in hospitalized patients. Although the development of fever in a hospitalized patient may be the clinical expression of a community-acquired infection that has completed its incubation period, this chapter focuses on the possible causes of new-onset fever occurring at least 48 hours after hospital admission. The reader, however, should keep other diagnoses in mind and inquire about the patient's history of travel, pet and animal exposure, hobbies (e.g., gardening, whitewater rafting and other adventure sports), sexual activity, dietary preferences, occupational exposures, recent immunizations, drug (including corticosteroids) and herbal ingestion within the past month, recent contact with febrile or ill individuals, and other epidemiologic factors such as season of the year.

Nosocomial fever occurs in 2% to 31% of medical inpatients. The wide range in prevalence rates has been attributed to differences in definition of fever, methods of temperature measurement, age of patients, and type of medical unit. Hospital-acquired fever may be due to an infectious and/or noninfectious cause, either happening alone or concurrently. An etiology can be identified after appropriate workup in 72% to 88% of patients. It is not uncommon for length of stay and resource utilization to be increased due to the management of the febrile episode.

Not surprisingly, nosocomial infections account for 56% to 74% of causes of fever in hospitalized patients and include bloodstream infections, lower respiratory tract infections, surgical site infections, and urinary tract infections (Table 105.1). Noninfectious causes comprise 14% to 31%. These are usually related to some form of vascular disruption (e.g., myocardial infarction, pulmonary embolism), inflammatory (e.g., gout) or collagen vascular disease (e.g., lupus), endocrine disorder (e.g., adrenal insufficiency), malignancy, or drug (Table 105.2). In some instances, the only identifiable factor may be an invasive procedure (e.g., surgery, bronchoscopy) performed within 24 hours of fever onset.

Table 105.1 Infectious causes of hospital-acquired fever

Bloodstream
Intravascular device-related (e.g., triple-lumen central venous catheter, Hickman, Broviac, Port)
Sepsis due to bacterial or fungal organisms
Central nervous system
Epidural abscess
Meningitis
Gastrointestinal
Cholangitis
Diverticulitis
Intra-abdominal abscess
Pseudomembranous colitis
Respiratory tract
Aspiration pneumonia
Empyema
Hospital-acquired pneumonia
Sinusitis
Ventilator-associated pneumonia
Skin and soft tissue
Cellulitis
Myonecrosis
Necrotizing fasciitis
Surgical site (incisional, deep space, or abscess)
Urinary tract
Catheter-related
Postinstrumentation (e.g., cystoscopy)
Other
Endocarditis
Prosthetic-device infection
Suppurative thrombophlebitis
Transfusion-related (bacterial, fungal, viral, parasitic)

A comprehensive review of the patient's history and a full physical exam should be performed to find clues to the source(s) of fever. Disorders of immune function, valvular heart disease, history of previous placement of prosthetic devices (e.g., orthopedic), prior illness and treatment including for multidrug-resistant

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Table 105.2 Examples of noninfectious causes of hospital-acquired fever

Biologic agents (e.g., vaccines, cytokines)/drugs
Alcohol or drug withdrawal
Drug fever
Drug overdose (e.g., anticholinergic agents)
Neuroleptic malignant syndrome
Cardiac causes
Myocardial infarction
Pericarditis
Collagen vascular diseases
Vasculitis
Endocrine disorders
Adrenal insufficiency
Thyroid storm
Factitious fever
Inflammatory diseases
Gout, pseudogout
Nonviral hepatitis
Intra-abdominal conditions
Acalculous cholecystitis
Acute pancreatitis
Mesenteric ischemia
Upper or lower gastrointestinal bleeding
Malignancy
Tumor fever
Neurologic conditions
Intracranial or subarachnoid hemorrhage
Seizures
Stroke
Subdural hematoma
Procedure related
Benign postoperative fever
Endobronchial intubation
Transfusion reaction
Thromboembolic disease
Deep venous thrombosis
Pulmonary embolus
Superficial thrombophlebitis
Vascular conditions
Sickle cell crisis

organisms, drug allergies, and history of transplantation should be reviewed with the patient. Attention should also be paid to risk factors for hospital-acquired fever such as recent surgical, endoscopic, or interventional radiologic procedures, recent urinary and respiratory tract instrumentation, intravascular devices, drug therapy, and immobilization. The physical examination should be complete but focus on vital signs; general appearance; signs of toxicity; skin rash; presence of genital, mucosal, and/or conjunctival lesions; presence of cardiac murmur or rub; new crackles; decreased breath sounds; egophony and/or pleural friction rub on lung auscultation; abdominal tenderness; hepatosplenomegaly; costovertebral angle tenderness; arthritis; spinal tenderness; meningismus; and/or neurologic dysfunction.

Obviously, the postoperative patient will have special attention given to the operative site and wounds. Consultation with the surgeon regarding the operative findings, technical difficulties, and complications is essential. Similarly, conferring with the endoscopist after bronchoscopy, endoscopic retrograde cholangiopancreatography, colonoscopy, or cystoscopy may reveal information regarding the etiology of postendoscopic fever in such a patient. The patient with cancer may receive a significant amount of blood products over time and may develop transfusion-related infections (see Chapter 106, Transfusion-related infection). Infections found in the alcoholic, drug abusing, thermally injured, diabetic, elderly, or immunocompromised patient require special consideration (see chapters covering these topics). The immunocompromised patient with cancer in particular may have a variety of possible infectious etiologies to consider (see Chapter 86, Infections in patients with neoplastic disease).

The investigation of hospital-acquired fever should take into consideration possible foci of infection. The initial evaluation typically includes a complete blood count, urinalysis, chest radiograph, and cultures of blood, urine, and, if indicated, sputum. Adequate sputum for microbiologic evaluation should contain few epithelial cells and numerous polymorphonuclear neutrophils if the patient is not neutropenic. However, obtaining a good specimen, particularly in critically ill and/or neutropenic patients, might be difficult. Appropriate cultures of wound sites and drainage are also important. It is essential to obtain fresh material from the drainage site rather than the material that has been dwelling in the collection apparatus. In the patient with diarrhea, stool specimens should be obtained and tested for *Clostridium difficile* toxin. When a rash is present, a biopsy of the skin should be obtained for both histologic and microbiologic examination. Vascular access devices are suspect. If possible, these should be removed, and the tips sent for culture.

It is important that the specimens are obtained correctly and are transported to the microbiology laboratory quickly. This aids in the recovery of fastidious organisms, particularly anaerobic bacteria. Examination of the Gram-stained specimen is useful in judging the adequacy of the specimen and aids in the presumptive etiologic diagnosis.

This information is invaluable as the clinician can better tailor empiric antimicrobial therapy until final culture results are available. New molecular (e.g., real-time polymerase chain reaction [PCR], antigen detection) and other nonculture-based (e.g., procalcitonin) techniques are increasingly being used as adjuncts to traditional cultures, can potentially reduce the time to diagnosis for infection, and may assist in optimizing antimicrobial use.

Further radiographic studies may be needed, depending on the clinical situation. Appropriate computed tomography scans should be conducted to locate a deep (i.e., pelvic) source of fever in a postoperative patient who underwent abdominal surgery. Ultrasonographic studies help in evaluating the liver and spleen and the vascular system. Sometimes, gallium scans or indium-labeled white blood cell scans may assist in locating occult foci of infection. Once located, radiographically guided drainage or open drainage of the abscess can be achieved.

In summary, determining the cause of fever in hospitalized patients can be very challenging. Although infection is common, the clinician needs to be aware that hospital-acquired fever may constitute a variety of other conditions.

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106. Transfusion-related infection

William R. Jarvis and Virginia R. Roth

The transfusion of blood and blood components is associated with a very low but ever-present risk of infection. It is estimated that 1 in every 2000 units of blood may carry an infectious agent and that about 4 in 10 000 recipients develop a chronic disease or die as a result of receiving contaminated blood. A wide variety of viral, bacterial, and parasitic agents have been associated with blood transfusion (Table 106.1). Concerns have also been raised about the potential for transmission of Creutzfeldt–Jakob disease (CJD) and its new variant (vCJD) through blood products. However, no human episodes of CJD or vCJD have been definitively linked to blood or blood component transfusion to date, and case–control studies have not found blood transfusion to be a risk factor for CJD. The risk of viral transmission has been markedly reduced with improved screening, particularly using nucleic acid testing (NAT). The risk is now estimated to be 1 in 2 million units for human immunodeficiency virus (HIV) or hepatitis C virus (HCV) and approximately 1 in 200 000 units for hepatitis B virus (HBV). Because the risk of viral or parasitic infection is very low and blood is screened for HCV, HBV, HIV, and human T-cell lymphoma/leukemia virus (HTLV) 1, the remainder of this chapter focuses on bacterial complications of blood transfusion, which can be diagnosed and treated.

Although the rate of bacterial contamination of blood products is unknown, the rate of bacterial infection associated with blood products is estimated to be similar to that of viral infection. The Bacterial Contamination of Blood Products (BaCON) study, a collaboration among the Centers for Disease Control and Prevention (CDC), American Red Cross, American Association of Blood Banks (AABB), and Department of Defense, conducted active surveillance for transfusion-transmitted bacteremia between 1998 and 2000. There were 34 bacteremic episodes and 9 deaths. The rate of transfusion-transmitted bacteremia (events per 106 units) was 9.98 for single-donor platelets, 10.64 for pooled platelets, and 0.21 for red blood cell units; for fatal reactions, the rates were 1.94, 2.22, and 0.13, respectively. The fatality rate associated with transfusion-related sepsis has been estimated to be 1 in 6 million transfused units. Transfusion-transmitted bacterial sepsis is the second most common cause of transfusion-related fatality (after clerical error). Between October 1995 and September 2004, 85 (13%) of 665 transfusion fatalities reported to the Food and Drug Administration were due to bacteria; 58/85 (68%) were due to gram-negative bacteria. In 2008, there were approximately 24 million blood components transfused. During FY2008, there were 46 FDA-reported transfusion-related fatalities, with subsequent reports of 44 in FY2009, 40 in FY2010, and 30 in FY2011. Of these, 5 (11%), 2 (5%), and 4 (13%) in FY 2009, FY2010, and FY2011, respectively, were traced to microbial infection. In FY2010 and FY2011, *Babesia*, *Staphylococcus aureus*, *Escherichia coli*, *Morganella morganii*, and *Klebsiella pneumoniae* accounted for all the fatalities. However, more common nonfatal episodes of transfusion reaction, which may result from bacterial contamination of blood or blood components, often are assumed to be an immune response to transfused leukocytes and are not fully investigated for contamination.

WHOLE BLOOD AND ERYTHROCYTES

After collection, whole blood may be maintained at room temperature for ≤8 hours before being stored at 1°C to 6°C (33.8°F to 42.8°F) up to 35 to 42 days, depending on the additives used (Table 106.2). Erythrocytes may be prepared from whole blood at any point during the normal storage period of the whole blood. Then, the erythrocytes may be stored at 1°C to 6°C up to the expiration date of the whole blood unit from which they were prepared. The growth of psychrophilic organisms, such as *Yersinia enterocolitica* or *Pseudomonas* species, is favored

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Table 106.1 Infections transmissible by blood transfusion

Viruses
Hepatitis
Hepatitis A virus (HAV)
Hepatitis B virus (HBV)
Hepatitis C virus (HCV)
Hepatitis D virus (HDV)
Hepatitis E virus (HEV)
Hepatitis G virus (HGV)
Cytomegalovirus (CMV)
Epstein–Barr virus (EBV)
Nonhepatitis
HIV-1 and -2
HTLV-1 and -2
Human herpesvirus 8 (HHV-8)[a]
Parvovirus B19
Colorado tick fever virus
West Nile virus
Dengue virus
Severe acute respiratory syndrome (SARS) virus
variant Creutzfeld–Jakob disease (vCJD)
Chikungunya virus
Avian influenza virus[a]
Bacteria
Yersinia
Pseudomonas
Staphylococcus
Other gram-positive or gram-negative bacteria
Rickettsia
Spirochetes
Syphilis
Recurrent fever
Lyme disease[a]
Ehrlichia[a]
Protozoa
Plasmodium spp. (malaria)
Babesia microti
Babesia spp.
Trypanosoma cruzi (Chagas disease)
Toxoplasma spp.
Leishmania spp.
Nematode (loasis, other microfilaria)
Treponema pallidum (syphilis)

Abbreviations: HIV = human immunodeficiency virus; HTLV = human T-cell lymphoma/leukemia virus.

[a] Potential risk only, no reported case.

by these storage conditions, accounting for most erythrocyte transfusion-related sepsis episodes (Table 106.3). These episodes tend to occur with units that have been stored for >14 to 25 days, which reflects a growth lag of about 7 to 14 days followed by exponential growth of the organism; levels of 10^9 organisms/mL are reached by 38 days, and 315 ng of endotoxin/mL (approximately 4000 EU/mL) by 28 to 34 days. Transfusion of such units can lead to both septic and endotoxic shock.

Table 106.2 Blood component storage conditions and estimated bacterial contamination rates

Component	Storage conditions	Estimated contamination rate
Whole blood CPDA-1 CPD plus AS	≤8 h at room temp ≤35 d at 1°C–6°C ≤45 d at 1°C–6°C	0.03%
Packed red blood cells CPDA-1 CPD plus AS	≤35 d at 1°C–6°C ≤45 d at 1°C–6°C	≤0.5%
Platelets	≤5 d at 20°C–24°C	Single donor, ≤2.5% Pooled, ≤10%
Plasma	Frozen, stored ≤18°C For use, thawed and stored ≤24 h at 1°–6°C	≤0.1%

Abbreviations: CPDA = citrate-phosphate-dextrose-adenine (additives); CPD = citrate-phosphate-dextrose; AS = adenine saline (additives).

PLATELETS

Each year, approximately 9 million platelet-unit concentrates are transfused in the United States. Platelets are stored in oxygen-permeable containers with agitation at 20°C to 24°C (68°F to 75.2°F) for ≤5 days. The most common transfusion-associated infection reported in the United States is bacterial contamination of platelet components. Bacterial contamination is estimated to occur at the incidence rate of 1:1000 to 1:3000 platelet units. Platelet transfusion-related sepsis usually involves common skin organisms, e.g., *Staphylococcus epidermidis, S. aureus*, or other aerobic bacteria that can grow rapidly at room temperature (Table 106.3). Sepsis episodes related to platelet transfusion also tend to occur with units that are late in the storage period (around 4 to 5 days), when there may be a higher titer of organisms than early in the storage period. In addition, sepsis episodes occur more frequently with pooled platelet units than with single-donor apheresis units. A pooled platelet unit is prepared by combining 6 to 10 random donor platelet concentrates up to 4 hours before transfusion. In contrast, an apheresis unit is prepared by separating platelets from the whole blood of a single donor and returning other blood components to the donor. The higher rate

Table 106.3 Reported episodes of transfusion-associated sepsis

		Duration in days from collection to transfusion	
PATHOGEN	PERCENTAGE	MEDIAN	RANGE
Erythrocytes			
Yersinia enterocolitica	49.0	24	7–41
Pseudomonas fluorescens	23.5	24	16–32
Serratia liquefaciens	7.8	21	17–26
Treponema pallidum	2.0	≤1	–
Pseudomonas putida	2.0	–	–
Other species	15.7	23	20–26
Platelets			
Staphylococcus epidermidis	33.3	4	3–5
Salmonella choleraesuis	11.7	≤1	–
Serratia marcescens	8.3	2	1–3
Staphylococcus aureus	5.0	5	3–6
Bacillus cereus	5.0	–	–
Streptococcus viridans group	3.3	3	1–6
Salmonella enteritidis	3.3	5	3–5
Other species	23.3	4	2–6

of sepsis associated with pooled platelets primarily is seen because, on average, pooled platelets are stored longer than apheresis platelets. With pooled platelets, there also is a higher risk of contamination associated with the exposure to multiple donors or with the manipulation of the concentrates. In March 2004, an AABB standard was introduced that required routine quality control testing for bacterial contamination of apheresis platelet products. On January 31, 2011, a new AABB Standard, 5.1.5.1.1, specified that bacterial detection methods for PLT components shall use assays either approved by the Food and Drug Administration (FDA) or validated to provide sensitivity equivalent to these FDA-approved methods. These were implemented in many US and Canadian blood centers and have reduced the risk of platelet-associated bacterial infection.

PLASMA AND PLASMA-DERIVED PRODUCTS

Plasma is either collected by apheresis or prepared from whole blood and is stored at below −18°C (−0.4°F) within 6 hours of collection. It can be thawed in a water bath using a plastic overwrap or in a microwave and subsequently stored at 1°C to 6°C up to 24 hours before transfusion. The survival of bacteria is not supported by these storage conditions. However, equipment may carry contamination; for example, one reported episode of sepsis associated with a plasma transfusion was attributed to a contaminated water bath used for thawing the unit.

Contamination of plasma-derived products also is thought to be rare. They are prepared from plasma stored under very stringent conditions, and many of the products also undergo viral inactivation procedures. However, contamination may still occur, as demonstrated by outbreaks of hepatitis C virus infections associated with the administration of contaminated intravenous immunoglobulin or hepatitis A virus associated with plasma-derived products.

SOURCES OF CONTAMINATION

Contamination of blood or blood components may occur intrinsically if a donor is bacteremic or viremic at the time of donation; it may also occur extrinsically from the skin during phlebotomy or from containers and other equipment used during processing and storage. The infecting organism may reflect the source of contamination. With *Y. enterocolitica*-contaminated erythrocytes, the implicated source is often an asymptomatic episode of gastrointestinal (GI) illness within the previous month. Because the GI illness is usually

mild, the donor may not recall or may neglect to report the episode during prescreening.

CLINICAL MANAGEMENT

Although these contamination episodes are rare, it is important to consider the possibility of blood and blood component contamination when a patient develops a fever during or soon after a transfusion (Figure 106.1). If bacteremia cannot be ruled out, the transfusion should be stopped immediately. Any residual blood product or administration set should immediately be quarantined and refrigerated. A Gram-stain and/or acridine orange-stain smear of the blood product should be performed. Stain and/or culture of blood component segments usually are negative, even when the unit itself is positive; this may reflect low-level contamination of the unit at the time of donation. Cultures of the blood product in the bag, the patient's blood before antimicrobials are begun, and any intravenous solution used during transfusion should be obtained promptly. Information about the donor should be reviewed completely. If organisms are recovered from the recipient and blood product, molecular typing of patient and donor isolates may prove causality.

After appropriate cultures are obtained, broad-spectrum empiric antimicrobial therapy should be started. Empiric treatment of suspected sepsis associated with blood products must be based on the component. Because most reported sepsis episodes associated with erythrocyte transfusion have been caused by *Y. enterocolitica* or *Pseudomonas* species, particularly *Pseudomonas fluorescens*, initial therapy may include trimethoprim–sulfamethoxazole or an antipseudomonal β-lactam plus an aminoglycoside. Because infectious complications associated with platelets usually are caused by aerobic bacteria, e.g., coagulase-negative staphylococci or *S. aureus* and occasionally gram-negative organisms, initial empiric therapy may include a penicillinase-resistant penicillin and an aminoglycoside. Empiric therapy should be narrowed as soon as an infecting pathogen is identified and antimicrobial susceptibility results are available.

Table 106.4 Prevention of transfusion-associated sepsis

Donors
Screen for infectious diseases (health questionnaire); inquire about travel, behaviors, dental work, signs and symptoms of recent illness
Phlebotomy
Inspect site; avoid dimpled areas of the skin Prepare site properly Use aseptic techniques
Bag and component preparation
Use aseptic techniques Perform proper cleaning and disinfection of processing equipment; use plastic overwraps in water baths for thawing Use appropriate storage conditions Visually inspect contents before transfusion

PREVENTION

Sensitive, rapid diagnostic tests for detecting bacterial contamination are not yet available. Therefore, minimizing the risk of transfusion-associated sepsis depends on appropriate donor screening, donor site inspection and preparation, and proper handling of the blood components (Table 106.4). Detection of infectious complications

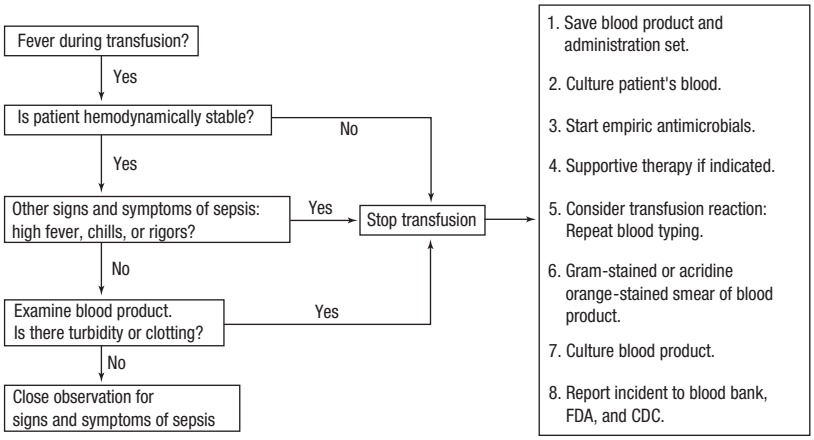

Figure 106.1 Algorithm for the evaluation of fever associated with transfusion.

associated with blood products may be increased by educating the medical and blood bank staff about the signs and symptoms of patients with transfusion reactions, the importance of immediately reporting transfusion reactions to the blood bank, promptly culturing the blood of the recipient, promptly performing stains and culture of the blood component, and ensuring quarantined refrigerated storage of the unit and administration set until contamination has been excluded.

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107. Intravascular catheter-related infections

Anne-Marie Chaftari and Issam Raad

Central venous catheters (CVC) secure vascular access for fluids, medications, blood products, total parenteral nutrition (TPN), and hemodialysis. They are employed for both inpatients and outpatients. The Centers for Disease Control and Prevention (CDC) estimates that 41 000 central line-associated bloodstream infections (CLABSIs) occur annually in hospital intensive care units in the United States. Among patients with long-term CVCs, more than 250 000 CLABSIs occur annually. The National Healthcare Safety Network (NHSN) reports a rate of 1.5 CLABSIs per 1000 central line-days in the United States with a mortality rate of 12% to 25%. A healthcare cost of $45 814 is estimated for each CLABSI in the United States.

PATHOGENESIS

Colonization is universal after insertion of a CVC, occurring as early as 1 day after insertion, and is independent of catheter-related infection. Electron microscopy studies of catheter surfaces show that adherent microorganisms can be found in either a free-floating form or a sessile form embedded in a biofilm.

The process of adherence results from the interaction of three factors: intrinsic properties of the catheter, microbial factors, and host-derived proteins. The surface irregularities and charge difference of the catheter facilitate bacterial adherence. Some microorganisms adhere better to polyvinyl chloride, silicone, and polyethylene surfaces than to Teflon polymers and polyurethane. Concomitantly, a thrombin sheath forms on the internal and external surfaces of the catheter. This sheath results from the deposition of proteins such as fibrinogen, fibronectin, laminin, and thrombospondin.

Microorganisms colonize vascular catheters through different sources: For short-term catheters, the skin of the site of insertion is the major source for colonization; bacterial skin flora migrate along the external surface of the catheter. The hub of the vascular device is the most common source of colonization for long-term catheters, with microorganisms introduced from the hands of medical personnel. In this case, colonizing bacteria migrate along the internal surface of the catheter. Hematogenous seeding and contamination of the infusate or additives such as contaminated heparin flush are rare causes of colonization and infection of vascular devices.

Colonizing microorganisms adhere via a biofilm of extracellular, polysaccharide-rich material, or glycocalyx. Biofilms form on the external surface of short-term catheters and internal surface of long-term catheters (dwell time of at least 30 days). This biofilm enables bacteria to adhere to the catheter and to resist antibiotics, making their eradication difficult.

Other factors increase the risk for CLABSI; femoral catheterization has higher rates of infections and thrombotic complications than subclavian catheterization; transparent occlusive dressing is associated with significantly increased rates of insertion site colonization, local catheter-related infection, and CLABSI when CVCs remain for more than 3 days, compared to gauze dressing.

Skin flora such as *Staphylococcus epidermidis, Staphylococcus aureus*, *Bacillus* species, and *Corynebacterium* species remain the predominant source of CLABSI, followed by microorganisms that contaminate the hands of medical personnel, such as *Pseudomonas, Acinetobacter, Stenotrophomonas maltophilia*, and *Candida*. Emerging pathogens such as *Achromobacter*, rapidly growing mycobacteria (*M. chelonae* and *M. fortuitum*), and fungal elements such as *Fusarium, Malassezia furfur*, and *Rhodotorula* species have been described in *specific* conditions (i.e., hyperalimentation, interleukin-2 therapy).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The clinical presentation of CLABSI consists of nonspecific systemic signs and local manifestations at the skin insertion site.

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Table 107.1 Diagnosis of central line-associated bloodstream infections (CLABSI) according to the Centers for Disease Control and Prevention (CDC) definition and to the Infectious Diseases Society of America (IDSA) 2009 guidelines for the diagnosis and management of intravascular catheter-related infections

CDC definition of central line-associated bloodstream infections (CLABSIs)[a].	IDSA 2009 definition of intravascular catheter-related bloodstream infection (CRBSI)

Patient has a CVC that was in place for > 2 days and CVC was present on the date of the LCBI or the day before. In addition, the LCBI must not be related to an infection at another site and must meet one of the following criteria:
• A recognized pathogen cultured from one or more blood cultures
• A common skin contaminant cultured from *two* or more blood cultures drawn on separate occasions within 2 days of each other and at least *one* of the following clinical signs or symptoms: fever (>38°C), chills, or hypotension *and* signs and symptoms
• For patient ≤ 1 year of age, a common skin contaminant is cultured from two or more blood cultures drawn on separate occasions within 2 days of each other and the patient has at least one of the following clinical signs or symptoms: fever (>38°C core), hypothermia (<36°C core), apnea, or bradycardia
	• **Diagnostic method sparing the catheter**: A definite CRBSI requires one of the following to be present:
	  • The same organism is cultured from two simultaneous quantitative blood cultures drawn from the catheter and peripheral site with a CVC/peripheral colony count ratio ≥3:1
	  • The differential time to positivity of at least 2 hours (microbial growth from blood drawn from a catheter is detected at least 2 hours before microbial growth from blood drawn from the peripheral site)
	• **Diagnostic method implicating catheter removal**:
	A definite CRBSI requires that the same organism is cultured from at least one percutaneous blood culture and from a culture of the catheter tip (in semiquantitative catheter culture ≥15 CFU per catheter segment, or in quantitative catheter culture ≥10^2 CFU per catheter segment)

[a] CDC definition of CLABSI does not require catheter removal.

Abbreviations: CVC = central venous catheter; LCBI = laboratory-confirmed bloodstream infection.

The systemic features include fever and chills, which may be accompanied by hypotension, hyperventilation, altered mental status, and nonspecific gastrointestinal manifestations such as nausea, vomiting, abdominal pain, and diarrhea. Deep-seated infections such as endocarditis, osteomyelitis, retinitis, and organ abscess may complicate CLABSI caused by virulent organisms such as *S. aureus*, *Pseudomonas aeruginosa*, and *Candida albicans*.

Local manifestations are neither sensitive nor specific. On one hand, they may be absent, especially in immunocompromised patients. On the other hand, peripherally inserted central catheter (PICC) lines may produce sterile exit site inflammation (26%).

The diagnosis of catheter-related infection is challenging. A definite diagnosis often requires catheter removal and culture and is thus retrospective. The CDC and the Infectious Diseases Society of America (IDSA) definitions of intravascular catheter-related bloodstream infections (CRBSI) are summarized in Table 107.1.

The CLABSI definition may lack specifity. For example, in some cancer patients, particularly those with compromised mucosal barrier, some laboratory-confirmed bloodstream infections (LCBI) that are labeled CLABSI may have resulted from bacteria translocation from the gastrointestinal tract. To distinguish LCBI related to central lines from those due to inapparent sources, the CDC recently developed a new definition termed mucosal barrier injury LCBI (MBI-LCBI) whereby a recognized intestinal organism is cultured from the blood of patients with clues to mucosal barrier injury such as gastrointestinal graft-versus-host disease, diarrhea, or neutropenia.

CRBSI as defined by the IDSA more specifically identifies the CVC as the source of the bacteremia.

PREVENTIVE STRATEGIES

Recent guidelines for the prevention of intravascular catheter-related infections emphasize the importance of educating and training healthcare personnel who insert and maintain catheters. CVCs should only be used when medically necessary and should be removed as soon as possible. The subclavian site is preferred for nontunneled CVC. Femoral sites should be avoided in adult patients.

Hand hygiene with soap and water or alcohol-based rubs should be performed before and after inserting, replacing, accessing, or dressing a CVC. The use of maximal sterile barrier precautions that includes the use of a cap, mask, sterile gown, and a sterile full body drape is recommended for CVC insertion.

Skin cleansing using chlorhexidine preparation before CVC insertion reduces the risk of CLABSI. Alternatively, tincture of iodine or 70% alcohol could be used when chlorhexidine is contraindicated.

Chlorhexidine impregnated sponge dressing may decrease CVC colonization.

Currently, the CDC guidelines for the prevention of intravascular catheter-related infections recommend the use of antimicrobial CVC particularly if the CVC is expected to remain in place for more than 5 days, if rates of CLABSI remain elevated despite the implementation of aseptic techniques including maximal sterile barrier precautions. A meta-analysis showed better efficacy of vascular catheters impregnated with the antiseptics chlorhexidine and sulfadiazine in preventing CLABSI when compared with non-impregnated catheters. Several meta-analyses demonstrated the effectiveness of antimicrobial catheters impregnated with CHSS or M-R. Catheters coated with minocycline and rifampin demonstrated a lower rate of catheter colonization and CLABSI when compared with uncoated catheters. Furthermore, when compared with antiseptic impregnated catheters, antibiotic-coated catheters lowered the rate of infection 12-fold.

Dressing choice may vary: sterile, transparemt dressing allows visual monitoring of the CVC and requires less frequent changes than sterile gauze.

Regular monitoring of CVC by visual inspection or by palpation through the dressing is recommended.

Antimicrobial catheter lock and flush solutions are recommended particularly in patients who have long-term catheters and a history of multiple CLABSIs.

Catheter lock solution technique consists of flushing the catheter lumen and then filling it with 1 to 3 mL of a combination of an anticoagulant plus an antimicrobial agent. The lock dwell time in the lumen of the CVC may vary from 2 to 12 hours depending on the solution. Although heparin has become widely used as an antithrombotic agent to maintain catheter patency, it has been shown to enhance staphylococcal biofilm formation at the concentration of 1000 U/mL used in catheter locks.

Antimicrobial agents used include vancomycin, gentamicin, ciprofloxacin, cefazolin, erythromycin, nafcillin, ceftriaxone, clindamycin, fluconazole, and amphotericin B. Vancomycin in combination with heparin as a daily flushing solution of tunneled CVCs has significantly decreased the frequency of catheter-related bacteremia caused by vancomycin-susceptible microorganisms.

However, with the emergence of resistant microorganisms, it is prudent to avoid using for prophylaxis antibiotics that are commonly used in the therapy of CLABSIs (such as β-lactam antibiotics, vancomycin, quinolones, and aminoglycosides). In addition, vancomycin has been shown to have little to no antimicrobial activity against organisms in biofilms.

Minocycline and EDTA (MEDTA) solution was superior to vancomycin–heparin lock solution both in an in vitro biofilm model and an animal model. In a prospective randomized trial involving patients with long-term hemodialysis CVCs, MEDTA flush solution significantly reduced rates of catheter colonization ($p = 0.005$).

Although small clinical trials have shown promising results with ethanol locks, prospective, controlled trials are needed to evaluate further its role in the prevention of CLABSI.

The CDC does not recommend routine catheter exchange over guidewire. However, the guidewire may be used to (1) replace a malfunctioning catheter, (2) convert an existing catheter to a different type, and (3) salvage the vascular access as an alternative strategy in patients with limited venous access along with the use of systemic antimicrobial therapy.

A summary of the preventive strategies are listed in Table 107.2.

THERAPY

The management of catheter-related infections involves confirming the source of infection, the choice of antimicrobials and duration of therapy,

Table 107.2 Measures for the prevention of CLABSI

- Traditional measures:
  - Education of healthcare personnel on vigilant catheter insertion and care
  - Use the subclavian vein as the preferred insertion site for nontunneled CVCs and avoiding femoral insertions
  - Hand hygiene
  - Use of maximal sterile barrier precautions during CVC (includes the use of a cap, mask, sterile gown, and a sterile full body drape)
  - Skin cleansing using chlorhexidine before CVC insertion
  - Skilled infusion therapy team
  - Removal of unnecessary CVCs
- Novel technology:
  - Strongly recommended or well-supported evidence:
    - Antimicrobial coating of catheters particularly if the catheter is expected to remain in place > 5 days
    - Flush solutions/antimicrobial catheter lock particularly in patients who have long-term catheters and a history of multiple CLABSI
    - Chlorhexidine sponges
    - Topical antibiotics at the insertion site
  - With limited supporting evidence:
    - Antimicrobial hubs and connectors

Table 107.3 Management of catheter-related infections

Microorganism	Duration of therapy	Catheter removal advisable
Coagulase-negative staphylococci		Consider
CVC removed	5–7 d	
CVC retained	10–14 d	
Staphylococcus aureus		
Uncomplicated	10–14 d	Yes
Complicated	4 wk	Yes
Gram-positive bacilli	7 d	Yes
Gram-negative rods	10–14 d	Yes
Candida species		Yes
Uncomplicated	14 d	
Complicated	6 wk	
Mycobacterium	14 d	Yes

Abbreviation: CVC = central venous catheter.

and the decision regarding the need for catheter removal (Table 107.3). To confirm the infection, microorganisms recovered from different cultures (i.e., blood through a venous catheter, a peripheral vein, catheter tip, and, if applicable, skin insertion site) must be the same. The duration of therapy is extended if the CLABSI is judged to be complicated (i.e., associated with septic thrombophlebitis, endocarditis, or metastatic infection) or if the CLABSI persists beyond 72 hours of initiation of appropriate antimicrobial therapy. Most of the CLABSIs will be treated for a period of 5 to 14 days, depending on the isolated microorganisms. However, in cases of complicated CLABSI, the vascular catheter should be removed and the infection treated with parenteral antibiotics for at least 4 weeks.

Coagulase-negative staphylococci

The optimal duration of therapy of CLABSI with coagulase-negative staphylococci (CNS) has not been defined. The Infectious Diseases Society of America (IDSA) guidelines recommend removing the CVC and treating for 5 to 7 days; otherwise, if the CVC is to be retained, duration of treatment should be 10 to 14 days in combination with antibiotic lock therapy. For methicillin-sensitive *S. aureus* (MSSA), penicillinase-resistant penicillin or cephalosporins are preferred to vancomycin. Because most CNS are nosocomially acquired and are resistant to penicillinase-resistant penicillins, the choice of a glycopeptide (i.e., vancomycin) is recommended pending susceptibility results. Daptomycin or quinupristin–dalfopristin could be used as alternative antimicrobial agents.

Staphylococcus aureus

Staphylococcus aureus CLABSI is associated with high rates of deep-seated infection such as osteomyelitis, septic phlebitis, and endocarditis. Failure to remove the catheter is associated with persistent bacteremia, relapses, and increased mortality. For methicillin-sensitive *S. aureus*, nafcillin or a first-generation cephalosporin is the first choice. Vancomycin, daptomycin, or quinupristin–dalfopristin could be used for the treatment of methicillin-resistant *S. aureus* (MRSA). Strains resistant to linezolid have been reported.

Ten to fourteen days of intravenous therapy is enough if the CVC is removed, no deep-seated infection is present, the patient is not diabetic and not immunosuppressed. A transesophageal echocardiography (TEE) should be done for all patients, particularly for those with persistent fever or bacteremia beyond 72 hours of initiation of antimicrobial therapy. The CVC should be removed unless there are major contraindications, in which case the patient should either receive an antibiotic lock therapy or have his/her CVC exchanged over guidewire with an antimicrobial-impregnated CVC along with 4 weeks of systemic antimicrobial therapy. If fever or bacteremia persists for more than 72 hours or if the patient has an intravascular prosthetic device or there is evidence of endocarditis, suppurative thrombophlebitis, or metastatic infection, the intravenous therapy duration should be expanded to at least 4 to 6 weeks.

Candida

IDSA guidelines recommend removing the CVC and treating for 14 days after the first negative blood culture in uncomplicated cases. Endophthalmitis (15% of untreated cases) merits 6 weeks of therapy. Fluconazole or echinocandin (caspofungin, micafungin, or anidulafungin) should be considered in documented cases of catheter-related candidemia; if the rates of fluconazole-resistant *Candida glabrata* and *Candida krusei* in the hospital are high, an echinocandin is the best alternative to amphotericin B.

Gram-positive bacilli

Vancomycin remains the antibiotic of choice in the treatment of CLABSI caused by gram-positive bacilli such as *Bacillus* and *Corynebacterium* species. Removal of the catheter is recommended.

Gram-negative bacilli

Enteric gram-negative bacilli are rare causes of CLABSI. However, *Klebsiella pneumoniae, Enterobacter* spp., *P. aeruginosa, Acinetobacter* spp., and *Stenotrophomonas maltophilia* were reported to be involved in CLABSI. Catheter removal is recommended in addition to therapy with an appropriate antimicrobial for 10 to 14 days.

Mycobacterial disease

Catheter removal is recommended, and surgical intervention may be needed in long-term catheters infected with *M. chelonae* or *M. fortuitum*. A 14-day course of antimicrobials is suggested. However, a longer duration of therapy is required in complicated cases.

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108. Infections associated with urinary catheters

Lindsay E. Nicolle

Urinary tract infections (UTIs) are a common and clinically important outcome of the use of urinary catheters. Urinary catheters may be (1) short-term (<30 days) indwelling urethral catheters, (2) long-term (>30 days) indwelling urethral or suprapubic catheters, or (3) intermittent catheterization. UTI with a catheter *in situ* is usually asymptomatic – referred to as catheter-associated asymptomatic bacteriuria (CA-ASB). Symptomatic infection is referred to as catheter-acquired urinary infection (CA-UTI). Different types of catheter are indicated for different populations and have different risks for the occurrence of infection (Table 108.1).

Table 108.1 Types of catheter use and frequency of urinary infection in catheterized populations

Catheter	Usual population	Infection rate
Indwelling urethral		
Short term	Acute-care facility Output monitoring Postsurgical Acute retention	5% per day Women > men
Long term	Long-term care: 5%–10% of residents Chronic retention – men Healing of pressure ulcer	100% prevalence
Intermittent catheter	Neurogenic bladder Spinal cord injury Multiple sclerosis Other impaired bladder emptying	1%–3% per catheterization

PATHOGENESIS

Acquisition of urinary infection with catheter use is virtually always through ascending infection (Table 108.2). For indwelling urethral catheters, bacteria usually ascend into the bladder on the biofilm which forms on the external and internal surfaces of the catheter tubing, but may also ascend through reflux of contaminated urine up the drainage tubing. Disruption of the closed drainage system from the bladder to the drainage bag may also introduce bacteria, and there is a high incidence of bacteriuria within 24 hours following such a break in the system. Bacteria introduced at the time of catheterization account for less than 5% of infections.

Bacteriuria is a predictable consequence when an indwelling catheter remains *in situ* for a long enough time. The likelihood of developing bacteriuria is 3% to 7% per day while the catheter remains *in situ*. The determinants of symptomatic infection are not well described, but trauma to the mucosa or catheter obstruction may precipitate CA-UTI.

With intermittent catheterization, organisms are repeatedly introduced into the bladder at catheterization. Individuals managed with intermittent catheterization usually have a neurogenic bladder with incomplete bladder emptying so organisms, once introduced, may persist in the bladder. The organisms which cause bacteriuria are usually present as colonizing bacteria in the periurethral area, but may also be introduced by contamination of the catheter or on the hands of the individual performing catheterization.

Table 108.2 Methods by which organisms gain access to the bladder in catheter-acquired urinary infection

Ascending infection
Introduced when the catheter is placed in the bladder
Ascending from periurethral area on biofilm on mucous sheath on external catheter surface
Ascending from interior drainage bag or tubing on biofilm
Intraluminal from drainage bag with urine reflux
Introduced with breaks in closed drainage
Other (uncommon)
Hematogenous from another body site

BACTERIOLOGY

Urinary infection identified in the setting of urethral catheterization is considered complicated UTI.

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Escherichia coli remains an important pathogen in these infections, but other organisms are also frequently isolated. These include other Enterobacteriaceae such as *Klebsiella pneumoniae*, *Citrobacter* species, *Enterobacter* species, and *Serratia marcesens*. For long-term indwelling catheters, in particular, infections with urease-producing organisms such as *Proteus mirabilis*, *Morganella morganii*, or *Providencia stuartii* are common. *Pseudomonas aeruginosa* and other gram-negative nonfermenters such as *Acinetobacter* species may be isolated, as well as gram-positive organisms, particularly enterococci and coagulase-negative staphylococci. *Candida albicans* and other yeast species also occur, usually isolated from subjects receiving antimicrobials. The high frequency of recurrent infection and repeated courses of antimicrobials promote emergence of more resistant organisms.

Polymicrobial bacteriuria is characteristic of infection in subjects with long-term indwelling catheters but may also occur with other types of catheterization. Long-term indwelling catheters or short-term catheters *in situ* for more than a few days are covered with a bacterial biofilm, on both interior and external surfaces. This biofilm is composed of microorganisms, bacterial extracellular glycopolysaccharides, and protein and minerals incorporated from the urine. There is a complex microbial flora with multiple organisms growing in the biofilm; usually two to five organisms are present in a mature biofilm. The biofilm is an environment within which microorganisms are relatively protected from both antimicrobials and the host inflammatory and immune response. Urine specimens obtained for culture through the biofilm-laden catheter are contaminated by organisms present in the biofilm which may not be present in bladder urine. The number, type, and quantity of organisms isolated from these specimens may differ from a specimen of simultaneous bladder urine.

MORBIDITY AND MORTALITY

Most catheter-acquired urinary infections are asymptomatic. However, catheterized subjects are at risk for increased morbidity from symptomatic UTI. Pyelonephritis, fever, and bacteremia may require hospitalization or result in extended hospitalization when nosocomially acquired. Local complications including prostatitis and epididymitis, purulent urethritis, urolithiasis, and urethral abscesses may occur. Crystalline biofilm formed by urease-producing organisms, principally *P. mirabilis*, is the most common cause of catheter obstruction. Acute urinary infection in subjects with spinal cord injury or other neurologic diseases may present as increased lower-limb spasticity or autonomic hyperreflexia. Urinary infection in residents with chronic indwelling urethral catheters is the most frequent cause of bacteremia in long-term care facilities, with these residents experiencing three times the incidence of fever as bacteriuric long-term care facility residents without an indwelling catheter. Occasionally, acute urosepsis occurs, but mortality directly attributable to urinary infection is uncommon relative to the high frequency of bacteriuria.

Table 108.3 Microbiologic diagnosis of urinary infection in subjects with catheter

Clinical presentation	Quantitative count of bacteria
Asymptomatic	$\geq 10^5$ CFU/mL single specimen
Symptomatic	
In and out catheter	$\geq 10^2$ CFU/mL[a]
Indwelling catheter	$\geq 10^5$ CFU/mL

[a] Including subjects with intermittent catheterization.
Abbreviation: CFU = colony-forming unit.

DIAGNOSIS

A diagnosis of urinary infection in a catheterized patient requires microbiologic confirmation. Clinical findings will then determine whether infection is symptomatic or asymptomatic. Culture of an appropriately collected urine specimen is essential. The specimen must be collected before antimicrobial treatment is initiated. It may be obtained directly at the time catheterization is initiated, by intermittent catheterization, from a newly placed catheter in subjects with long-term indwelling urethral catheters, or by aspiration from the catheter port of a short-term indwelling catheter. Quantitative criteria for the microbiologic diagnosis of urinary infection are shown in Table 108.3. Lower quantitative counts in subjects with indwelling catheters often reflect contamination from catheter biofilm rather than bladder bacteriuria.

A diagnosis of symptomatic urinary infection requires a positive urine culture. However, a positive urine culture is common in catheterized patients at any time. Patients with short-term indwelling catheters have an increasing prevalence of bacteriuria the longer the catheter remains *in situ*; those maintained on intermittent catheterization have a prevalence of about 50% at

Table 108.4 Clinical presentations of acute urinary infection in subjects with bladder catheters

Asymptomatic
Symptomatic
Systemic
Acute pyelonephritis
Fever with catheter obstruction
Fever with acute hematuria
Bacteremia with urinary isolate
Increased lower leg spasms or autonomic hyperreflexia in spinal cord injury
Fever without genitourinary localizing findings and no alternate source (≤50% urinary source)
Local[a]
Urethritis
Epididymitis
Urethral abscess
Bladder stones
Catheter obstruction
Prostatitis
Scrotal abscess

[a] Local complications are primarily seen with long-term indwelling urethral catheters.

any time. Virtually all individuals with chronic long-term indwelling catheters are persistently bacteriuric. Thus, although a positive urine culture is necessary for diagnosis of urinary infection, it is not sufficient to identify symptomatic infection – clinical symptoms must also be present.

Clinical presentations consistent with urinary infection are listed in Table 108.4. Localizing genitourinary symptoms or signs such as flank pain and tenderness, fever with an obstructed catheter, acute hematuria, or recent catheter trauma support a diagnosis of symptomatic urinary infection with a high degree of confidence. However, most patients with indwelling catheters and symptomatic urinary infection will not have localizing genitourinary symptoms. A frequent clinical scenario is fever and a positive urine culture without localizing findings to the genitourinary tract or another potential site of infection. Catheterized patients often present with fever alone as a manifestation of urinary infection but other potential sources must always be considered. In one study of subjects with long-term indwelling catheters, only 33% of such episodes were confirmed to be due to a urinary source. Thus, in the absence of localizing genitourinary findings or bacteremia with the urinary isolate, symptomatic urinary infection is a diagnosis of exclusion.

Pyuria is a universal accompaniment of bacteriuria in individuals with indwelling catheters and is also present in most bacteriuric patients who use intermittent catheterization. Pyuria may also be present in the absence of bacteriuria due to irritation of the bladder by the catheter. The presence of pyuria or level of pyuria associated with bacteriuria has not been shown to have any prognostic clinical significance. Thus, pyuria is insufficient to make a diagnosis of urinary infection, and the presence of pyuria is not, by itself, an indication of symptomatic infection.

TREATMENT

Treatment of asymptomatic bacteriuria is not indicated for subjects managed by intermittent catheterization or with an indwelling urethral catheter. For subjects with long-term indwelling catheters, antimicrobial treatment of CA-ASB does not decrease the frequency of subsequent symptomatic episodes but leads to recurrent bacteriuria with more resistant bacteria. As previously noted, pyuria by itself or with bacteriuria is not an indication for treatment in an individual who is asymptomatic. For women, if bacteriuria persists for 48 hours after removing a short-term indwelling catheter, treatment may be indicated. This clinical question has not been addressed for men, and no definitive recommendation can be given.

When symptomatic infection is diagnosed clinically, a urine specimen for culture should be obtained in every case before initiation of antimicrobial therapy. For individuals with catheters *in situ* for 2 weeks or longer, the catheter should be replaced and a specimen for culture obtained from the newly placed catheter before initiating antimicrobial therapy. This allows collection of a urine specimen that is representative of bladder organisms without biofilm contamination. Replacing the catheter immediately prior to antimicrobial therapy has also been shown to shorten the time to defervescence and decrease the likelihood of symptomatic relapse in short-term follow-up. It is assumed these beneficial effects result from removal of the biofilm with its high concentration of organisms. For short-term indwelling catheters, where mature biofilm formation is less likely, routine catheter replacement is not recommended.

Oral antimicrobials appropriate for treatment of urinary infection are listed in Table 108.5, and parenteral antimicrobials are listed in Table 108.6. Parenteral therapy should be initiated in patients

Table 108.5 Oral antimicrobials for treatment of urinary tract infection in catheterized patients with normal renal function

Antimicrobial	Dosage
Penicillins	
Amoxicillin	500 mg TID
Amoxicillin–clavulanic acid	500/125 mg TID or 875/125 mg BID
Cephalosporins	
Cephalexin	500 mg QID
Cefaclor	500 mg QID
Cefadroxil	1 g OD or BID
Cefuroxime axetil	250 mg BID
Cefixime	400 mg OD
Cefpodoxime proxetil	100–400 mg BID
Fluoroquinolones[a]	
Norfloxacin	400 mg BID
Ciprofloxacin	250–500 mg BID
Ofloxacin	200–400 mg BID
Levofloxacin	250–500 mg OD
Other	
Nitrofurantoin	50–100 mg QID
Trimethoprim	100 mg BID
Trimethoprim–sulfamethoxazole	160/800 mg BID

[a] Recommended for oral empiric therapy.

Table 108.6 Parenteral antimicrobials for treatment of urinary tract infection in individuals with normal renal function

Antimicrobial	Dosage
Aminoglycoside	
Amikacin[a]	5 mg/kg q8h or 15 mg/kg q24h
Gentamicin[a]	1–1.5 mg/kg q8h or 4–5 mg/kg q24h
Tobramycin[a]	1–1.5 mg/kg q8h or 4–5 mg/kg q24h
Penicillin	
Ampicillin	1–2 g q6h
Piperacillin	3 g q4h
Piperacillin/tazobactam	4 g/500 mg q8h
Ticarcillin/clavulanic acid	50 mg/kg q6h
Cephalosporins	
Cefazolin	1–2 g q8h
Ceftriaxone	1 – 2 g q24h
Cefotetan	1 g q12h
Cefotaxime	1–2 g BID or TID
Cefepime	2 g q12h
Ceftazidime	0.5–2 g q8h
Other	
Aztreonam	1 g q6h
Imipenem/cilastatin	500 mg q6h
Ertapenem	1g q24h
Meropenem	500 mg q8h
Doripenem	500 mg q8h
Vancomycin	500 mg q6h or 1 g q12h

[a] Recommended for initial empiric therapy with ampicillin if renal function is normal.

who are hemodynamically unstable, are vomiting, have impaired gastrointestinal absorption, or have a high likelihood of being infected with an organism resistant to oral agents.

If symptoms are mild but persistent, antimicrobial therapy should not be initiated until the urine culture results are available. This allows for selection of antimicrobial therapy specific for the infecting organism. Empiric antimicrobial therapy should be initiated pending urine culture results when a patient is significantly ill with fever or other systemic symptoms or when the patient has severe irritative symptoms. The selection of initial empiric therapy should consider bacteriology and susceptibilities of previous urine cultures from the patient, when available, and resistance patterns of endemic flora in an institution. An aminoglycoside, with or without ampicillin for enterococci, is usually appropriate for initial empiric parenteral therapy. In the presence of moderate to severe renal failure, an extended-spectrum β-lactam antimicrobial or fluoroquinolone may be preferred rather than an aminoglycoside. When there is a concern about resistant organisms, alternative empiric therapy with coverage specific for the expected susceptibilities should be selected. Once urine culture and susceptibility results from the pretherapy urine specimen are available, usually 48 to 72 hours after initiation of therapy, the antimicrobial regimen can be reassessed and, if appropriate, changed to alternative specific therapy. This will often include a change to oral therapy for patients in whom parenteral therapy was initiated.

If the patient continues to require an indwelling catheter, the treatment duration should be for as short a period as possible (5 to 7 days). Longer courses of therapy will promote the emergence of organisms of increasing resistance, potentially increasing the difficulty in treating future episodes of symptomatic infection. If the catheter is removed, 7 to 14 days of therapy should be given. For subjects managed with intermittent

Table 108.7 Prevention of catheter-acquired urinary tract infection

Effective
Restrict indications for catheter use
Limit duration of catheter use
Daily review of continuing need for catheter
Aseptic insertion (for indwelling catheter)
Maintain closed drainage system
Antibiotics first 4 days (not recommended)[a]
Antibiotics at removal (not recommended)[a]
Not effective
Bladder irrigation with antimicrobial
Periurethral care with soap or disinfectant
Routine catheter replacement
Disinfectant in drainage bag
Coating of catheter with antimicrobial substances[b]
Antimicrobial prophylaxis

[a] Not recommended because of emerging antimicrobial resistance.
[b] Nitrofurazone coating may decrease symptomatic infection but has increased adverse effects.

catheterization, 7 days is recommended for lower tract symptoms and 10 to 14 days for systemic infection.

PREVENTION

The most effective means of preventing catheter-associated infection is not to use a catheter or, if there is a clear clinical indication for use, to limit the duration of catheterization to as short a period as possible (Table 108.7). Where possible, alternate strategies to manage voiding, such as a condom catheter for men, should be used. For short-term indwelling catheters, the maintenance of a closed drainage system is important in delaying acquisition of infection. Antimicrobial therapy given during the first 3 days of catheterization or at the time of catheter removal is associated with a decreased frequency of infection. However, these antimicrobial strategies are not recommended because they are associated with an increased frequency of reinfection with more resistant organisms. Other interventions that have been systematically evaluated, such as daily periurethral cleaning with either soap or a disinfectant and addition of disinfectants to the drainage bag, are not effective in decreasing the frequency of symptomatic infection.

It is not clear that any interventions will decrease the frequency of urinary infection in subjects with chronic indwelling urethral catheters. Preventive strategies in these patients must focus on limiting symptomatic infection through early identification of catheter obstruction and prevention of catheter trauma to the genitourinary mucosa. Routine replacement of chronic indwelling catheters is not recommended. The catheter should be replaced only if there is obstruction or other catheter malfunction, or prior to treatment of symptomatic urinary infection.

For spinal cord-injured patients managed with intermittent catheterization, use of prophylactic antimicrobials may decrease the frequency of infection in the early postinjury period but is not effective in the long term as infection with organisms of increased antimicrobial resistance occurs. Thus, prophylactic antimicrobials are not recommended in patients using intermittent catheterization. Maintenance of bladder volumes of less than 500 mL in these subjects may decrease the frequency of symptomatic infection. For nursing home patients, rates of infection with intermittent catheterization are similar if either a clean or sterile catheter technique is used. Thus, clean technique is recommended because it is less costly.

Antimicrobial therapy should be given to subjects with asymptomatic bacteriuria before an invasive genitourinary procedure, such as transurethral prostatic resection or stone extraction, where there is a high likelihood of mucosal trauma. Antimicrobial therapy is initiated before the surgical procedure and is conceptually "prophylaxis" to prevent bacteremia and sepsis rather than treatment of asymptomatic bacteriuria. Antimicrobial therapy is not indicated before a chronic indwelling urethral catheter change because this is not a high-risk procedure.

UTI in catheterized patients is primarily a technologic problem of biofilm formation on inert devices. Thus, substantive progress in preventing these infections will require technologic development of devices resistant to biofilm formation. Many antimicrobial-coated or -impregnated urinary catheters have been developed, and some of these are widely used. Nitrofurazone-coated catheters may be associated with a small decrease in the incidence of symptomatic infection in hospitalized patients with short-term catheters but have an increased frequency of adverse effects. Silver alloy catheters have not consistently been shown to improve outcomes. Catheters developed using other biomaterials or coatings are under further investigation, but none have yet been documented to decrease morbidity.

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PART XIV

Infections related to surgery and trauma

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109. Postoperative wound infections

E. Patchen Dellinger

Postoperative wound infection is the archetypal surgical infection because it follows a surgical procedure and requires surgical intervention for resolution. As with many infections, best results are obtained by prompt diagnosis and treatment, which is facilitated by understanding the risk factors. The most obvious factor influencing risk of infection is the density of bacterial contamination of the incision. This was recognized several decades ago in the wound classification system that divides all surgical wounds into the following four categories: clean, clean-contaminated, contaminated, and dirty. Clean wounds result from an elective procedure without break in technique that does not involve any area of the body other than skin normally colonized by resident bacteria. Clean-contaminated wounds result from a procedure such as elective bowel resection that intentionally opens the gastrointestinal (GI) tract or other colonized region such as the female genital tract but does not result in grossly visible spill of contents during the procedure. Contaminated procedures are those with gross spill from the GI tract or trauma and emergency procedures in which a wound has been created without normal antisepsis and sterile technique. A dirty wound is one that results from an operation in an area of active infection or previous bowel injury and leak. Among these categories, infection risk ranges historically, before modern understanding and practice of perioperative antibiotic prophylaxis, from 2% for clean wounds to 30% to 40% for dirty wounds when the skin is closed primarily.

Studies done many decades ago demonstrate that essentially all surgical incisions, even in clean operations, have some bacteria in the wound at the end of the procedure. Clinicians have recognized that the nature of host defenses and the extent to which the operative procedure or preexisting disease impairs these defenses also influences the risk of wound infection. Modern wound classifications that include underlying risk as well as the risk of bacterial contamination predict infection more accurately. The most widely used system now assigns one point each for wound classification of contaminated or dirty, an operation lasting longer than the 75th percentile for that procedure, and an American Society of Anesthesiology (ASA) physical status classification of 3 or 4. In this system, the risk of postoperative wound infection for patients with risk points of 0, 1, 2, or 3 is 1.5%, 2.9%, 6.8%, and 13.0%, respectively (Table 109.1). These data reflect modern use of perioperative prophylactic antibiotics, as discussed in Chapter 114, Surgical prophylaxis. Efforts at the Centers for Disease Control and Prevention (CDC) are currently trying to develop more precise procedure-specific risk predictions for surgical site infections, but are in very preliminary stages.

DIAGNOSIS

The diagnosis of postoperative wound infection is obvious when the wound opens and discharges pus. However, the diagnosis is ideally made earlier and prompt therapeutic intervention undertaken. It is rare for a postoperative wound infection to be clinically evident before the fourth or fifth postoperative day. The sole exceptions to this are infections caused by β-hemolytic streptococci and by histotoxic *Clostridium* species and, more rarely, wound toxic shock. These infections can be clinically evident within fewer than 24 hours, and although they are rare, they tend to be devastating. The wound of any patient with severe systemic signs of infection during the first few days after an operation should be inspected for signs of infection (Figure 109.1). Streptococcal infections are marked by local signs of inflammation and at times an exudate containing white blood cells (WBCs) and gram-positive cocci. Clostridial infections lack signs of inflammation and produce a thin exudate lacking WBCs because of the action of clostridial exotoxins, but

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Table 109.1 Comparison of National Research Council (NRC) wound classification with National Nosocomial Infectious Surveillance (NHSN) risk index for prediction of surgical site infections (SSI) risk

	NHSN risk index					
NRC class	0	1	2	3	All	**Maximum ratio (NRC)[a]**
Clean	1.0	2.3	5.4	–	2.1	5.4
Clean-contaminated	2.1	4.0	9.5	–	3.3	4.5
Contaminated	–	3.4	6.8	13.2	6.4	3.9
Dirty	–	3.1	8.1	12.8	7.1	4.1
All	1.5	2.9	6.8	13.0	2.8	–
Maximum ratio (NHSN)[a]	2.1	1.7	1.8	1.0	–	–

[a] Ratio of the lowest to the highest infection rate in wound class or risk index. Note that the highest maximum ratio for any of the NHSN indices is 2.1, whereas the lowest maximum ratio for any of the NRC wound classes is 3.9. Clearly, the NHSN index more accurately describes the infection risk of operative procedures.

Modified from Dellinger EP, Ehrenkranz NJ. Surgical infections. In: Bennett JV, Brachman PS, eds. *Hospital Infections*, 4th edn. Philadelphia, PA: Lippincott-Raven; 1998:571–585.

gram-positive rods without spore formation are evident on Gram smear. Thirteen cases of wound toxic shock were confirmed by the CDC during an 18-month period, representing less than 1% of all cases of toxic shock reported during that period. More than half of these cases presented within 48 hours of an operation. The earliest signs were fever, diarrhea, and vomiting. Profuse watery diarrhea, erythroderma, and hypotension were also characteristic. Initially, local signs of wound infection were often absent. Drainage and irrigation of the wound in combination with a systemic antistaphylococcal antibiotic is recommended. Although most wound infections are diagnosed between 5 and 15 days after the procedure, in some cases, diagnosis may be delayed considerably. This is more likely with wounds with a significant amount of tissue overlying the area such as abdominal wounds in morbidly obese patients and wound infections under chest wall musculature following a posterolateral thoracotomy.

Because most patients have some fever in the first several days after a major operative procedure such as abdominal exploration or thoracotomy, fever is not a specific sign of postoperative infection (Figure 109.2). It is tempting for the surgeon to continue prophylactic antibiotics or to restart antibiotics if the patient shows early postoperative fever, but this impulse should be resisted because these infections will not resolve without opening the wound. When antibiotics are given without a commitment to open the wound, the most likely results are a delay in diagnosis and definitive treatment, a consequent increase in morbidity, and risk of additional complication such as wound dehiscence or herniation. A few surgical wounds exhibit erythema adjacent to the incision, either concentrated around skin sutures or staples or diffusely. In the absence of marked induration and/or drainage, this erythema usually does not indicate wound infection. The average clinician will be sorely tempted to prescribe antibiotics for a patient with such a wound, but most resolve without any specific treatment, and no data suggest that administration of antibiotics in such a situation will prevent the need to open the wound for a real infection.

THERAPY

Incisional drainage

The primary treatment for a wound infection is to open the wound and evacuate the infected material. Antibiotics are used as adjunctive treatment only for patients who exhibit signs of significant systemic response to the infection or in whom there is evidence of invasive soft-tissue infection beyond the boundaries of the surgical incision. The evidence for infection may be most prominent in a portion of the incision, but in most cases, the entire incision will be involved under the skin and will have to be opened. If necrotic tissue is found in the wound, some preliminary debridement may be helpful, but small shreds of involved tissue will separate by themselves over time if the wound is left open and subjected to gauze dressing changes two to three times daily, decreasing in frequency as the wound clears. The importance of dressing

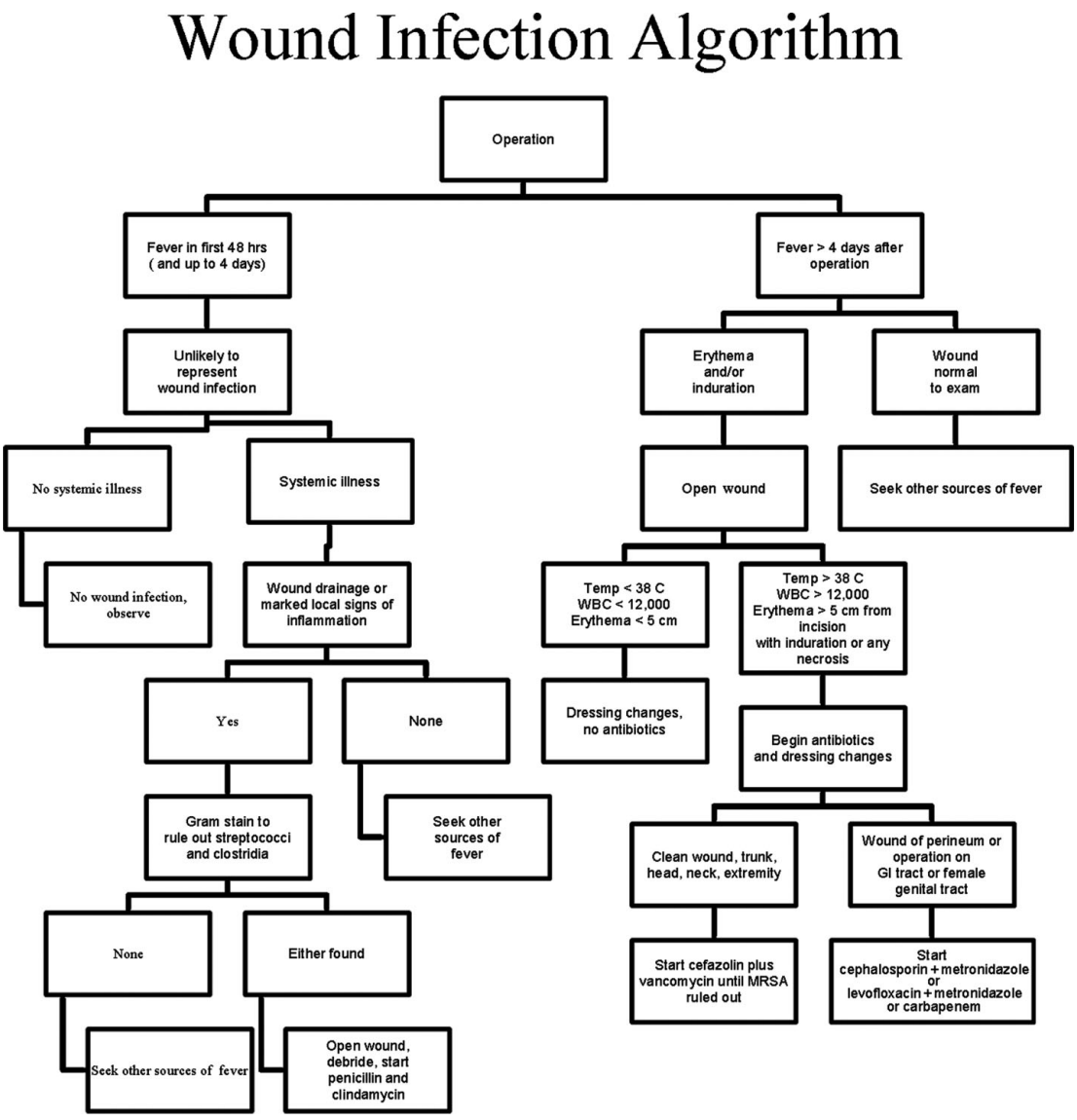

Figure 109.1 Wound infection algorithm. (With permission from Jarvis WR, ed. *Hospital Infections*, 5th edn. Philadelphia: Lippincott Willliams & Wilkins; 2007.)

changes is greater if the wound is deep, as in patients with severe obesity or in posterolateral thoracotomy wounds in muscular patients. If the wound is undermined, it is important to place the dressing so that gauze is in contact with all areas of the wound, but the dressings should not be put in forcefully or under pressure because this causes pain, inhibits drainage of exudate, and stimulates excess scar formation and slows wound closure, which occurs through the normal mechanism of contracture of granulation tissue.

When an incision is opened initially, it should be inspected by a physician who understands the procedure and the underlying anatomy. If the procedure was a celiotomy or a thoracotomy, the integrity of the closure of the abdominal or chest wall should be verified and evidence sought for purulent fluids originating deep to the abdominal or chest wall. In some cases, the incisional infection is not the primary event but is a signal of more severe and more extensive infection at a deeper level (see Chapters 55 and 57, Abdominal abscess and Peritonitis, respectively).

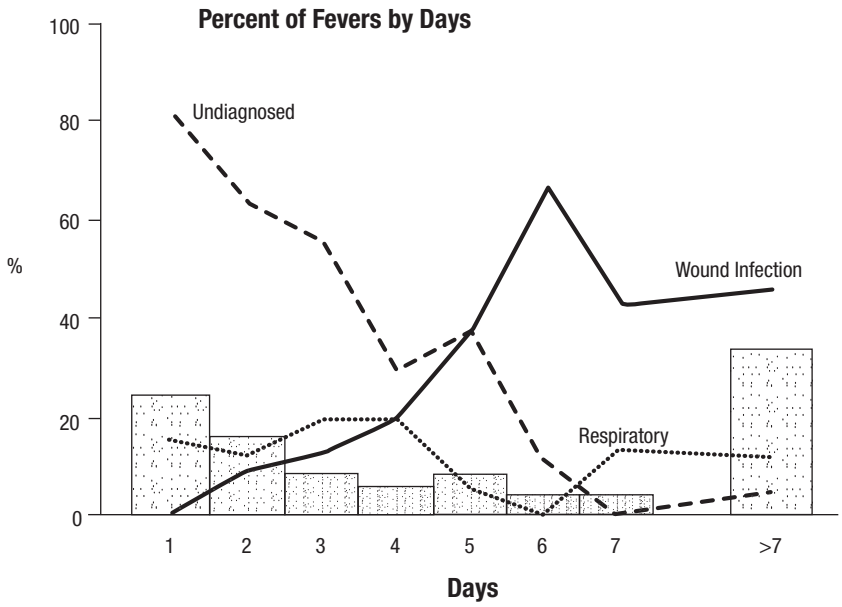

Figure 109.2 Bars represent the percent of all postoperative fevers occurring on the indicated day following an operative procedure. Lines indicate the percentage of fevers occurring on each day attributable to the cause indicated. (From Dellinger EP. Approach to the patient with postoperative fever. In: Gorbach SL, Bartlett JG, Blacklow NR, eds. *Infectious Diseases*, 3rd edn. Philadelphia, PA: Lippincott Williams & Wilkins; 2004:817–823.)

Antibiotics

At the time of diagnosis, and opening of the wound, empiric antibiotic administration should only occur when there are signs of a significant systemic reaction with temperature above 38°C (100.4°F), elevated pulse rate, or absolute WBC count above 12 000; when inspection of the wound reveals invasive infection in the subcutaneous space or at the fascial level; or when surrounding erythema and induration extend >5 cm from the line of incision. The agent chosen should be guided by Gram smear of the wound exudate and the nature of the procedure. Infections following clean operations that have not entered the GI tract and that involve the head and neck, trunk, or extremities tend to be caused by *Staphylococcus aureus* or, less commonly, streptococcal species. If Gram smear confirms gram-positive cocci and if antibiotics will be given, treatment is appropriate with an initial parenteral dose of cefazolin or oxacillin, 1 g intravenously (IV). For patients allergic to penicillin and cephalosporins, clindamycin, 900 mg, or vancomycin, 1 g IV, is acceptable. If the patient can take oral fluids and is not thought to have bacteremia, subsequent treatment can be with oral cephalexin or cephradine, 500 mg, or clindamycin, 450 mg four times daily. As community-acquired methicillin-resistent *S. aureus* (CA-MRSA) increase in frequency, consideration should be given to initiating treatment with sulfamethoxazole/trimethoprim, 800/160 mg orally (PO) every 12 hours, doxycycline, 100 mg PO every 12 hours, or vancomycin, 1 g IV every 12 hours, or linezolid or daptomycin or telavancin or ceftaroline, until susceptibility data are available. Antibiotic treatment should be continued only as long as systemic signs of infection or local cellulitis continue to be present, usually 3 days or less.

For infections that follow operations in the axilla, gram-negative enteric bacilli are more commonly causative, and after operations on the perineum or involving the GI tract or the female genital tract both facultative and obligate anaerobic bacilli and cocci are often involved. In these cases, if antibiotic treatment is thought necessary, initial treatment can be a cephalosporin or a fluoroquinolone combined with metronidazole. Patients allergic to penicillin and cephalosporins can receive levofloxacin, 500 mg IV every 12 hours, combined with metronidazole, 1 g IV every 12 hours. Again, the treatment should usually be 3 days or less. If the patient is able to take oral agents, switching to an oral regimen of levofloxacin, 500 mg every 24 hours, combined with metronidazole, 500 mg every 6 hours, should be considered.

In the rare patient who has an invasive wound infection caused either by β-hemolytic streptococci or by a histotoxic *Clostridium* species diagnosed in the first 48 hours after operation,

aggressive antimicrobial therapy is necessary in addition to opening the wound and inspecting it in the operating room under general anesthesia, with the option of aggressive soft-tissue debridement if evidence of spreading soft-tissue invasion and necrosis is found. Penicillin G, 4 million units IV every 4 hours, is appropriate if the diagnosis of streptococcal or clostridial infection is firm. If in doubt, cefazolin or vancomycin provides treatment for staphylococcal infections in addition to streptococcal and clostridial infections, but the addition of metronidazole for anaerobic coverage may be prudent. CA-MRSA have recently been reported to cause necrotizing soft-tissue infections, so initial treatment of these infections with gram-postive cocci should include the use of vancomycin, 1 g IV every 12 hours.

WOUND CLOSURE

The most reliable method for handling an infected wound that has been opened is to continue dressing changes and allow the wound to close spontaneously by secondary intention. In straightforward wound infections, this results in a very satisfactory result in most cases. In a minority of wounds, the incision can be reclosed, usually with tapes, after the incision has cleared up and is lined by healthy granulation tissue. The failures that occur at this time are as often caused by the geometry of the wound as they are by the bacterial content.

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110. Trauma-related infection

Mark A. Malangoni

Infection is a relatively common complication of trauma, particularly among patients who have a greater severity of injury. Although exsanguination and central nervous system injury are the most common causes of mortality in the first 48 hours following injury, patients who die later often succumb to infectious complications or their consequences.

Trauma-related infection represents either infection at an original site of injury or infection that occurs as a direct result of injury. Examples of the former are an infected laceration or osteomyelitis at the site of an open fracture. The latter includes empyema after a penetrating wound to the chest and an intra-abdominal abscess that follows a gunshot wound to the colon. Infection also may occur at sites remote from the area of injury; however, these infections usually are not directly related to the immediate injury, and will not be discussed further.

Similar to other infections, trauma-related infections occur when there is an imbalance in the normal relationship among microorganisms, the local environment, and innate or acquired host defenses. Trauma-related infection occurs either from the introduction of small numbers of highly pathogenic bacteria or following contamination from a large inoculum of less pathogenic organisms. Several potential pathogens are found consistently throughout the body (Table 110.1).

Injury can lead to infection by (1) direct contamination of a sterile site with exogenous microorganisms; (2) disruption of the natural epithelial barriers of the gastrointestinal, respiratory, or gynecologic tracts, with contamination from endogenous microorganisms; (3) impairment of local antimicrobial clearance mechanisms by direct damage to tissue and the introduction of foreign bodies, seromas, or hematomas that act as adjuvants to promote infection; and (4) weakening of systemic host defenses through secondary mechanisms related to the consequence of injury.

Table 110.1 Potential pathogens and their anatomic locations

Staphylococcus epidermidis	Skin, oropharynx
Staphylococcus aureus	Skin, oropharynx, upper gastrointestinal tract
Enterococci	Gastrointestinal tract
β-hemolytic streptococci	Oropharynx
Streptococcus pneumoniae	Oropharynx
Anaerobic streptococci	Oropharynx, vagina
Enterobacteriaceae (e.g., *Escherichia coli*, *Klebsiella*, *Enterobacter*)	Gastrointestinal tract, vagina, perineum
Candida albicans	Oropharynx, gastrointestinal tract
Clostridium perfringens	Skin, perineum
Bacteroides fragilis	Distal gastrointestinal tract
Bacteroides species (non-*fragilis*)	Oropharynx, gastrointestinal tract

Various pre-existing conditions may also contribute directly to the development of trauma-related infections through detrimental effects on local or systemic defense mechanisms. Examples include diabetes mellitus, obesity, malnutrition, advanced age, alcoholism, and single or multiple organ dysfunction. Hyperglycemia, hypoxemia, and hypothermia also increase the likelihood of developing a trauma-related infection. Importantly, the adequacy of the blood supply to the area of injury can affect the propensity to develop infection, and impaired perfusion because of pre-existing disease or perturbations due to the injury per se increases the risk of developing an infection. Necessary invasive and diagnostic interventions such as the placement of endotracheal tubes, intravascular catheters, and urinary catheters provide microorganisms with a portal of entry to sterile body sites, bypassing the normal defenses. These microorganisms may cause infection at the site of entry or may cause a distant infection following hematogenous

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dissemination of pathogens. Improper treatment can also predispose to infection by impairing the clearance of subpathologic concentrations of bacteria.

Efforts to prevent infection should begin immediately after injury. The general principles of initial management of injury include examination of external wounds to determine the extent and severity of injury and to identify foreign bodies, hematomas, damaged or devitalized tissue, and associated fractures. Wounds should be covered with a sterile dressing, preferably moistened with 0.9% normal saline, as soon as possible to prevent further contamination and tissue desiccation. Bleeding should be controlled by the application of direct pressure or by identification and ligation of bleeding points. Hematomas should be evacuated and injury to specialized tissues such as muscle, tendon, nerve, and blood vessels assessed. Debridement of all devitalized soft tissues, removal of foreign material, and control of bleeding are essential to proper wound management. The injury site should be irrigated with a physiologic solution such as 0.9% normal saline as soon as possible; however, this process should not impede definitive care or transfer to a trauma center.

In traumatic wounds associated with fractures, there is a direct relationship between the risk of infection and the severity of related soft-tissue injury. Early immobilization of the fracture reduces additional soft-tissue damage, limits hematoma formation, and can help decrease the risk of infection by preventing dissemination of contaminating bacteria.

After appropriate cleansing, debridement, and hemostasis are completed, the type and technique of wound closure can be addressed. In general, simpler techniques are preferred over more elaborate ones. Traumatic wounds with a low risk for infection should undergo primary closure. Wounds at increased risk for infection include those that have devitalized or ischemic tissue, are located near areas of heavy colonization (groin or perineum), have a delay of 6 hours or more to definitive care, or are complicated by the presence of associated diseases that compromise clearance of contaminating organisms. Crush injury, high-velocity and shotgun injuries, coexisting thermal injury, and irregular or stellate wound configurations are other indicators of high-risk wounds. Heavily contaminated wounds or wounds that are at high risk for infection should not be closed primarily. In this situation, it is more prudent to repeat cleansing and debridement of the site of injury and delay closure until it can be done safely. Unless the wound environment is sufficient to allow for closure with a low risk of infection, wounds should be allowed to heal by secondary intention or have delayed primary closure. Although this may seem inconvenient for the patient, it often avoids substantial consequences associated with infection.

Stab wounds and low-velocity gunshot wounds can usually be irrigated and closed primarily as long as there has not been significant exogenous or endogenous contamination. With intestinal injury the concentration of microorganisms contaminating the site of injury is increased, particularly at the exit site, and these wounds should not be closed primarily. High-velocity missile track and shotgun wounds are best managed by debridement and irrigation of entrance and exit sites, followed by coverage with sterile dressings. They should not be closed primarily. Complex wounds with extensive areas of devitalized soft-tissue are best managed by debridement and irrigation with dressing care. Exposed soft tissue can be managed with wet-to-dry dressing changes using 0.9% normal saline to promote a healthy granulating bed that can be covered later either with a split-thickness skin graft or with full-thickness skin or can be allowed to heal by secondary intention. Although it may be tempting to use antiseptic or antimicrobial-containing agents for irrigation, these substances offer no advantage in the early treatment of wounds and can impair healing. When wounds that are healing by secondary intention begin to granulate and contract, it may be appropriate to switch to hydrocolloid gels or alginates, which are associated with less discomfort and a less frequent need for dressing changes. Negative pressure wound therapy is useful in the treatment of large open wounds once contamination has been minimized as it accelerates wound contraction and reduces the time to healing. It also has the advantage of requiring less frequent dressing changes.

Antibiotic therapy is not a substitute for sound clinical judgment, excellent local wound care, aseptic technique, and careful handling of tissues. For uncomplicated minor wounds with minimal contamination and a low risk of infection, antibiotic therapy is unnecessary. Empiric antibiotic therapy is beneficial when there is heavy bacterial contamination, an open fracture, involvement of a joint space, major soft-tissue injury, or delay of initial management for greater

Table 110.2 Antibiotic therapy for traumatic wounds[a]

Clean lacerations	No antibiotics recommended
Heavily contaminated lacerations or wounds at risk for infection	Cefazolin, 1–2 g IV q8h Amoxicillin–clavulanate, 500 mg PO q12h, or 250 mg PO q8h For penicillin-allergic patients, use Ciprofloxacin 400 mg IV or 500 mg PO q12h plus metronidazole 500 mg IV or PO q6h or Moxifloxacin 400 mg IV or PO q24h
Farm injuries and human bites; soil contamination; delays in care of heavily contaminated wounds	Piperacillin–tazobactam, 3.375 g IV q6h, or Amoxicillin–clavulanate, 500 mg PO q12h, or 250 mg q8h (see Chapter 23, Human and animal bites) For penicillin-allergic patients, use Ciprofloxacin 400 mg IV or 500 mg PO q12h plus metronidazole 500 mg IV or PO q6h, or Moxifloxacin 400 mg IV or PO q24h
Penetrating abdominal injury[b]	Cefotetan, 2 g IV q8–12h, or Piperacillin–tazobactam, 3.375 g IV q6h For penicillin-allergic patients, use Ciprofloxacin 400 mg IV q12h plus metronidazole 500 mg IV q6h, or Moxifloxacin 400 mg IV q24h

[a] Local infection data and resistance patterns may require additional coverage when methicillin-resistant *Staphylococcus aureus* (MRSA) is suspected (see text).

[b] Doses should be repeated for every 5 units of blood loss.

Abbreviations: IV = intravenously; PO = orally; q8h = every 8 hours.

than 6 hours, as well as for patients with impaired local or systemic host defenses. Cultures of contaminated wound sites usually add little to treatment decisions. Tetanus toxoid and tetanus immunoglobulin should be administered in accordance with established guidelines for contaminated wounds.

Empiric antibiotic therapy should be directed primarily against gram-positive bacteria in most wounds. When contamination with anaerobes and gram-negative enteric bacteria is suspected, such as with a farm-related injury or a human bite, the antimicrobial spectrum must include agents effective against these organisms. Treatment should be continued only for 24 hours in wounds with a minor or moderate degree of contamination; a longer duration of treatment is recommended when contamination is greater. Recommended antibiotic choices are listed in Table 110.2.

The high prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in the community and among hospitalized patients or those who reside in long-term care facilities mandates a reassessment of the approach to the treatment of patients who are potentially contaminated or infected with these organisms. When MRSA is suspected, empirical therapy should be chosen based on whether this is a community-acquired or hospital-acquired strain. Hospital-acquired strains usually require treatment with vancomycin, linezolid, or daptomycin, whereas community-acquired MRSA, in addition to the preceding agents, is often susceptible to trimethoprim–sulfamethoxazole, clindamycin, and tetracyclines. Cultures should be done at the time of drainage or debridement in patients who develop an infection in order to identify the antimicrobial susceptibility profile of these organisms and to direct therapy.

Intra-abdominal infection after penetrating abdominal trauma is a paradigm that defines risk factors for trauma-related infection in a single body cavity. Increased patient age, number and degree of organ injuries, units of blood products transfused, and presence of severe contamination, such as with colon injury, identify patients at high risk for infection after penetrating abdominal trauma. These factors are indicators of decreased physiologic reserve, impairments that result from the systemic effects of injury, the detrimental effects of hemorrhagic shock and transfusion, and the contribution of heavy bacterial contamination to the risk of infection. Because these risk factors cannot be completely defined before operation, empiric treatment with a broad-spectrum cephalosporin effective against gram-negative facultative organisms and anaerobes is indicated (Table 110.2). Patients with a low risk of infection need only a single dose of antibiotic, but those at high risk, such as with colon injury, should be treated for 24 hours. Treatment longer than 24 hours is of no added value. Patients who need operation for blunt abdominal injury are much less likely to have contamination from injury to the gastrointestinal tract. In this circumstance, cefazolin alone is adequate empiric treatment. Metronidazole should be added when bowel injury is suspected or confirmed. Intra-abdominal infection following penetrating trauma is a serious healthcare-acquired infection and often involves antimicrobial-resistant organisms. Recommended intravenous treatment regimens include either a carbapenem or piperacillin–tazobactam alone or cefepime in combination with metronidazole. Ciprofloxacin plus metronidazole or moxifloxacin alone are useful alternatives for patients who are allergic to β-lactams. Vancomycin or linezolid should be

added when MRSA is suspected. Cultures must be done to identify pathogens and delineate their antimicrobial sensitivity profile and therapy adjusted based on culture results.

Bullets or pellets that penetrate the gastrointestinal tract and lodge in soft tissues can result in soft-tissue infections through a combination of direct tissue injury and bacterial contamination. In this situation, the contaminating foreign material should be removed, debridement done, and definitive closure delayed.

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111. Infected implants

Gordon Dickinson and John C. Oeltjen

This chapter addresses infections associated with artificial devices of a specialized nature. The rate of infection is generally low, but collectively, there are millions of these devices implanted yearly, so the infections are not rare. Optimal treatment requires participation of surgical specialists experienced in the management of these difficult infections, especially for pseudophakic endophthalmitis, in which therapy includes intraocular injections.

INTRAOCULAR LENS-ASSOCIATED INFECTIONS (PSEUDOPHAKIC ENDOPHTHALMITIS)

Pseudophakic endophthalmitis is thought to occur as a consequence of contamination with flora of conjunctival sac or lid margin at the time of surgery. There also have been reports of infections arising from contamination of lenses and neutralizing and storage solutions.

The differential diagnosis of endophthalmitis following cataract extraction includes sterile inflammation as well as bacterial and fungal infection. The most common presenting signs and symptoms include pain in the involved eye, decreased visual acuity, red eye, lid edema, hypopyon, and absent or poor red reflex. A single bacterial strain is usually isolated; the most common pathogen is a coagulase-negative staphylococcus (approximately 50% in one large series) followed by *Staphylococcus aureus*. Virtually any microorganism can be implicated. Delayed-onset pseudophakic endophthalmitis has been reported after uncomplicated initial cataract surgery. This entity presents one or more months after surgery and is manifest by waxing and waning ocular inflammation. The leading cause of delayed-onset pseudophakic endophthalmitis is *Propionibacterium acnes*. Diagnostic evaluation requires aqueous and vitreous samples for Gram stain and culture. Vitrectomy may have therapeutic as well as diagnostic value.

Patients should be seen by an ophthalmologist immediately. Antimicrobials administered intraocularly and topically are the mainstay of treatment for this localized infection. Because of unpredictable antibiotic penetration, systemic antibiotics are of secondary importance and generally unnecessary. (See also Chapter 15, Endophthalmitis).

COCHLEAR IMPLANTS

Cochlear device implantation is available to adults and children as young as 1 year of age to correct severe hearing loss. The device consists of a subcutaneous receiver, a lead wire that passes through the middle ear, and fibers that contact the cochlear nerve. An external component with microphone and transmitter is positioned adjacent to the receiver. Infections, reported to occur in 1.5% to 4% of cases, may be classified as surgical wound infection, otitis media, or meningitis. Surgical wound infections generally arise in the immediate postoperative period and are manifest by tenderness, erythema, and swelling. Meningitis may occur in the postoperative period, but may also be encountered in the months following implantation. Otitis media in an ear with a cochlear device may also occur either in the postoperative period or long afterwards. Symptoms suggestive of a surgical wound infection or otitis media deserve immediate attention, with collection of a specimen for culture if possible and prompt initiation of antibiotics to minimize the infection and preserve the device. Many infections can be managed medically without removal of the device, although wound dehiscence over the receiver or progression of symptoms generally mandates device removal. Meningitis, encountered more frequently in children, may be associated with or without otitis media. The pathogens are typical of otitis-associated meningitis seen in children without cochlear implants. Because *Streptococcus pneumoniae*

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is a leading cause, empiric antibiotic therapy should include antimicrobials appropriate for this pathogen. Once an infection obviously involves the cochlear implant, it is difficult to salvage the device, a very serious matter because reimplantation may not be feasible. Prior to implantation of a cochlear device, both 13-valent conjugated polysaccharide and 23-valent polysaccharide pneumococcal vaccines should be administered, according to current guidelines.

BREAST IMPLANT-ASSOCIATED INFECTIONS

Breast prosthesis implantation, for augmentaion or reconstruction post-mastectomy, is a common procedure. In 2012 in the United States, an estimated 286 274 augmentation mammoplasty procedures were performed. US Food and Drug Administration (FDA)-approved prostheses consist of a silcone rubber shell filled with either saline or silicone polymer gel. They are implanted in a subglandular or submuscular pocket through inframammary, periareolar, transaxillary, transareolar or transumbilical approaches. Infection rates following augmentation mammoplasty range from 1.1% to 2.5%, and are up to 35% following reconstruction. Vascular compromise of the soft tissue in mastectomy and longer operative times are thought to contribute to the overall higher incidence of infections in breast reconstruction. Intraoperative breakdown of sterile technique, contaminated supplies, and hematogenous seeding are all possible sources of implant-associated infection. Endogenous flora of human breast tissue is similar to skin flora and accounts for most infections. The most common pathogens are *Staphylococcus* species including *S. aureus*, and *S. epidermidis*, followed by a broad spectrum of gram-positive and -negative organisms including *Serratia marcescens*, *Pseudomonas aeruginosa*, *Escherichia coli*, group B streptocococcus, *Enterobacter*, and *Morganella morganii*. Fungal infection is rare. A combination of patient comorbidities and surgical techniques are the major risk determinants. The signs and symptoms are variable, but common findings are malaise, fever, tenderness, induration, breast erythema, asymmetry, and ultrasonographic evidence of periprosthetic fluid accumulation. Severe sepsis can develop, and there are case reports of toxic shock syndrome occurring in the early postoperative period.

Clusters as well as sporadic infections caused by *Mycobacterium abscessus* and *Mycobacterium fortuitum* have been reported. The source of the pathogen is usually not identified, but inadequate equipment sterilization is suspected. Local signs and symptoms are similar to other bacterial infections, with a more subtle or delayed onset, and a lack of improvement on standard antibiotic therapy. Gram stain of the fluid usually reveals no organisms but many polymorphonuclear leukocytes. Stain for acid-fast bacilli is sometimes positive. A definitive diagnosis is established by culture of the organism.

Although oral fluoroquinolones have been suggested as treatment for early, subtle symptoms, breast implant-associated infections are treated with systemic antibiotics. As methicillin-resistant *S. aureus* and methicillin-resistant coagulase-negative staphylococci have become increasingly common, empiric regimens should include vancomycin along with coverage for gram-negative organisms, such as imipenem. Subsequent adjustment is made according to culture results. Duration of the therapy will depend on the causative organism, severity of infection, and clinical response; it usually ranges from 10 to 14 days. Agents with potential activity for most atypical mycobacteria include amikacin, cefoxitin, fluoroquinolones, clarithromycin, azithromycin, doxycycline, and imipenem; but susceptibility studies should be obtained, and combination of two or more effective agents is recommended to prevent development of resistance. Infections caused by mycobacteria require months of therapy. Although early aggressive antibiotic treatment of infections can sometimes preserve the implant, continued, severe, or systemic symptoms require implant removal with capsule debridement and postsurgical drain placement. Rarely will the contralateral implant have to be removed. Surgical replacement is possible once all symptoms resolve; most surgeons prefer to wait for 6 months to allow tissue recovery.

PENILE IMPLANT-ASSOCIATED INFECTION

Infection is a major complication for implantation of penile prostheses, occurring in an estimated 3% of cases. Most penile prosthesis-associated infections likely originate at the time of the implantation. Common sources of infection include skin, colorectal, and perianal flora; urine; and operating room environment. Infection can present within days after surgery to several weeks or months post implantation. *S. epidermidis* is isolated in more than 50% of cases; other bacteria include *S. aureus* and gram-negative enteric

bacteria such as *E. coli*, *P. aeruginosa, Klebsiella* spp. and *Proteus* spp. Gonococcal and fungal infections have been reported. Signs and symptoms of infections include new-onset pain, swelling, tenderness, erythema, induration, fluctuance, erosion, and extrusion of prosthesis. Infections caused by *S. epidermidis* are often subtle and may present with dysfunction of the prosthesis or pain upon manipulation of the device.

Empiric antibiotic therapy treatment should be directed at both gram-positive bacteria and gram-negative coliform bacteria, pending isolation of the causative pathogen. There is universal consensus that if a penile implant-associated infection occurs, the implant and all associated foreign material should be removed. There are, however, diverging views about surgical management. The preferred approach is a two-stage operation with the infection-associated device removed, the wound allowed to heal, and then replacement 4 to 6 months later. For selected patients, surgeons may elect to remove the infection-associated device, debride the wound, and implant a new device in a single-stage operation. For uncomplicated infections a 10- to 14-day course of systemic antibiotics is given, whereas for complicated infections, antibiotic therapy should be continued for a week or more after all signs of infection have resolved.

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112. Infection in the burn-injured patient

Roger W. Yurt and Rafael Gerardo Magaña

The diagnosis of infection in the patient with major burn injury is especially problematic because the signs of infection are the same as those of the response to injury.

The tissue injury that occurs with a major burn and the associated inflammatory response to it cause one of the greatest perturbations of homeostasis that occurs in any disease state. Thus the greatest challenge in developing a differential diagnosis in the burn-injured patient is to distinguish between the injury state and infection. That the manifestation of infection may be blunted by diminished immune response further complicates evaluation of the patient while also contributing to an increased susceptibility to infection.

The challenge posed in the clinical and laboratory evaluation of the burn-injured patient is summarized in the outline of injury-related changes in Table 112.1.

Table 112.1 Clinical and laboratory signs related to injury that complicate the evaluation of the patient with burn injury

Sign	Abnormality
General condition	Lethargy-electrolyte imbalance Analgesic effects Hyperventilation Pain, topical agents Tachycardia Pain, volume depletion, hypermetabolism
Fluid balance	Hypovolemia Initial injury Delayed-evaporative loss
Fluid composition	Hypernatremia Free water loss Inadequate fluid replacement Hyponatremia Excessive free water Effects of topical silver nitrate Hyperglycemia Stress
Temperature	Hypothermia Heat loss to the environment Large fluid requirement Hyperthermia Hypermetabolism Endotoxin from the wound
Neutrophil response	Neutrophilia Acute 5–7 days after injury Neutropenia 2–3 days after injury

INJURY PATHOPHYSIOLOGY AND SUSCEPTIBILITY TO INFECTION

The initial approach to the burn-injured patient is oriented toward limiting the progression of the injury by stabilization of the patient and maintenance of blood flow to the wound. The zone of coagulative necrosis consists of tissue that has been irreversibly damaged, whereas the surrounding zone of stasis contains areas of potentially reversible injury. Adjacent areas, known as the hyperemic zone, may also evolve to become necrotic if the blood flow is not maintained. For this reason, the primary goal of early burn therapy is to ensure adequate delivery of oxygen, nutrients, and circulating cells to the wound. In addition to prevention of progression of the injury, immediate burn care focuses on maintenance of a viable tissue interface at which both specific and nonspecific defenses against infection can be mounted.

The depth of burn injury is categorized as partial or full thickness. Full-thickness injuries will heal only by contraction, ingrowth of surrounding epidermis, or grafting of tissue because all epidermis in the wound has been destroyed. These wounds are leathery and dry, contain thrombosed vessels, and are insensate. Partial thickness wounds contain residual epidermis, which can close the wound if blood flow is maintained and infection does not supervene.

Partial thickness wounds are red and moist, and pain is elicited by touch. Deep partial-thickness wounds contain only epithelial elements associated with organelles of the skin. They take longer to heal (2 to 3 weeks) than superficial partial-thickness

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wounds, and there is a greater functional and cosmetic deformity if they are allowed to heal primarily. These wounds are difficult to differentiate by clinical evaluation from superficial partial-thickness injuries, which usually heal within 10 days to 2 weeks.

The dynamic aspect of burn wounds is dramatically seen when partial-thickness wounds convert to full-thickness wounds during a difficult resuscitation of a patient. Although this is rarely seen with current methods of resuscitation, resuscitation that is delayed or performed on patients at extremes of age occasionally will show this progression.

Any agent that causes cellular death can lead to a deeper wound. With this in mind, caustic topical agents and vasopressors are avoided, the wound is not allowed to desiccate, and the patient is kept warm.

Both mortality and susceptibility to infection correlate directly with the extent of the surface area injury. Distribution of surface area varies with age, so a chart is used to plot accurately the extent and depth of surface area burned. The rule of nines may be used to estimate the extent of injury as follows: torso, back and front, each 18%; each leg 18%; each arm 9%; and head 9%. Calculation of the extent of injury is helpful in estimating fluid requirements and prognosis. Patients with greater than 25% to 30% total body surface area burn exhibit the pathophysiologic features already described.

PREVENTION OF INFECTION

Current data do not support the general use of prophylactic systemic antibiotics in the inpatient population. Frequent evaluation of the wound and surrounding tissue allows early and appropriate therapy of cellulitis while sparing a majority of patients exposure to unnecessary antibiotics. However, some practitioners give systemic antibiotics (cephalexin) to outpatients with burns because it is not possible to observe closely and ensure appropriate care of the wound. The use of systemic antibiotics in these patients is individualized such that those who are likely to follow up with their care and recognize changes in their wounds are not given antibiotics. The one time that prophylactic systemic antibiotics are used in inpatients is at the time of surgical manipulation because this may cause bacteremia. Antibiotics are administered immediately before and during burn wound excision. The choice of antibiotics is dictated by knowledge of the current flora in the burn center or, more specifically, by the burn wound flora of the individual patient.

The mainstay of prevention of burn wound infection is aggressive removal of the necrotic tissue and closure of the wound with autograft. In the interim, topical antimicrobial prophylaxis will decrease the incidence of conversion of partial-thickness to full-thickness wound by local infection, and these agents may prolong the sterility of the full-thickness burn wound. Silver sulfadiazine is the most commonly used topical agent and is a soothing cream with good activity against gram-negative organisms. Because it does not penetrate the wound, it is used only as a prophylactic antimicrobial. Bacterial resistance to silver sulfadiazine has been reported, and it has been reported to cause neutropenia. Silver nitrate in a 0.5% solution is an effective topical agent when used before wound colonization. This agent does not penetrate the eschar, and therefore its broad-spectrum gram-negative effectiveness is diminished once bacterial proliferation has occurred in the eschar. Additional disadvantages of this agent include the need for continuous occlusive dressings, which limits the evaluation of wounds and restricts range of motion. The black discoloration of the wound, as well as the environment, contributes to the decrease in the use of silver nitrate. Mafenide acetate (Sulfamylon) cream has a broad spectrum of activity against staphylococci. A significant advantage of this agent is that it penetrates burn eschar and therefore is effective in the colonized wound. The disadvantages of Sulfamylon are a transient burning sensation, an accentuation of postinjury hyperventilation, and inhibition of carbonic anhydrase activity.

Recent experience with a new silver-impregnated dressing that does not have to be changed daily suggests that this agent is a good alternative for prophylaxis against infection in partial-thickness wounds.

The goal of burn therapy is to prevent burn wound infection by permanent closure of the wound as rapidly as possible. Early removal of necrotic tissue and wound closure has the advantages of removal of eschar before colonization, which typically occurs 5 to 7 days after injury, and of reduction of the overall extent of injury. A drawback of early excisional therapy is the possibility that burned tissue that may heal if left alone over a 2- to 3-week period may be unnecessarily excised.

Advances in resuscitation have led to the ability to salvage an increasing number of patients from the shock phase immediately after injury and have resulted in a greater number of patients surviving to the time (3 to 4 days after the injury) when the effects of inhalation injury become clinically prominent. In patients without inhalation injury but with large burns, postinjury hyperventilation and subsequent decreases in tidal volume may lead to

atelectasis and subsequent pneumonia. Diminished mucociliary function and destruction of the airways by inhalation of products of combustion lead to airway obstruction and infection.

Frequent diagnostic and therapeutic bronchoscopies are necessary in this group of patients. Attempts at specific prophylaxis of the sequelae of inhalation injury, such as nebulization of antibiotics and treatment with steroids, have failed to show any benefit.

Nosocomial infections are of even greater concern in the burn intensive care setting than other units because of the large open colonized wounds. Cross-contamination is avoided by use of gowns, gloves, and masks by nurses, medical staff, and visitors. The patient is not touched except with a gloved hand, and each patient is restricted to his or her own monitoring and diagnostic equipment. If adequate nursing care can be provided, it is preferable to isolate patients who have large open wounds in individual rooms. Cohort patient care has been shown to be effective in reducing endemic infections.

DIAGNOSIS AND TREATMENT OF INFECTIONS

Wound infection

Because the full-thickness burn wound is at high risk for infection, routine clinical and laboratory surveillance of the wound is an absolute necessity. Daily observation of the wound for discoloration, softening or maceration of the eschar, or the development of cellulitis provides early detection of wound-associated infection. Although surface cultures of the burn wound provide insight into the organisms that are colonizing the wound, evaluation of a biopsy of the burn wound is the only way to obtain accurate assessment of the status of the wound. Systematic evaluation of burn wounds with quantitative culture of biopsies of all areas of wound change documents the clinical diagnosis of wound infection and provides identification and antimicrobial sensitivity of the involved organism. Routine biopsy of full-thickness burn wounds on an every-other-day schedule provides evidence of advancing wound infection and serves as a basis for initiating therapy. A rapid fixation technique allows histologic diagnosis of invasive infection within 3 hours, whereas quantitative counts and identification of the organism are available in 24 hours.

This combined use of histologic and culture techniques provides early diagnosis as well as the identity of the organism and its sensitivity to antimicrobials. When the findings are consistent with invasive infection (greater than or equal to 10^5 organisms/g of tissue), aggressive surgical therapy is instituted to excise the involved wound. In preparation for surgery or in patients who require stabilization before general anesthesia is given, a penetrating topical agent is used (Sulfamylon). The choice of antibiotic is based on previous biopsy sensitivity data or data accumulated on sensitivities of the current flora in the patient population.

A growing number of patients present with primary nonsuppurative gram-positive infections. These infections are often caused by methicillin-resistant *Staphylococcus aureus* (personal observation), and whether diminished neutrophil response or a change in the nature or the virulence of such organisms may explain this phenomenon is unknown.

Pulmonary infection

From a practical standpoint, inhalation injury is diagnosed by history, physical examination, and bronchoscopy. A history of exposure to fire in a closed space along with findings of carbonaceous sputum, singed nasal vibrissae, and facial burns are associated with a high incidence of inhalation injury. In the burn patient, pulmonary complications after injury are not uncommon and may increase the mortality rate of ventilator-associated pneumonia (VAP), which may increase from 40% to 77% in the presence of significant inhalation injury. Bronchoscopy reveals upper airway edema and erythema, whereas bronchorrhea, carbon in the bronchi, and mucosal slough suggest lower airway and parenchymal injury.

Carboxyhemoglobin levels may be elevated, but with a half-life of 45 minutes on 100% oxygen the level may be normal. Chest x-ray studies are of little value in making the diagnosis of inhalation injury because they are often normal for the first 72 hours after injury. Xenon ventilation–perfusion lung scan reveals trapping of xenon in the ventilation phase and is supportive of a diagnosis of small airway obstruction secondary to injury of the distal airways and parenchyma. Although hematogenous pneumonia is less common than in the past, it remains a significant problem in the patient with burns. When it occurs, the source (most commonly the wound or suppurative vein) must be defined and eradicated. Prophylactic antibiotics are not used for either bronchopneumonia or hematogenous pneumonia; specific therapy is based on knowledge of previous endobronchial culture, and sensitivity is substantiated by repeat cultures at the time of diagnosis. Diagnosing pneumonia in

this population may be difficult. Different clinical scores have been developed to this end; however, they are of little value because they have low specificity and sensitivity when compared with specimens obtained via bronchoalveolar lavage. A culture with 10^4 organisms/mL is generally considered to be significant enough to warrant antibiotic therapy. Bronchoalveolar lavage with negative results also reduces the usage of unnecessary antibiotics.

Suppurative thrombophlebitis

Suppurative thrombophlebitis is mentioned in particular in relation to the patient with burn injury because it is the most common cause of repeatedly positive blood cultures in the presence of appropriate antibiotics in this population. These findings alone should lead to a presumptive diagnosis of a suppurative process in a previously cannulated vein. The process may be insidious, with only minimal clinical findings. Because of this complication, venous cannulation should be minimized, but when it is necessary catheters should be changed on a regular basis. In some centers this is done as often as every 3 days. Treatment consists of surgical excision of the entire involved vein to the level of normal bleeding vessel. In this setting the differential diagnosis should include endocarditis.

Chondritis/suppurative chondritis

Burn wounds that involve the ear are of particular concern, because its cartilage has no intrinsic blood supply and thus has the potential to develop chondritis and subsequent suppurative chondritis. Because the ear is covered only by skin and has no subcutaneous tissue, the cartilage is at risk for infection when there is a full-thickness burn causing local necrosis. This often leads to loss of tissue and permanent deformity and, in some cases, loss of the ear.

Damaged skin acts as a portal of entry. In addition, local edema may predispose to thrombosis of central vessels. *Pseudomonas* and *Staphylococcus* are the most common pathogens involved in this pathology.

Sulfamylon is of benefit in this condition because it can penetrate eschar to the level of cartilage and prevent bacterial invasion. Pressure-related damage to the ear must be avoided. Therefore, the ear should be dressed in topical only or topical and one layer of nonadherent gauze. To avoid pressure on the ear, a pillow for the head should not be allowed.

Once suppurative chondritis ensues, surgical intervention is mandatory and consists of drainage and debridement of all nonviable tissue. This can be accomplished by making an incision on the helical rim of the ear (bivalving), with subsequent drainage and excision of nonviable tissue. The ear is then dressed with an antibacterial solution, changed on a twice-daily schedule, and allowed to heal by secondary intention. Special attention should be given to avoid any form of compression to keep the dressings in place, because this may increase the extent of necrosis.

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PART XV

Prevention of infection

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113. Nonsurgical antimicrobial prophylaxis

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PREVENTION

Chemoprophylaxis is the use of an antimicrobial agent to prevent infection. Chemoprophylaxis is often administered after exposure to a virulent pathogen or before a procedure associated with risk of infection. Chronic chemoprophylaxis is sometimes administered to persons with underlying conditions that predispose to recurrent or severe infection. Antibiotics can also be used as pre-emptive therapy (sometimes referred to as secondary prophylaxis) to prevent clinical disease in persons infected with a microorganism such as *Mycobacterium tuberculosis*. Immunization, another excellent means of preventing infection, is discussed in Chapter 115. For information on prophylaxis of bacterial endocarditis, see Chapter 37, Endocarditis of natural and prosthetic valves: treatment and prophylaxis; for information on prophylaxis in persons infected with the human immunodeficiency virus (HIV), see Chapter 102, Prophylaxis of opportunistic infections in HIV disease; for malaria prophylaxis, see Chapter 200, Malaria; for prophylaxis related to transplant recipients and neutropenic patients, see Chapter 89, Infections in transplant recipients, and Chapter 85, Infections in the neutropenic patient; and for surgical prophylaxis, see Chapter 114, Surgical prophylaxis.

Several concepts are important in determining whether chemoprophylaxis is appropriate for a particular situation. In general, prophylaxis is recommended when the risk of infection is high or the consequences significant. The nature of the pathogen, type of exposure, and immunocompetence of the host are important determinants of the need for prophylaxis. The antimicrobial agent should eliminate or reduce the probability of infection or, if infection occurs, reduce the associated morbidity. The ideal agent is inexpensive, orally administered in most circumstances, and has few adverse effects. The ability to alter the normal microbiota and select for antimicrobial resistance should be limited. The emerging crisis of antibiotic-resistant bacteria underscores the importance of rational and not indiscriminate use of antimicrobial agents.

The efficacy of chemoprophylaxis is well established in situations such as perioperative antibiotic administration, exposure to invasive meningococcal disease, prevention of recurrent rheumatic fever, and prevention of tuberculosis. Chemoprophylaxis is accepted in other situations without supporting data. When the risk of infection is low, such as with bacterial endocarditis following dental procedures, randomized clinical trials of prophylaxis are not feasible. However, the consequences of infection may be catastrophic, providing a compelling argument for chemoprophylaxis despite the low risk of infection. When prophylaxis is advocated without data confirming efficacy, there should be a scientific rationale to support the use of a particular antimicrobial agent.

Table 113.1 lists the situations in which antimicrobial prophylaxis is indicated after exposure to certain pathogens. Because the duration of exposure is usually brief, the duration of chemoprophylaxis is short, which helps limit adverse reactions, minimizes the potential for resistance, and limits cost. Table 113.1 includes chemoprophylaxis for human, dog, and cat bites. It is important to remember that, aside from antibiotics, immunization (rabies and tetanus vaccines), irrigation, and debridement are crucial in the management of both animal and human bites. Table 113.1 also includes microorganisms that have gained notoriety as possible agents of biologic warfare or terrorism and infections that are sexually transmitted. Recent evidence supports the use of tenofovir–emtricitabine for the prevention of HIV infection in high-risk populations prior to exposure (pre-exposure prophylaxis). This approach requires strict adherence, regular HIV and sexually transmitted disease testing, frequent monitoring, and carries the potential risk of developing HIV drug resistance. Pre-exposure

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Table 113.1 Prophylaxis following selected exposures

Exposure	Pathogen	Prophylaxis[a]	Comments
Meningitis and meningococcal bacteremia	*Neisseria meningitidis* (see Chapters 143, Meningococcus and miscellaneous neisseriae, and 74, Bacterial meningitis)	Rifampin, 600 mg (5 mg/kg for children ≤1 mo and 10 mg/kg for children >1 mo) q12h for 4 doses Ciprofloxacin, 500 mg (single dose) (adults only and if not resistant to ciprofloxacin) Ceftriaxone, 250 mg IM 1 dose (125 mg for children ≤15 yr)	Recommended for close contacts only (e.g., household contacts, roommates, day-care contacts); prophylaxis not recommended for healthcare workers unless very close contact such as mouth-to-mouth resuscitation or intubation: secondary cases reported with meningococcal pneumonia, but role of prophylaxis is uncertain; sulfonamide resistance precludes routine use of sulfadiazine
Meningitis	*Haemophilus influenzae*	Rifampin, 600 mg (20 mg/kg for children) daily for 4 d	Recommended for all household contacts (except pregnant women) if unvaccinated children ≤ 4 yr present In day-care settings, prophylaxis (and vaccination) recommended for unvaccinated children 2 yr and less following exposure
Perinatal group B streptococcus (GBS)	Group B streptococcus	Penicillin G, 5 million units IV initial dose then 2.5 to 3 million q4h, or ampicillin, 2 g IV initial dose then 1 g IV q4h, until delivery If penicillin allergic use clindamycin, 900 mg IV q8h, or cefazolin, 2 g loading dose then 1 g IV q8h, or vancomycin, 1 g IV q12h until delivery	Women should be screened with vaginal and rectal swabs at 35–37 wk of gestation and intrapartum prophylaxis given if GBS isolated. Prophylaxis should also be given if (1) history of GBS bacteriuria, (2) GBS disease during previous pregnancy, or (3) with unknown GBS status and either intrapartum temperature >38°C or >18 h of ruptured membranes or delivery ≤37 wk of gestation
Human bite	*Streptococcus viridans*, other streptococci, oral anaerobes, *Staphylococcus aureus*, *Eikenella corrodens*	Amoxicillin–clavulanic acid, 875/125 mg BID or 500/125 mg TID for 3–5 d For penicillin allergy, consider clindamycin, 300 mg QID, plus either ciprofloxacin, 500 mg BID, or TMP–SMX, 1 double-strength tablet BID	Risk of infection depends on the depth of the wound, extent of tissue damage, and the etiologic pathogen: *Eikenella* is resistant to clindamycin, first-generation cephalosporins, and erythromycin Clenched-fist injuries often require parenteral antibiotics
Cat bite	*Pasteurella multocida*, *S. aureus*, streptococci	Amoxicillin–clavulanic acid, 875/125 mg BID or 500/125 mg TID for 3–5 d For penicillin allergy, consider doxycycline, 100 mg BID, or cefuroxime axetil, 500 mg BID	A high percentage of cat bites become infected without prophylaxis Clindamycin and first-generation cephalosporins are not as active as penicillin against *P. multocida*, which is present in oral flora of 50% to 70% of cats
Dog bite	*S. viridans*, oral anaerobes, *S. aureus*, *P. multocida*, *Capnocytophaga canimorsus* (formerly DF-2)	Amoxicillin–clavulanic acid, 875/125 mg BID or 500/125 mg TID for 3–5 d For penicillin allergy, consider clindamycin, 300 mg QID, plus either ciprofloxacin, 500 mg BID, or TMP–SMX, 1 double-strength tablet BID	Infection less common than with cat or human bites; need for routine prophylaxis for all bites uncertain; persons without spleens at risk of overwhelming *Capnocytophaga* sepsis, should receive prophylaxis following any dog bite
Sexual assault	*Trichomonas vaginalis*, *Chlamydia trachomatis*, *Treponema pallidum*, *Neisseria gonorrhoeae*, HIV	Ceftriaxone, 250 mg IM single dose, plus metronidazole, 2 g single dose, plus doxycycline, 100 mg BID for 7 d, or azithromycin, 1 g single dose Nonoccupational HIV postexposure prophylaxis (nPEP) may be given to the exposed person within 72 h of unprotected sexual contact with a known HIV-positive source and often consists of the following regimens: (1) Emtricitabine + tenofovir + raltegravir (2) Tenofovir + emtricitabine + either ritonavir-boosted atazanavir OR ritonavir-boosted darunavir. However, the regimen should be individualized if the source patient's antiviral regimen, viral	Consider use of antiretroviral agents following selected high-risk exposures

Table 113.1 *(continued)*

Exposure	Pathogen	Prophylaxis[a]	Comments
		load, or genotype is known. This should be done by an experienced HIV practitioner HIV nPEP is typically given for 28 days. For prophylaxis following occupational HIV exposure, see Chapter 104, Percutaneous injury: risks and prevention	
Sexual contacts	*T. pallidum*	Benzathine penicillin G, 2.4 million units IM	Treat if exposed within the previous 90 days. Doxycycline is an alternative in patients allergic to penicillin
	N. gonorrhoeae	Single dose of ceftriaxone, 250 mg IM	Because of possibility of concomitant chlamydial infection, contacts of persons with gonorrhea should also receive azithromycin or doxycycline. Resistance to quinolones, first observed in men who have sex with men (MSM) and in certain geographic locations, is now sufficiently widespread to preclude routine use of ciprofloxacin or levofloxacin
	C. trachomatis	Azithromycin, 1 g single dose, or doxycycline, 100 mg BID for 7 d	Use azithromycin in pregnant women
	T. vaginalis	Metronidazole, 2 g single dose or 500 mg BID for 7 days or tinidazole, 2 g single dose	No satisfactory alternatives are available in the United States
Influenza	Influenza A and B	Oseltamivir, 75 mg, or zanamivir, 10 mg (or 2 inhalations) once daily used after exposure to influenza or for the duration of the influenza outbreak in the community in high-risk population	Chemoprophylaxis should not be a substitute for vaccination. Oseltamivir approved for chemoprophylaxis in children >1 yr and zanamivir in children >5 yr. Historically, amantadine and rimantadine have been used for prophylaxis for influenza A. However, high levels of resistance (>80%) have occurred in recent years. Consequently, these agents should not be used unless the circulating strain of influenza is known to be susceptible
Whooping cough	*Bordetella pertussis*	Azithromycin, 500 mg single dose on day 1 then 250 mg/d on days 2–5, or erythromycin, 500 mg QID for 14 d, or clarithromycin, 500 mg BID for 7 d. TMP–SMX, 160/800 mg BID for 14 d, used as an alternate regimen	Use pediatric dosing for children
Lyme disease	*Borrelia burgdorferi*	Doxycycline 200 mg single dose	Antimicrobial prophylaxis following tick bite is not recommended in most situations. However doxycycline is recommended (1) within 72 h of the removal of an adult or nymph *Ixodes scapularis* tick and (2) if the tick has been attached more than 36 h and (3) if the exposure occurred in a region where prevalence of *B. burgdorferi* in ticks is greater than 20%.
Anthrax	*Bacillus anthracis*	Ciprofloxacin, 500 mg BID, or levofloxacin, 500 mg daily for 60 d; alternatives include doxycycline, 100 mg bid, and amoxicillin, 500 mg TID	Inhalational anthrax is considered one of the major threats associated with bioterrorism
Plague	*Yersinia pestis*	Doxycycline, 100 mg BID for 7 d or for duration of exposure, or tetracycline, 500 mg QID, or ciprofloxacin, 500 mg BID	Incubation period for pneumonic plague is short (2–3 d); for established infection, streptomycin IM or gentamicin remains the agent of choice
Tularemia	*Francisella tularensis*	Doxycycline, 100 mg BID for 14 d, or ciprofloxacin, 500 mg BID	Can produce disease following inhalation or percutaneous exposure

Abbreviation: TMP–SMX = trimethoprim–sulfamethoxazole.

[a] All regimens are administered orally unless otherwise specified.

Table 113.2 Chronic prophylaxis in specific clinical settings

Underlying condition or recurrent infections	Pathogens	Prophylaxis[a]	Comments
Acute rheumatic fever (prevention of recurrences)	*Streptococcus pyogenes*	Penicillin G, 1.2 million units IM every 3–4 wk; alternatives include penicillin V, 250 mg BID; erythromycin, 250 mg BID; sulfadiazine, 1 g daily (0.5 g if weight ≤27 kg)	Risk diminishes with increasing age and time since initial attack; optimal duration unknown but continue prophylaxis at least until the early 20s or for 5 yr after most recent attack; some authorities advocate lifelong prophylaxis, especially after rheumatic carditis; risk of prophylaxis failure may be greater with 4-wk dosing of penicillin compared to 3-wk dosing
Recurrent urinary tract infection (UTI)	Gram-negative bacilli	TMP–SMX, 1/2 single-strength tablet (40 mg, 200 mg) daily or 3 times/wk, or trimethoprim, 100 mg, or ciprofloxacin, 250 mg, or nitrofurantoin, 50–100 mg, or cephalexin, 125–250 mg daily	For selected patients with more than three infections yearly; consider prophylaxis for 6–12 mo; alternative strategy is postcoital TMP–SMX, 1 tablet or ciprofloxacin, 500 mg, or cephalexin, 125–250 mg, or nitrofurantoin 50–100 mg
Recurrent otitis media	*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*	Sulfisoxazole, 50 mg/kg, or amoxicillin, 20 mg/kg daily	Recommended for children with more than three infections in 6 mo; increasing antibiotic resistance has decreased the efficacy of this strategy and has led some experts to abandon it
Chronic bronchitis, bronchiectasis	*S. pneumoniae*, *H. influenzae*, *M. catarrhalis*	Amoxicillin, 500 mg TID, or TMP–SMX, 1 double-strength tablet BID, or azithromycin 250 mg daily, or tetracycline, 500 mg QID	May be useful in selected patients with frequent exacerbations (>4/yr); some authorities prefer antibiotics at first sign of infection. Recent placebo-controlled randomized trial found azithromycin daily for 1 yr decreased frequency of exacerbations and improved quality of life in patients with chronic obstructive pulmonary disease; hearing loss noted in some subjects
Asplenia, including sickle cell disease	Predominantly *S. pneumoniae;* also *H. influenzae* *Neisseria meningitidis*	Penicillin V, 250 mg BID (125 mg BID for children ≤5 yr), or benzathine penicillin G, 1.2 million units IM every 4 wk; prophylaxis generally continued 2 yr after splenectomy; for children with sickle cell disease, prophylaxis continued at least until aged 5 yr	Efficacy of chemoprophylaxis clearly established for children with sickle cell disease; some authorities recommend amoxicillin or TMP–SMX for children aged ≤5 yr because of risk of *H. influenzae* infection; however, this risk has been dramatically reduced because of immunization; chemoprophylaxis generally not recommended for adults (lower risk); penicillin-resistant pneumococcus diminishes attractiveness of antibiotic prophylaxis and increases the importance of vaccination
Lymphedema with recurrent cellulitis	*S. pyogenes*	Benzathine penicillin G, 1.2 million units IM monthly, or penicillin, 250–500 mg BID In penicillin-allergic patients, use macrolides	Given only to patients with frequent episodes of cellulitis; efficacy is limited in patients with significant underlying disease
Spontaneous bacterial peritonitis (SBP)	*Escherichia coli*, *S. pneumoniae*, *Klebsiella pneumoniae*	Ciprofloxacin 750 mg weekly, or TMP–SMX, 1 double-strength tablet 5 d/wk	Used in persons with ascites protein concentration of ≤1 g/dL and in persons with previous SBP

Abbreviation: TMP–SMX = trimethoprim–sulfamethoxazole.

[a] All regimens are administered orally unless otherwise specified.

prophylaxis should be used in combination with other methods to prevent HIV.

Persons with an underlying predisposition to infection may benefit from prophylactic antimicrobial agents (Table 113.2). In contrast to short-term prophylaxis administered after exposures, chronic prophylaxis is often required. Because of the duration of antibiotic administration, the complications of chemoprophylaxis, including alteration of the microbiota and antibiotic resistance, are major considerations. The emergence of antibiotic-resistant *Streptococcus pneumoniae* may force reassessment of the standard chemoprophylactic recommendations when pneumococcus is

Table 113.3 Regimens for chemoprophylaxis[a] or pre-emptive therapy for *M. tuberculosis*

Drug(s)	Regimen	Duration	Comments
Isoniazid (INH)	300 mg daily or 900 mg twice weekly	6 to 9 months	9-month regimen preferred (more effective) and should be used for HIV-infected patients, patients with evidence of healed TB on CXR and in children $\leq$ age 4 years; 6-month regimen more cost-effective and has better compliance. Intermittent regimens provided by directly observed therapy (DOT)
Isoniazid and rifapentine (RPT)	900 mg INH and 900 mg RPT weekly	3 months	Alternative to INH with advantage of shorter duration and fewer doses. Typically given by DOT. Not recommended for children under 2 years, HIV infected persons on antiretroviral therapy, pregnant women
Rifampin (RIF)	600 mg daily	4 months	Use for those intolerant of INH or if exposed to INH resistant tuberculosis

[a] Chemoprophylaxis recommended for high-risk patients including children $\leq$ age 4 years during the "window period" after exposure to active tuberculosis and before follow-up skin testing. Depending on intensity of exposure and rate of skin test conversion among others exposed, full course treatment should be considered in exposed persons with HIV infection, those on immunosuppressive therapy following transplantion or in persons taking TNF-α antagonists.
Abbreviations: TB = tuberculosis; CXR = chest x-ray; TNF-α = tumor necrosis factor-α.

Table 113.4 Controversial areas regarding the use of prophylactic antibiotics[a]

Condition	Comments
Prosthetic device prophylaxis	Routine chemoprophylaxis before dental work, or other procedures that cause transient bacteremia in patients with prosthetic joints or vascular prostheses, may not be warranted although it is commonly used; prosthetic joint infections caused by oral microbiota, including α-streptococci, are uncommon, with a rate approaching that of endocarditis in patients with mitral valve prolapse without regurgitation, for which chemoprophylaxis is not recommended; coronary stents do not appear to be prone to infection
Catheter-associated UTI	Systemic antibiotics reduce incidence of UTI during initial 4 to 5 days after Foley catheter insertion; with prolonged catheterization antibiotic-resistant bacteria appear in urine with increasing frequency, dissuading most authorities from routine use of prophylaxis; prophylactic antibiotics possibly useful in selected high-risk patients during short-term catheterization
IV catheter-associated infections	Antibiotic or ethanol "lock" therapy to prevent central venous catheter-associated bloodstream infections may have a role in some high-risk patients including those with recurrent catheter infections but the optimal role for locking is not clear
Pancreatitis	In severe pancreatitis with necrosis, antibacterial (as well as antifungal) prophylaxis has been suggested. However, even if antimicrobials appear to decrease mortality, in pancreatic necrosis they do not prevent infections

Abbreviations: UTI = urinary tract infection; IV = intravenous.
[a] See also Chapter 68, Infection of native and prosthetic joints.

a prominent pathogen, as with anatomic or functional asplenia and recurrent otitis.

Chemoprophylaxis for *M. tuberculosis* is used to prevent acquisition of infection in high-risk groups following exposure to a patient with contagious tuberculosis disease. More commonly, pre-emptive therapy is given to those latently infected as demonstrated by a positive tuberculin or purified protein derivative (PPD) skin test or a positive interferon-gamma release assay (IGRA) to prevent the development of tuberculosis disease. The regimens for chemoprophylaxis or treatment of latent *M. tuberculosis* infection are listed in Table 113.3. Prior to initiating prophylaxis for latent infection, the clinician should rule out active disease with a chest radiograph. In the setting of suspected infection with multidrug-resistant *M. tuberculosis*, the decision to provide chemoprophylaxis and the choice of regimen should be made by experienced healthcare professionals.

Chemoprophylaxis has been advocated for other situations, but at this time, there is debate about the optimal role (Table 113.4). Although data are limited, it is likely that cost–benefit analyses may not favor routine prophylaxis in some of these settings or that the benefits of prophylaxis in the short term would be outweighed by long-term consequences such as the development of antibiotic-resistant organisms.

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114. Surgical prophylaxis

Joseph S. Solomkin and Giorgio Tarchini

The prevention of surgical site infection (SSI) remains a focus of attention because such infections continue to be a major source of expense, morbidity, and even mortality. SSIs are the third most frequently reported nosocomial infection, accounting for 14% to 16% of nosocomial infections in hospitalized patients. Approximately 40% of healthcare-associated infections occurring among surgical patients are SSIs. A patient who develops a surgical site infection while still hospitalized has an approximately 60% greater risk of being admitted to the intensive care unit, and an attributable extra hospital stay of 6.5 days, at an additional direct cost of $3000. Risk of readmission within 30 days is five times more likely for infected patients, at a cost of more than $5000.

Depending on the procedure, between one-half and two-thirds of SSIs affect the incision and the remainder involve deep tissue or organ/space infection. Nearly all deep and organ/space SSIs require hospitalization, operative or radiologic intervention, and intravenous antibiotic therapy. These are the most expensive healthcare-associated infections. Three-quarters of deaths of surgical patients with SSI are attributed to that infection, nearly all of which are organ/space infections. Conversely, superficial incisional infections commonly are noted after discharge, rarely require rehospitalization or intervention, and have little if any documented social or financial cost. The National Healthcare Safety Network no longer publicly reports superficial incisional infection rates.

2014 GUIDELINES FROM CDC/HICPAC ON PREVENTION OF SURGICAL SITE INFECTIONS

The Hospital Infection Control Practices Advisory Committee (HICPAC) of the Centers for Disease Control and Prevention (CDC) has updated the 1999 guidelines for the prevention of surgical site infection. The recommendations in this update are based upon use of the GRADE (Grades of Recommendation Assessment, Development and Evaluation) system (www.gradeworkinggroup.org). The standards for this update required GRADE level 1, meaning "strong," evidence, for a recommendation. In turn, this requires randomized controlled trials.

The relevant recommendations made are detailed in Table 114.1. In certain critical areas for antimicrobial prophylaxis, such as in timing of administration, weight-based dosing, and intraoperative redosing, clinical outcomes data from randomized control trials do not exist. The CDC update deals with these issues by referencing external clinical practice guidelines.

The recent guidelines developed by the American Society of Health-System Pharmacists (ASHP), and endorsed by the Infectious Diseases Society of America (IDSA), the Surgical Infection Society (SIS), and the Society for Healthcare Epidemiology of America (SHEA) are an update to the previously published ASHP Therapeutic Guidelines on Antimicrobial Prophylaxis in Surgery. Because they are referenced by the CDC update, these ASHP guidelines will become a de facto standard for antibiotic usage for prophylaxis.

One goal of this chapter is to review these guidelines in depth, and to provide a contrarian critique. In certain cases, where we believe recommendations to be not justified by recent data, we provide alternatives. We also note that administration of systemic anti-infectives is part of a broad program of infection control involving adequate operating room ventilation, sterilization, site preparation, barrier usage, and delicate surgical technique.

We also believe that surgical prophylaxis administered per current guidelines has little if any impact on bacterial resistance patterns. In comparison to the substantial quantity of

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Table 114.1 CDC/HICPAC update to the 1999 guidelines on surgical site infection prevention

Recommendations for parenteral antimicrobial prophylaxis

1A. No recommendation can be made regarding the optimal timing of preoperative parenteral prophylactic antimicrobial agent administration for the prevention of surgical site infection. **(No recommendation/ unresolved issue)**
Clinical practice guidelines recommend administering by the intravenous route a single dose of prophylactic antimicrobial agent. For most prophylactic agents, administration should be within 60 minutes prior to incision. Administer vancomycin and fluoroquinolones within 60–120 minutes prior to incision.[12,22-27]
1B. Administer the appropriate parenteral prophylactic antimicrobial agent prior to skin incision in all cesarean sections. **(Category IA)**[28-31]
1C. No recommendation can be made regarding the safety and effectiveness of weight-adjusted dosing of parenteral prophylactic antimicrobial agents for the prevention of surgical site infection. **(No recommendation/unresolved issue)**
Clinical practice guidelines recommend that for obese and morbidly obese patients, the prophylactic antimicrobial agent dose should be based on the patient's weight where pharmacokinetic data support it (e.g., cefazolin, vancomycin, and aminoglycosides).[22-26]
1D. No recommendation can be made regarding the safety and effectiveness of intraoperative redosing of parenteral prophylactic antimicrobial agents for the prevention of surgical site infection. **(No recommendation/unresolved issue)**[32]
Clinical practice guidelines recommend maintaining therapeutic levels of the prophylactic antimicrobial agent in serum and tissues throughout the operation based on individual agent pharmacokinetics.[12] *Redose intraoperatively at intervals 1–2 times the prophylactic antimicrobial agent half-life (measured starting at the beginning of the single preoperative dose) or when there is excessive blood loss.*[23-26,33]
1E. In clean and clean-contaminated procedures, do not administer additional prophylactic antimicrobial agent doses after the surgical incision is closed in the operating room, even in the presence of a drain. **(Category IA)**[34-72]

antibiotics prescribed in the community for upper respiratory infections, which affects gram-positive resistance (consider community-associated *Staphylococcus aureus*), and the 4-fold greater amount of antibiotics used as growth promoters in agriculture (consider quinolone resistance and extended-spectrum β-lactamase-producing Enterobacteriaceae) the volume of antimicrobials provided to surgical patients for prophylaxis is quite small and very brief (typically one dose). Conversely, this is not an argument for use of important therapeutic classes (e.g., carbapenems) for prophylaxis when equivalent results are obtained by agents (cefazolin/ cefuroxime) not used for treatment of gram-negative infections.

PHARMACOKINETIC/PHARMACODYNAMIC (PK-PD) CORRELATES OF EFFECTIVE ANTIBIOTIC PROPHYLAXIS

β-lactam antibiotics exhibit time-dependent bactericidal action, with therapeutic efficacy maximized when concentrations exceed a threshold value for prolonged portions of the dosing interval. This threshold value is typically assumed to be the minimum inhibitory concentration for targeted pathogens (MIC), although other work suggests a multiple of four times the MIC may be more effective. Because intraoperative contamination may occur at any time during the procedure, the theoretical goal of antimicrobial prophylaxis is to maintain serum and tissue drug concentrations that exceed the MIC for the duration of the operative procedure.

One difficulty in identifying the correct dose and timing of antimicrobial prophylaxis has to do with the role of extracellular fluid concentrations versus serum concentrations in determining success or failure of antimicrobial prophylaxis. There is a general consensus that extracellular fluid concentrations are most accurate as an efficacy parameter, and that studies done using tissue homogenates provide highly *inaccurate* information. More recently, information generated by Monte Carlo simulations has been proposed and in some cases accepted as surrogates for in vivo data. This seems preferable to the extrapolation of inconsistent data obtained from relatively small clinical trials. Further, these simulations have, at least in retrospect, explained failure of prophylaxis in high-risk procedures including those performed in the colon and rectum.

An additional problem is that antibiotic susceptibilities of clinically isolated anaerobes and enteric gram-negative facultatives and aerobes have substantially changed over the past two decades. Before 2010, the breakpoints for parenteral cephalosporins and Enterobacteriaceae had been those that were set several decades ago. In the case of the first-generation cephalosporins cephalothin and cefazolin, the breakpoints had been in existence for >30 years. Since first publication of these breakpoints, the science of antimicrobial PK-PD emerged, and matured to the point that it became an essential tool to assist breakpoint setting and revision, and PK-PD analyses were included in the essential data requirements by the Clinical and Laboratory Standards Institute (CLSI) Subcommittee.

WOUND CLASSIFICATION SYSTEMS FOR IDENTIFYING RISK OF INFECTION

To understand the potential risk elements for SSI, accurate risk models are required to identify modifiable variables. It is assumed that at least three categories of variables serve as predictors of SSI risk: (1) those that estimate the intrinsic degree of microbial contamination of the surgical site; (2) those that measure the duration of the operation and other less easily quantifiable elements of the procedure, a presumptive surrogate for a range of variables including surgeon skill, anatomic difficulties, and a concomitant requirement for extensive dissection; and (3) those that serve as markers for host susceptibility.

The CDC, through the National Nosocomial Infection Survey (NNIS), tested a risk index for acquiring an SSI. The risk index score, ranging from 0 to 3, is the number of risk factors present among the following: (1) an operation classified as contaminated or dirty-infected (Table 114.2); (2) a patient with an American Society of Anesthesiologists preoperative assessment score of 3, 4, or 5 (Table 114.2); and (3) an operation lasting over T hours, where T depends on the operative procedure being performed (Table 114.2). The SSI rates for patients with scores of 0, 1, 2, and 3 were 1.5, 2.9, 6.8, and 13.0, respectively.

The yes or no single-point award obviously provides no gradation particularly for the "host" resistance wherein patients with mild chronic diseases (ASA 3) are considered at the same risk as moribund patients. Similarly, there is no grading discriminating a procedure 1 minute over the T time from that several hours beyond.

Another problem is that the numbers of patients in each of these groups, however, were not provided and it is highly likely that category 3 contains very few patients, while categories 0 and 1 contain the bulk of patients undergoing operation in the USA. This means that infections in the 0 and 1 groups are outside of the current risk model, and that the model does not well apply to the bulk of the patients treated. This is very important in estimating the effects of a process change such as increasing doses and shortening dosing intervals, because the reasons for the infections are not explained.

More recent efforts to utilize CDC/NHSN (National Healthcare Safety Network) administrative data to improve the system have not demonstrated substantial improvement. Creating a more explanatory risk model will be difficult for administrative reasons. Data collection tools

Table 114.2 The NNIS risk system for surgical site infections

2A: Surgical wound classification

Class I/Clean: An uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or uninfected urinary tract is not entered. In addition, clean wounds are primarily closed and, if necessary, drained with closed drainage. Operative incisional wounds that follow nonpenetrating (blunt) trauma should be included in this category if they meet the criteria.
Class II/Clean-Contaminated: An operative wound in which the respiratory, alimentary, genital, or urinary tracts are entered under controlled conditions and without unusual contamination. Specifically, operations involving the biliary tract, appendix, vagina, and oropharynx are included in this category, provided no evidence of infection or major break in technique is encountered.
Class III/Contaminated: Open, fresh, accidental wounds. In addition, operations with major breaks in sterile technique (e.g., open cardiac massage) or gross spillage from the gastrointestinal tract, and incisions in which acute, nonpurulent inflammation is encountered are included in this category.
Class IV/Dirty-Infected: Old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera. This definition suggests that the organisms causing postoperative infection were present in the operative field before the operation.

2B: American Society of Anesthesiology Risk Score

ASA PS Category	Preoperative Health Status Comments	Examples
ASA PS 1	Normal healthy patient	
ASA PS 2	Patients with mild systemic disease	No functional limitations; has a well-controlled disease of one body system
ASA PS 3	Patients with severe systemic disease	Some functional limitation; has a controlled disease of more than one body system or one major system
ASA PS 4	Patients with severe systemic disease that is a constant threat to life	Has at least one severe disease that is poorly controlled or at end stage
ASA PS 5	Moribund patients who are not expected to survive without operation	

2C: Times for selected surgical procedures

Procedure	75% Percentile for Time (hours)
CABG – chest and donor site	5
Liver and pancreas	4
Other GI	3
Herniorraphy	2
Mastectomy	3
Abdominal hysterectomy	2

would have to be developed, tested, and then sent to every hospital in the United States. Creating software/hardware for this and retraining the surveyors doing this work would be extremely expensive and may not be worth the effort. It is extremely unlikely that mathematically superior models would be useful with current levels of deep/organ space infections, the only ones reported by NHSN, of 0.5% to 2% for clean and most clean-contaminated procedures. Given how infrequently infections occur at an individual hospital with "average" procedure volumes, hospital level risk modeling is and will continue to be enormously inaccurate.

The point is, measuring the outcome effects of changes in process is very difficult and the absence of level 1 data argues that additional complexity *not* be added to the perioperative care system. We have major concerns for increasing the frequency of redosing of intraoperative antimicrobial prophylactic agents. With infection rates <2% for clean surgery and no evidence that doing so would further lower rates, such a change seems unneeded. Further, the benefits, if any, would be limited. About half of these infections are superficial, and do not cause prolonged hospitalization, reoperation, or risk of mortality. There are a few problem areas, but there is no evidence that high continuous levels of antibiotics will substantially avert these problems. Because of the large size of the population needed to be treated to theoretically protect a small number, toxicity becomes a real risk.

Certainly prolonged procedures (>75% of time for all such procedures) are an independent risk for infection. The risk of this may be partly explained by deficient plasma levels at the end of the procedure. However, prolonged procedures reflect items such as surgeon skill, difficulty of procedure, adhesions and difficult dissection, and other nonpharmaceutical problems, and it is not known that higher antibiotic levels will do much. Three-hourly dosing is too frequent for cefazolin; 4-hour dosing seems a reasonable compromise.

A CRITIQUE OF THE ASHP GUIDELINES

We are concerned about the system used for evaluating available evidence and therefore defining the strength and believability of the recommendations. Most guideline development groups have moved to use of the GRADE system. These include IDSA, CDC, the Society for Healthcare Epidemiology of America (SHEA), the World Health Organization (WHO), and a range of other groups detailed on the GRADE working group web site. HICPAC described the rationale for requiring that the 2014 update to the CDC guideline for prevention of surgical site infections was done with GRADE methodology.

Instead, ASHP chose to use a system that is heavily biased towards expert opinion, providing the argument that historically it has been used by those organizations that, in fact, have now moved to GRADE.

Strengths of recommendation are then given as: A: Levels I–III; B: Levels IV–VI; and C: Level VII.

In fact many randomized clinical trials are not well designed or well conducted, and there are serious concerns about the value of cohort or case–control studies, wherein the rationale for providing one therapy versus another is not known but is assumed to be based upon physicians' beliefs about "optimal" treatment. Effect sizes in these types of trials are notoriously large (Health Technology Assessment Report) and therefore overstate the benefits of a particular therapy. At the other extreme, expert opinion is not data.

The benefit of GRADE evaluations is that the studies are analyzed into predefined tables, and the strength of the individual studies cited as bases for recommendations can therefore be scrutinized by the reader.

The point is that the evidence rating system used in the ASHP guidelines does not provide confidence that the recommendations are robust, nor does it provide any assurance that as a future policy statement change is unlikely.

CHOICE OF ANTI-INFECTIVES FOR PROPHYLAXIS

The anticipated pathogens from various operative sites are detailed in Table 114.3. It is most convenient to discuss antimicrobial prophylaxis in clean and clean-contaminated procedures since contaminated and dirty wounds typically require therapeutic use of antibiotics.

Colorectal surgical prophylaxis

Colorectal procedures continue to have the highest postoperative SSI rates, reported variously between 6% and 20%. The reasons for this include dense inocula and presence of adjuvants. It is likely that mechanisms not well understood, such

Table 114.3 Pathogens causing surgical site infections and antimicrobial drugs of choice for prophylaxis

Procedure	Likely pathogen(s)	Drug/dosing	For history of penicillin anaphylactoid reactions
Clean procedures for which prophylaxis is accepted	*Staphylococcus aureus* and *epidermidis*	Weight-based cefazolin ×1, repeat at 4 hours if procedure lasts >4 hours	Clindamycin 600 mg or vancomycin 1 g
Head and neck procedures entering the oropharynx; esophageal procedures	Streptococci; oropharyngeal anaerobes (e.g., peptostreptococci)	Weight-based cefazolin ×1, repeat at 4 hours if procedure lasts >4 hours	Clindamycin 600 mg or vancomycin 1 g
High-risk gastroduodenal and biliary	Enterobacteriaceae and streptococci	Weight-based cefazolin ×1, repeat at 4 hours if procedure lasts >4 hours	Ceftriaxone 1 g
Placement of all grafts, prostheses, or implants	*S. aureus*; coagulase-negative staphylococci	Weight-based cefazolin ×1, repeat at 4 hours if procedure lasts >4 hours See text for indications for vancomycin	Clindamycin 600 mg or vancomycin 1 g
Cardiac	*S. aureus*; coagulase-negative staphylococci	Weight-based cefazolin ×1, repeat at 4 hours if procedure lasts >4 hours See text for indications for vancomycin	Clindamycin 600 mg or vancomycin 1 g
Neurosurgery	*S. aureus*; coagulase-negative staphylococci	Weight-based cefazolin preoperatively	Clindamycin 600 mg or vancomycin 1 g
Breast	*S. aureus*; coagulase-negative staphylococci	Weight-based cefazolin ×1, repeat at 4 hours if procedure lasts >4 hours	Clindamycin 600 mg or vancomycin 1 g
Orthopedic Total joint replacement Closed fractures/use of nails, bone plates, other internal fixation devices Functional repair without implant/device Trauma	*S. aureus*; coagulase-negative staphylococci; gram-negative bacilli	Weight-based cefazolin ×1, repeat at 4 hours if procedure lasts >4 hours See text for indications for vancomycin	Gentamicin 5 mg/kg + clindamycin 600 mg q12h ×2
Noncardiac thoracic Thoracic (lobectomy, pneumonectomy, wedge resection, other noncardiac mediastinal procedures) Closed tube thoracostomy	*S. aureus*; coagulase-negative staphylococci; *Streptococcus pneumoniae*; gram-negative bacilli	Weight-based cefazolin ×1, repeat at 4 hours if procedure lasts >4 hours	Clindamycin 600 mg
Vascular	*S. aureus*; coagulase-negative staphylococci	Weight-based cefazolin ×1 See text for indications for vancomycin	Clindamycin 600 mg
Appendectomy for perforated appendicitis	Gram-negative bacilli; anaerobes	Weight-based cefazolin + metronidazole 500 mg q8h ×3 or ertapenem 1 g preoperatively	Ciprofloxacin 400 mg + metronidazole 500 mg q12h ×2
Colorectal	Gram-negative bacilli; anaerobes	Weight-based cefazolin ×1, repeat at 4 hours if procedure lasts >4 hours + metronidazole 500 mg preoperatively	Ciprofloxacin 400 mg + metronidazole 500 mg preoperatively Ertapenem 1 g preoperatively
Obstetric and gynecologic	Gram-negative bacilli; enterococci; group B streptococci; anaerobes	Weight-based cefazolin ×1, repeat at 4 hours if procedure lasts >4 hours	Ciprofloxacin 400 mg + metronidazole 500 mg preoperatively
Urologic (may not be beneficial if urine is sterile)	Gram-negative bacilli	Weight-based cefazolin ×1, repeat at 4 hours if procedure lasts >4 hours	Ciprofloxacin 400 mg preoperatively

as wound contamination with unique biofilm, are also involved. The controversies in prevention of SSI following elective colorectal operation include selection of parenteral antimicrobial therapy, the role of nonabsorbable antibiotics, and the use of mechanical cleansing of the bowel. In addition to appropriate administration of prophylactic antibiotics, other perioperative strategies for preventing

SSIs have included control of temperature, glucose, and inspired oxygen. For hyperoxia, however, the magnitude of benefit is relatively small and might not exceed treatment hazards.

There is an ongoing and seemingly endless debate about optimal antimicrobial prophylaxis. The important point is that regimens that are effective against three groups of organisms provide equivalent results. These organisms include *Escherichia coli*, streptococci, and anaerobes, most importantly, *Bacteroides fragilis*.

A recent Cochrane review and meta-analysis dedicated exclusively to antimicrobial prophylaxis for colorectal surgery examined 182 trials published between 1980 and 2007, including over 30 880 patients and 50 different antibiotics. The results confirmed that the use of antimicrobial prophylaxis is effective for the prevention of surgical wound infection after colorectal surgery. There was no significant difference when comparing short- and long-term duration of prophylaxis. Similarly, no significant difference was found between single dose (administered before the operation) versus multiple doses of antibiotics. On the other hand, combined oral and intravenous antibiotic prophylaxis was significantly superior in reducing SSIs to intravenous alone. A more recent Veterans Administration (VA) study has confirmed these findings.

In a recent retrospective review of 5700 colectomies performed in the VA system, ampicillin/sulbactam, cefotetan, and cefoxitin were inferior to either cefazolin–metronidazole or ertapenem. This is well explained by the widely recognized resistance of *E. coli* to ampicillin/sulbactam, the resistance of *B. fragilis* to cefotetan, and the short half-life of cefoxitin.

The most striking area of concern in the ASHP guideline is the recommendation for the use of cefotetan for colorectal operations. This agent has been shown inferior to ertapenem in a very well done and large double-blind controlled trial. The explanation for this is not difficult to see. Recent surveys of susceptibility of *B. fragilis* show substantial decreases in cefotetan activity. It is also important to recognize toxicities of this agent. Cefotetan is an inhibitor of vitamin D carboxylase, and after relatively brief therapeutic use, abnormalities in clotting are identified.

There is increasing resistance of community-acquired strains of gram-negative organisms to selected antibiotics in many locales. These include the widespread prevalence of ampicillin/sulbactam-resistant *E. coli* worldwide.

The role of mechanical bowel preparation has also undergone scrutiny. There have been several randomized trials, and a plethora of meta-analyses. One published by the Cochrane Collaboration in 2011, in keeping with other such studies, found that there is no statistically significant evidence that patients benefit from mechanical bowel preparation, nor the use of rectal enemas. The few studies focused in rectal surgery suggested that mechanical bowel preparation could be used selectively, even though no significant effect was found. Conversely, many surgeons prefer to have an empty colon when operating. There is a continuing concern about spillage, a known risk factor for wound infection (indeed an element in escalating CDC wound class to "contaminated") and difficulties in sewing or using mechanical staplers when solids are present.

The use of oral antibiotics was found to be associated with significantly lower infection rates, a finding supported by two other recent observational studies.

In North America, it is common to use a regimen of erythromycin base and neomycin given at 1 p.m., 2 p.m., and 11 p.m. (1 g of each drug per dose) the day before a procedure. Times of administration are shifted according to the anticipated time of starting the procedure, with the first dose given 19 hours before operation. Metronidazole can be substituted for erythromycin, which also fulfills the role of parenteral prophylaxis.

Prophylaxis is also recommended for appendectomy. Although the intrinsic risk of infection is low for uncomplicated (non-perforated) appendicitis, the preoperative status of the patient's appendix may not be known. Even in settings where CT or ultrasound imaging is routinely used, we recommend perioperative prophylaxis with a regimen with facultative, anaerobic, and streptococcal coverage. Cefoxitin, cefazolin plus metronidazole, or ceftriaxone plus metronidazole are all recommended agents in North America. For uncomplicated appendicitis, coverage should not be extended to the postoperative period.

Biliary tract procedures

The recommendations for antibiotic prophylaxis for procedures of the biliary tract depend on the presence of specific risk factors. Prophylaxis for elective laparoscopic cholecystectomy in low-risk patients is not necessary. Risk factors associated with an increased rate of postoperative infection include age over 60 years, disease of the common duct, diagnosis of cholecystitis, presence of

jaundice, previous history of biliary tract surgery, immunosuppression, and diabetes. Only one factor is necessary to establish the patient as high risk. Antibiotic prophylaxis is therefore recommended for all of these cases and for all open cholecystectomies. Cefazolin is an acceptable agent as antibiotics with theoretically superior antimicrobial activity have not been shown to produce a lower postoperative infection rate.

Single-dose prophylaxis is recommended for patients with common duct disease without inflammation or established infection undergoing either operative or endoscopic intervention.

Neurosurgical procedures

Studies evaluating the efficacy of antibiotic prophylaxis in neurosurgical procedures have shown variable results. Nonetheless, prophylaxis is currently recommended for craniotomy, spinal, and shunting procedures. Coverage targets *S. aureus* and coagulase-negative staphylococci. Cefazolin remains the antibiotic of choice despite the relatively high rate of resistance found in these organisms. This is based on the lack of data showing superiority of any other agent.

It is not known if these patients should be under screening for methicillin-resistant *S. aureus* (MRSA), but the consequences of these infections can be severe and we do screen locally.

Head and neck procedures

No antibiotic prophylaxis is deemed necessary for clean procedures such as thyroidectomy and lymph node excisions. For clean-contaminated procedures, which are defined as the ones necessitating entry into the oropharynx or esophagus, coverage of aerobic bacteria is indicated. In these cases, prophylaxis has been shown to reduce the incidence of severe wound infection by approximately 50%. Cefazolin or cefuroxime plus metronidazole is commonly used. Prophylaxis is not routinely indicated for dentoalveolar procedures, although it is warranted in immunocompromised patients undergoing these procedures or in patients with prosthetic cardiac valves, congenital heart disease, or a history of endocarditis.

General thoracic procedures

Prophylaxis is routinely used for nearly all thoracic procedures. This is particularly true if there is a significant likelihood of encountering high numbers of microorganisms during the procedure. Pulmonary resection in cases of partial or complete obstruction of an airway is a procedure in which prophylaxis is clearly warranted. Likewise, prophylaxis is strongly recommended for procedures entailing entry into the esophagus. Although the range of microorganisms encountered in thoracic procedures is extensive, most are sensitive to cefazolin and ampicillin–sulbactam and either one can be used.

Obstetric and gynecologic procedures

Prophylaxis is indicated for cesarean section and abdominal and vaginal hysterectomy. Numerous clinical trials have demonstrated a reduction in risk of wound infection or endometritis by as much as 60% in patients undergoing cesarean section. Although historically in cesarean sections the antibiotic was administered immediately after the cord was clamped to avoid exposing the newborn to antibiotics, newer data support administering the antibiotic before surgical incision. This practice in now endorsed by both the American Congress of Obstetricians and Gynecologists (ACOG) and the American Academy of Pediatrics (AAP). Despite the theoretic need to cover gram-negative and anaerobic organisms, studies have not demonstrated a superior result with broad-spectrum antibiotics compared with cefazolin. Therefore, it is the recommended agent.

Urologic procedures

The range of potential urologic procedures and intrinsic risk of infection varies widely. In general, it is recommended to achieve preoperative sterilization of the urine if clinically feasible. For procedures entailing the creation of urinary conduits, recommendations are similar to those for procedures pertaining to the specific segment of the intestinal tract being used for the conduit.

Three randomized controlled trials of patients undergoing transrectal prostate needle biopsy have found significant decreases in infections in patients who received preoperative antimicrobial prophylaxis. Several meta-analyses in patients undergoing transurethral resection of the prostate (TURP) have shown that antibiotic prophylaxis can reduce the risk of developing both bacteriuria and septicemia. Furthermore, reductions in bacteriuria have been found in several studies investigating cystoscopies and urodynamic studies. In terms of antibiotic choice, the efficacy of fluoroquinolones for antimicrobial prophylaxis in urologic surgical procedures has been well

documented in the past. However, there is growing concern regarding the increasing resistance rates of enteric bacteria. Therefore, local resistance patterns should be taken into consideration when considering a fluoroquinolone as the prophylactic agent. If the local resistance rate is high, cefazolin should be used.

SCREENING FOR *STAPHYLOCOCCUS AUREUS*

The emergence of MRSA in postoperative surgical infections has become an increasing problem for in-hospital patients and those discharged home. Although the cause of an increasing presence of MRSA in the community is hotly debated, it is futile to ignore this pathogen as a cause of SSIs. Several studies have demonstrated increased 90-day mortality, greater length of stay, and increased costs associated with MRSA postoperative infection compared to methicillin-sensitive *S. aureus* (MSSA). Significantly, MRSA has been demonstrated to be the leading pathogen in cardiac surgery and an independent risk factor for increased mortality in these patients.

Although MRSA has long been considered a healthcare-associated infection, increasingly MRSA is brought into the hospital by patients who are carriers of the pathogen. The CDC currently estimates the prevalence of MRSA colonization in the general population at about 2%. Therefore, specific recommendations can be made to limit the spread of MRSA and the occurrence of SSIs due to MRSA. Patients who are known or suspected to be colonized with MRSA (which may include institutionalized patients from nursing homes or long-term acute care facilities) should have perioperative anti-infective prophylaxis targeted to the usual pathogens and MRSA.

Vancomycin remains the drug of choice despite the advent of other agents effective against this organism. In addition to institutionalized patients and known carriers, cardiac and orthopedic surgery patients should also be screened for colonization with MRSA. A meta-analysis of studies comparing mupirocin use versus placebo or no therapy in surgical patients with *S. aureus* nasal carriage included a total of 1372 patients, most of them undergoing cardiac and orthopedic surgery. An overall decrease in nosocomial *S. aureus* infections from 6.7% to 3.6% was demonstrated, resulting in a relative risk reduction of 55%. Nasal swabs are usually sufficient to determine colonization and initiate therapy with intranasal mupirocin for these patients while modifying operative anti-infective prophylaxis. Meanwhile, MRSA prophylaxis is not necessary for every surgical patient, but those patients meeting risk factors for increased incidence (e.g., institutionalized) and for increased morbidity from MRSA infection (in particular cardiac and orthopedic surgery patients) should be tested for nasal carriage. Patients found to have nares colonization should receive mupirocin therapy and their antimicrobial prophylaxis should be adapted to cover this organism.

Approximately 20% to 30% of SSIs are caused by *S. aureus*, and over half of these arise from the endogenous flora. One of the most contentious issues in the area of surgical antimicrobial prophylaxis is whether or not patients should be screened for *S. aureus* colonization and, for screen-positive patients, whether specific interventions should be undertaken. The discussion about appropriate strategies to deal with this problem are driven by how complex and expensive any proposed strategy is, how many patients must be surveyed and/or treated to prevent one infection, and what the cost of the infection prevented would be.

Results of a recent meta-analysis suggested that topical mupirocin applied intranasally would reduce the rate of SSIs due to *S. aureus* by 45% in the subgroup of patients who are carriers. It is also known that the skin is an important extranasal reservoir not only for *S. aureus* but also for other organisms implicated in postoperative infections.

Although the reduction in *S. aureus* SSIs in the study by Bode *et al*. was impressive, the relative contributions of the intervention components – that is, decolonization in the nares and the use of chlorhexidine soap – are unclear. A total of 250 patients would need to be screened and 23 carriers would need to be treated to prevent one *S. aureus* infection. The value of this well-conducted study is that it suggests a prophylactic approach for carriers of *S. aureus* who are candidates for surgical procedures associated with a high risk of deleterious outcomes should *S. aureus* infection develop at the surgical site. In this category, we would include all cases of open-heart surgery, any procedure in which a foreign body is placed (e.g., orthopedic and neurosurgical implant procedures), and any surgical procedure in patients whose immune systems are severely impaired as especially high-risk operations.

The use of intranasal mupirocin and chlorhexidine baths for carriers of *S. aureus* who have been identified preoperatively by means of a

real-time polymerase chain reaction assay could be reserved primarily for patients who are undergoing cardiac surgery, all patients receiving an implant, and all immunosuppressed surgical candidates.

An important dilemma is use of vancomycin as prophylaxis for the indications described above. There is observational evidence that the addition of vancomycin to cefazolin reduces MRSA infection. We recently reviewed this information, and concluded that there were important problems in methodology and interpretation in those studies, and that the benefits were unproven. This represents a critical clinical research question, in part because alternative agents are available, and in part because of the unexplored toxicities of vancomycin in prophylactic use.

Prophylaxis for patients undergoing cardiac surgery or receiving an implant, and all immunosuppressed patients

Prophylaxis against *S. aureus* and *Staphylococcus epidermidis* is indicated for patients undergoing the above listed procedures, and will be considered as one group. Although the risk of infection is low, the morbidity of infection with these procedures is great. Antimicrobial prophylaxis in these procedures has been shown in several studies to reduce the risk of postoperative SSIs by up to 80% and is now considered mandatory. These include ankle fusion, revision of a prosthetic joint, reduction of hip fractures, reduction of high-energy closed fractures, reduction of open fractures, and any procedures where foreign material is implanted.

Cephalosporins have been the most extensively studied agents for prophylaxis in these procedures. Although both first-generation and second-generation cephalosporins have been shown to be effective, there is no conclusive evidence that one class is superior to the other.

We recommend that vancomycin should be used in patients that are known to be colonized with MRSA. In institutions that use vancomycin in this manner, surveillance of susceptibility of *S. aureus* isolated from SSIs to mupirocin is recommended.

Prophylaxis for noncardiac vascular procedures

Available data support the recommendation for anti-infective coverage for vascular procedures using synthetic material, those requiring groin incisions, and those affecting the aorta. Cefazolin is the recommended agent, because most infections are caused by *S. aureus* and *S. epidermidis*. Prophylaxis is not recommended for patients undergoing brachiocephalic procedures without implantation of foreign material.

ANTI-INFECTIVE PROPHYLAXIS FOR CLEAN PROCEDURES

The biggest controversy regarding antibiotic prophylaxis centers on prophylaxis for clean surgery. Prophylaxis has prevented postoperative wound infection after clean surgery in a majority of clinical trials with sufficient power to identify a 50% reduction in risk. The low control rates of infection mean that very large studies must be done to see a significant effect; studies of greater than 1000 procedures are needed to reliably detect such reductions.

The major study on this subject was a randomized, double-blind trial of 1218 patients undergoing herniorrhaphy or surgery involving the breast, including excision of a breast mass, mastectomy, reduction mammoplasty, and axillary-node dissection. The prophylactic regimen was a single dose of cefonicid administered approximately half an hour before surgery. The patients were followed up for 4 to 6 weeks after surgery. The patients who received prophylaxis had 48% fewer probable or definite infections than those who did not. For patients undergoing a procedure involving the breast, infection occurred in 6.6% of the cefonicid recipients and 12.2% of the placebo recipients; for those undergoing herniorrhaphy, infection occurred in 2.3% of the cefonicid recipients and 4.2% of the placebo recipients. There were comparable reductions in the numbers of definite wound infections, wounds that drained pus, and *S. aureus* wounds as well as the need for postoperative antibiotic therapy, nonroutine visits to a physician for problems involving wound healing, incision and drainage procedures, and readmission because of problems with wound healing.

An observational study was then done on the effects of antibiotic prophylaxis on definite wound infections in 3202 patients undergoing herniorrhaphy or selected breast surgery procedures identified preoperatively and monitored for 4 or more weeks. Thirty-four percent of patients received prophylaxis at the discretion of the surgeon; 86 definite wound infections (2.7%) were

identified. Prophylaxis recipients were identified preoperatively as being at higher risk for infection, with a higher proportion of mastectomies, longer procedures, and other factors. Patients who received prophylaxis experienced 41% fewer definite wound infections and 65% fewer definite wound infections requiring parenteral antibiotic therapy after adjustment for duration of surgery and type of procedure. Additional adjustment for age, body mass index, the presence of drains, diabetes, and exposure to corticosteroids did not change the magnitude of this effect.

The argument then is not whether such therapy lowers infection rates but rather whether it is cost-effective. Additionally, the control infection rate is so low that physicians will not be aware of a decreased infection rate unless very careful surveillance is performed, and then only after pooling together information about patients from several practices. Comparing one effective regimen with another, as has been done with colorectal surgical prophylaxis, is simply not feasible.

To justify the use of prophylaxis for clean procedures at a single institution, an accurate assessment of infection rates must be available. This requires a considered effort at post-discharge follow-up. When these data are available, the risk/benefit ratio can be more accurately assessed. Without reliable information on infection rates by procedure, known risk factors described above may serve as guides. Extremes of age, poor nutritional status, diabetes, and obesity are recognized as significant additional risk factors.

The use of systemic prophylaxis for hernia repair entailing the insertion of mesh is considered desirable because the morbidity of infected mesh in the groin is substantial. However, no prospective trials demonstrate the effectiveness or necessity of this practice. Modified radical mastectomy and axillary-node dissection also warrant prophylaxis, because wounds near or in the axilla have an intrinsic risk of infection. If prophylaxis is desired or indicated for any of these procedures, cefazolin is the agent of choice.

Laparoscopic and thoracoscopic procedures

Antimicrobial prophylaxis has not been shown to be beneficial in patients undergoing laparoscopic cholecystectomies with no high risks for infection and should not be provided. For other laparoscopic procedures and for thoracoscopies the data are scant. Therefore, pending the availability of new studies, recommendations for the same procedure performed using the "open technique" should be followed.

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115. Immunizations

Elaine C. Jong

Long-lasting immunity against many serious infectious diseases can be elicited through active immunization, the administration of specific antigens (killed or attenuated microorganisms; purified polysaccharides, proteins, or other components; or recombinant antigens produced by genetic engineering) that stimulate the recipient host's production of protective antibodies. Vaccine doses may be given orally, administered as mucosal vaccines, or given by injection using intradermal, subcutaneous, or intramuscular routes. Passive immunization is the process by which protective immunity is obtained through transfer of preformed antibodies from an immune host to a nonimmune recipient, either as immunoglobulin or antibody-specific immunoglobulin.

Protective efficacy resulting from active immunization with a vaccine depends on several factors: the age of the host, with decreased efficacy of certain vaccines observed in the very young and very old; the immune status of the host, with decreased efficacy observed in persons with compromised immune status because of disease or therapy; and the characteristics of the vaccine product itself.

In active immunization, protective levels of specific antibodies usually develop within 2 to 4 weeks upon completion of the primary immunization regimen. The antibody response may be recalled and boosted when the immune system is challenged by additional "booster" doses of the vaccine antigen(s) or by exposure to the naturally occurring pathogen. Passive immunization can confer rapid protection, but serum levels of protective antibodies in recipients are highest immediately after receipt, decreasing with the passage of time and there is no immune recall on challenge.

Several different vaccines may be administered concomitantly at separate sites without decreased efficacy, although the timing and sequence of vaccines have to be taken into account. For example, when immunoglobulin is given for passive immunization against hepatitis A, antibodies against several common infections may be present in sufficient amounts to interfere with the response to the corresponding vaccines. Immunoglobulin should not be given for 3 months before or 3 weeks after measles, mumps, and rubella vaccine and not for 2 months after varicella vaccine. However, vaccines against tetanus, diphtheria, yellow fever, typhoid fever, hepatitis B, rabies, and meningococcal meningitis can be given on the same day as immunoglobulin. If immunoglobulin is given on the same day as hepatitis A vaccine, the vaccine is still efficacious, although the resulting peak antibody titer is lower than when the vaccine is given alone.

The federal Food and Drug Administration (FDA) is responsible for licensure of all pharmaceuticals including vaccine products for use in the United States. The Advisory Committee on Immunization Practices (ACIP) at the Centers for Disease Control and Prevention (CDC) issues recommendations for routine use of vaccines in children and adolescents, harmonizing its recommendations to the greatest extent possible with those issued by the American Academy of Pediatrics (AAP), the American Academy of Family Physicians (AAFP), and the American College of Obstetrics and Gynecology (ACOG). The ACIP recommendations for routine use of vaccines in adults are harmonized with those of the AAFP, ACOG, and the American College of Physicians (ACP).

Federal law requires that potential vaccine recipients be informed of the potential benefits and possible adverse side effects of each vaccine. Vaccine Information Statements (VISs) prepared by the CDC are used for this purpose: these forms can be downloaded and copies printed for use in patient education from the CDC web site (http://www.cdc.gov/vaccines/hcp/vis/index.html). The VISs are available in English and 40 additional languages.

Tolerance to minor adverse effects associated with each vaccine and the potential for more

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serious vaccine-associated symptoms must be taken into account in the person who is a candidate for multiple vaccine doses on the same day. If clinically significant adverse events are associated with any vaccination, such occurrences should be reported to the Vaccine Adverse Event Reporting System (VAERS) online (http://www.vaers.hhs.gov) or by telephone (800-822-7967).

CHILDHOOD AND ADOLESCENT IMMUNIZATIONS

The routine immunizations recommended during childhood and adolescence cover communicable diseases of public health importance that cause significant morbidity and mortality in susceptible populations. The ACIP immunization schedules are updated and published on an annual basis, and interim updated recommendations are published in the *Morbidity and Mortality Weekly Report* (*MMWR*) as needed. Figure 115.1 shows the immunization schedule for persons aged 0 through 18 years according to recommendations from the CDC ACIP (http://www.cdc.gov/vaccines/acip/index.html).

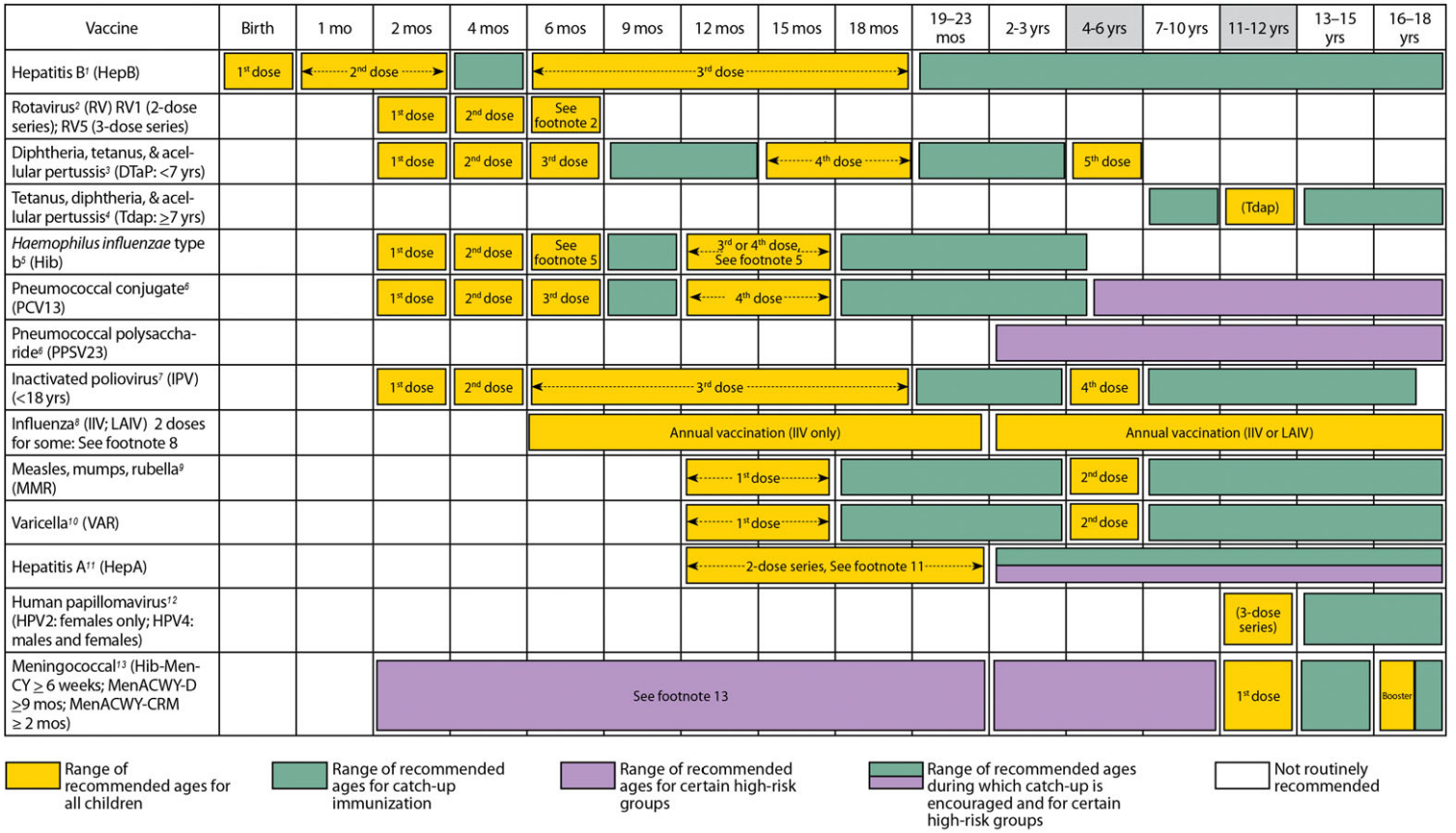
In the following summary, minimal ages for administration of the first dose of the various vaccines are given, and the detailed schedule for subsequent doses may be found in Figure 115.1. Figure 115.2 provides the CDC ACIP schedule for catch-up immunizations. The minimal interval between doses shown in this figure can be used to reset the schedule for a given vaccine series in persons aged 4 months through 18 years who start late or who are more than 1 month behind the recommended schedule. If more time elapses than the recommended interval between scheduled doses in a vaccine series, the series does not need to be restarted, but the next dose(s) should be administered according to the recommended intervals until the series is complete.

At birth, hepatitis B (HepB: Recombivax HB, Merck; Engerix-B, GlaxoSmithKline) vaccination is initiated, and at 6 weeks of age, rotavirus (RV-1: Rotarix, GlaxoSmithKline; RV-5: RotaTeq, Merck), diphtheria and tetanus toxoids and acellular pertussis (DTaP: Daptacel, sanofi pasteur; Infanrix, GlaxoSmithKline), *Haemophilus influenzae* type b conjugate (Hib: HibTITER, Wyeth; PedvaxHIB, Merck; ActHIB, sanofi pasteur), pneumococcal conjugate (PCV13: Prevnar 13, sanofi pasteur) and inactivated poliovirus (IPV: Ipol, sanofi pasteur) vaccines are administered. At 6 months of age, annual vaccination with inactivated influenza vaccine (IIV: Fluarix, GlaxoSmithKline; Fluvirin, Chiron; Fluzone, sanofi pasteur) commences, and at 12 months of age, the first dose of measles, mumps, and rubella (MMR: M-M-R II, Merck), varicella (VAR: Varivax, Merck) and hepatitis A (HepA: Havrix, GlaxoSmithKline; Vaqta, Merck) vaccines are recommended. Varicella vaccine may be administered at the same time as the MMR vaccine. Both VAR and MMR are live-virus vaccines administered by injection. If the two vaccines are not given simultaneously at different sites, the vaccine doses should be separated by 28 days if possible to reduce or eliminate possible interference of the vaccine given first with the vaccine given second. A second dose of VAR is recommended for children, between 4 and 6 years old, on entry into school to boost waning immunity from the first dose received in infancy. At 2 years of age and older, annual vaccination against influenza may be done with either the inactivated influenza vaccine (IIV) given by injection, or the live attenuated influenza vaccine (LAIV: FluMist, MedImmune) administered intranasally.

The ACIP recommends vaccination of adolescents at 11 to 12 years of age with quadrivalent meningococcal conjugate vaccine (MCV4) with a booster at 16 years old. Until recently, two meningococcal conjugate vaccines are licensed: meningococcal (Groups A, C, Y-W-135) polysaccharide diphtheria toxoid conjugate vaccine (MCV4-D: Menactra, sanofi pasteur); and meningococcal (Groups A, C, Y, W-135) polysaccharide CRM197 conjugate vaccine (MCV4-CRM: Menveo, Novartis). If the first dose of MCV4-D or MCV4-CRM is received between 13 and 15 years old, a booster should be given at 18 years of age. Recently, a serogroup B vaccine has become available (see p. 940 for more details).

The immunization status of tetanus, diphtheria, and acellular pertussis vaccine should be reviewed among 11- to 12-year-olds as well. The ACIP recommends a single dose of the tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine for persons aged 11 through 18 years who completed the recommended childhood DTP/DTaP vaccinations series. There are two Tdap vaccines: one is licensed for use in persons aged 10 through 64 years (Boostrix, GlaxoSmithKline) and the other is licensed for use in persons aged 11 through 64 years (Adacel, sanofi pasteur), and both are licensed for use at an interval of at least 5 years between the Td and Tdap dose. However, due to the poor control of pertussis observed in the

These recommendations must be read with the footnotes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars in Figure 1. To determine minimum intervals between doses, see the catch-up schedule (Figure 2). School entry and adolescent vaccine age groups are in bold.



This schedule includes recommendations in effect as of January 1, 2014. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines. Vaccination providers should consult the relevant Advisory Committee on Immunization Practices (ACIP) statement for detailed recommendations, available online at http://www.cdc.gov/vaccines/hcp/acip-recs/index.html. Clinically significant adverse events that follow vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS) online (http://www.vaers.hhs.gov) or by telephone (800-822-7967).Suspected cases of vaccine-preventable diseases should be reported to the state or local health department. Additional information, including precautions and contraindications for vaccination, is available from CDC online (http://www.cdc.gov/vaccines/recs/vac-admin/contraindications.htm) or by telephone (800-CDC-INFO [800-232-4636]).

This schedule is approved by the Advisory Committee on Immunization Practices (http://www.cdc.gov/vaccines/acip), the American Academy of Pediatrics (http://www.aap.org), the American Academy of Family Physicians (http://www.aafp.org), and the American College of Obstetricians and Gynecologists (http://www.acog.org).

NOTE: The above recommendations must be read along with the footnotes of this schedule.

Figure 115.1 Recommended immunization schedule for persons 0 through 18 years – United States – 2014. Source: http://cdc.gov/vaccines/schedules. Accessed December 7, 2014.

The figure below provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Use the section appropriate for the child's age. Always use this table in conjunction with Figure 1 and the footnotes that follow.

Persons aged 4 months through 6 years					
Vaccine	Minimum Age for Dose 1	Minimum Interval Between Doses			
		Dose 1 to dose 2	Dose 2 to dose 3	Dose 3 to dose 4	Dose 4 to dose 5
Hepatitis B[1]	Birth	4 weeks	8 weeks and at least 16 weeks after first dose; minimum age for the final dose is 24 weeks		
Rotavirus[2]	6 weeks	4 weeks	4 weeks[2]		
Diphtheria, tetanus, & acellular pertussis[3]	6 weeks	4 weeks	4 weeks	6 months	6 months[3]
Haemophilus influenzae type b[5]	6 weeks	4 weeks if first dose administered at younger than age 12 months 8 weeks (as final dose) if first dose administered at age 12 through 14 months No further doses needed if first dose administered at age 15 months or older	4 weeks[5] if current age is younger than 12 months and first dose administered at < 7 months old 8 weeks and age 12 months through 59 months (as final dose)[5] if current age is younger than 12 months and first dose administered between 7 through 11 months (regardless of Hib vaccine [PRP-T or PRP-OMP] used for first dose); OR if current age is 12 through 59 months and first dose administered at younger than age 12 months; OR first 2 doses were PRP-OMP and administered at younger than 12 months. No further doses needed if previous dose administered at age 15 months or older	8 weeks (as final dose) This dose only necessary for children aged 12 through 59 months who received 3 (PRP-T) doses before age 12 months and started the primary series before age 7 months	
Pneumococcal[6]	6 weeks	4 weeks if first dose administered at younger than age 12 months 8 weeks (as final dose for healthy children) if first dose administered at age 12 months or older No further doses needed for healthy children if first dose administered at age 24 months or older	4 weeks if current age is younger than 12 months 8 weeks (as final dose for healthy children) if current age is 12 months or older No further doses needed for healthy children if previous dose administered at age 24 months or older	8 weeks (as final dose) This dose only necessary for children aged 12 through 59 months who received 3 doses before age 12 months or for children at high risk who received 3 doses at any age	
Inactivated poliovirus[7]	6 weeks	4 weeks[7]	4 weeks[7]	6 months[7] minimum age 4 years for final dose	
Meningococcal[13]	6 weeks	8 weeks[13]	See footnote 13	See footnote 13	
Measles, mumps, rubella[9]	12 months	4 weeks			
Varicella[10]	12 months	3 months			
Hepatitis A[11]	12 months	6 months			
Persons aged 7 through 18 years					
Tetanus, diphtheria; tetanus, diphtheria, & acellular pertussis[4]	7 years[4]	4 weeks	4 weeks if first dose of DTaP/DT administered at younger than age 12 months 6 months if first dose of DTaP/DT administered at age 12 months or older and then no further doses needed for catch-up	6 months if first dose of DTaP/DT administered at younger than age 12 months	
Human papillomavirus[12]	9 years	Routine dosing intervals are recommended[12]			
Hepatitis A[11]	12 months	6 months			
Hepatitis B[1]	Birth	4 weeks	8 weeks (and at least 16 weeks after first dose)		
Inactivated poliovirus[7]	6 weeks	4 weeks	4 weeks[7]	6 months[7]	
Meningococcal[13]	6 weeks	8 weeks[13]			
Measles, mumps, rubella[9]	12 months	4 weeks			
Varicella[10]	12 months	3 months if person is younger than age 13 years 4 weeks if person is aged 13 years or older			

NOTE: The above recommendations must be read along with the footnotes of this schedule.

Figure 115.2 Catch-up immunization schedule for persons aged 4 months through 18 years – United States – 2014. Source: http://cdc.gov/vaccine/schedules. Accessed December 7, 2014.

Footnotes — Recommended immunization schedule for persons aged 0 through 18 years—United States, 2014

For further guidance on the use of the vaccines mentioned below, see: http://www.cdc.gov/vaccines/hcp/acip-recs/index.html.
For vaccine recommendations for persons 19 years of age and older, see the adult immunization schedule.

Additional information

- For contraindications and precautions to use of a vaccine and for additional information regarding that vaccine, vaccination providers should consult the relevant ACIP statement available online at http://www.cdc.gov/vaccines/hcp/acip-recs/index.html.
- For purposes of calculating intervals between doses, 4 weeks = 28 days. Intervals of 4 months or greater are determined by calendar months.
- Vaccine doses administered 4 days or less before the minimum interval are considered valid. Doses of any vaccine administered ≥5 days earlier than the minimum interval or minimum age should not be counted as valid doses and should be repeated as age-appropriate. The repeat dose should be spaced after the invalid dose by the recommended minimum interval. For further details, see *MMWR, General Recommendations on Immunization and Reports* / Vol. 60 / No. 2; Table 1. *Recommended and minimum ages and intervals between vaccine doses* available online at http://www.cdc.gov/mmwr/pdf/rr/rr6002.pdf.
- Information on travel vaccine requirements and recommendations is available at http://wwwnc.cdc.gov/travel/destinations/list.
- For vaccination of persons with primary and secondary immunodeficiencies, see Table 13, "*Vaccination of persons with primary and secondary immunodeficiencies*," in General Recommendations on Immunization (ACIP), available at http://www.cdc.gov/mmwr/pdf/rr/rr6002.pdf.; and American Academy of Pediatrics. Immunization in Special Clinical Circumstances, in Pickering LK, Baker CJ, Kimberlin DW, Long SS eds. *Red Book: 2012 report of the Committee on Infectious Diseases. 29th ed.* Elk Grove Village, IL: American Academy of Pediatrics.

1. **Hepatitis B (HepB) vaccine. (Minimum age: birth)**
   Routine vaccination:
   At birth:
   - Administer monovalent HepB vaccine to all newborns before hospital discharge.
   - For infants born to hepatitis B surface antigen (HBsAg)-positive mothers, administer HepB vaccine and 0.5 mL of hepatitis B immune globulin (HBIG) within 12 hours of birth. These infants should be tested for HBsAg and antibody to HBsAg (anti-HBs) 1 to 2 months after completion of the HepB series, at age 9 through 18 months (preferably at the next well-child visit).
   - If mother's HBsAg status is unknown, within 12 hours of birth administer HepB vaccine regardless of birth weight. For infants weighing less than 2,000 grams, administer HBIG in addition to HepB vaccine within 12 hours of birth. Determine mother's HBsAg status as soon as possible and, if mother is HBsAg-positive, also administer HBIG for infants weighing 2,000 grams or more as soon as possible, but no later than age 7 days.

   Doses following the birth dose:
   - The second dose should be administered at age 1 or 2 months. Monovalent HepB vaccine should be used for doses administered before age 6 weeks.
   - Infants who did not receive a birth dose should receive 3 doses of a HepB-containing vaccine on a schedule of 0, 1 to 2 months, and 6 months starting as soon as feasible. See Figure 2.
   - Administer the second dose 1 to 2 months after the first dose (minimum interval of 4 weeks), administer the third dose at least 8 weeks after the second dose AND at least 16 weeks after the **first** dose. The final (third or fourth) dose in the HepB vaccine series should be administered no earlier than age 24 weeks.
   - Administration of a total of 4 doses of HepB vaccine is permitted when a combination vaccine containing HepB is administered after the birth dose.

   Catch-up vaccination:
   - Unvaccinated persons should complete a 3-dose series.
   - A 2-dose series (doses separated by at least 4 months) of adult formulation Recombivax HB is licensed for use in children aged 11 through 15 years.
   - For other catch-up guidance, see Figure 2.
2. **Rotavirus (RV) vaccines. (Minimum age: 6 weeks for both RV1 [Rotarix] and RV5 [RotaTeq])**
   Routine vaccination:
   Administer a series of RV vaccine to all infants as follows:
   1. If Rotarix is used, administer a 2-dose series at 2 and 4 months of age.
   2. If RotaTeq is used, administer a 3-dose series at ages 2, 4, and 6 months.
   3. If any dose in the series was RotaTeq or vaccine product is unknown for any dose in the series, a total of 3 doses of RV vaccine should be administered.

   Catch-up vaccination:
   - The maximum age for the first dose in the series is 14 weeks, 6 days; vaccination should not be initiated for infants aged 15 weeks, 0 days or older.
   - The maximum age for the final dose in the series is 8 months, 0 days.
   - For other catch-up guidance, see Figure 2.
3. **Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine. (Minimum age: 6 weeks. Exception: DTaP-IPV [Kinrix]: 4 years)**
   Routine vaccination:
   - Administer a 5-dose series of DTaP vaccine at ages 2, 4, 6, 15 through 18 months, and 4 through 6 years. The fourth dose may be administered as early as age 12 months, provided at least 6 months have elapsed since the third dose.

   Catch-up vaccination:
   - The fifth dose of DTaP vaccine is not necessary if the fourth dose was administered at age 4 years or older.
   - For other catch-up guidance, see Figure 2.
4. **Tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccine. (Minimum age: 10 years for Boostrix, 11 years for Adacel)**
   Routine vaccination:
   - Administer 1 dose of Tdap vaccine to all adolescents aged 11 through 12 years.
   - Tdap may be administered regardless of the interval since the last tetanus and diphtheria toxoid-containing vaccine.
   - Administer 1 dose of Tdap vaccine to pregnant adolescents during each pregnancy (preferred during 27 through 36 weeks gestation) regardless of time since prior Td or Tdap vaccination.

   Catch-up vaccination:
   - Persons aged 7 years and older who are not fully immunized with DTaP vaccine should receive Tdap vaccine as 1 (preferably the first) dose in the catch-up series; if additional doses are needed, use Td vaccine. For children 7 through 10 years who receive a dose of Tdap as part of the catch-up series, an adolescent Tdap vaccine dose at age 11 through 12 years should NOT be administered. Td should be administered instead 10 years after the Tdap dose.
   - Persons aged 11 through 18 years who have not received Tdap vaccine should receive a dose followed by tetanus and diphtheria toxoids (Td) booster doses every 10 years thereafter.
   - Inadvertent doses of DTaP vaccine:
     - If administered inadvertently to a child aged 7 through 10 years may count as part of the catch-up series. This dose may count as the adolescent Tdap dose, or the child can later receive a Tdap booster dose at age 11 through 12 years.
     - If administered inadvertently to an adolescent aged 11 through 18 years, the dose should be counted as the adolescent Tdap booster.
   - For other catch-up guidance, see Figure 2.
5. ***Haemophilus influenzae* type b (Hib) conjugate vaccine. (Minimum age: 6 weeks for PRP-T [ACTHIB, DTaP-IPV/Hib (Pentacel) and Hib-MenCY (MenHibrix)], PRP-OMP [PedvaxHIB or COMVAX], 12 months for PRP-T [Hiberix])**
   Routine vaccination:
   - Administer a 2- or 3-dose Hib vaccine primary series and a booster dose (dose 3 or 4 depending on vaccine used in primary series) at age 12 through 15 months to complete a full Hib vaccine series.
   - The primary series with ActHIB, MenHibrix, or Pentacel consists of 3 doses and should be administered at 2, 4, and 6 months of age. The primary series with PedvaxHib or COMVAX consists of 2 doses and should be administered at 2 and 4 months of age; a dose at age 6 months is not indicated.
   - One booster dose (dose 3 or 4 depending on vaccine used in primary series) of any Hib vaccine should be administered at age 12 through 15 months. An exception is Hiberix vaccine. Hiberix should only be used for the booster (final) dose in children aged 12 months through 4 years who have received at least 1 prior dose of Hib-containing vaccine.

Figure 115.2 (*continued*)

5. ***Haemophilus influenzae*** **type b (Hib) conjugate vaccine (cont'd)**
   - For recommendations on the use of MenHibrix in patients at increased risk for meningococcal disease, please refer to the meningococcal vaccine footnotes and also to *MMWR* March 22, 2013; 62(RR02);1-22, available at http://www.cdc.gov/mmwr/pdf/rr/rr6202.pdf.

   Catch-up vaccination:
   - If dose 1 was administered at ages 12 through 14 months, administer a second (final) dose at least 8 weeks after dose 1, regardless of Hib vaccine used in the primary series.
   - If the first 2 doses were PRP-OMP (PedvaxHIB or COMVAX), and were administered at age 11 months or younger, the third (and final) dose should be administered at age 12 through 15 months and at least 8 weeks after the second dose.
   - If the first dose was administered at age 7 through 11 months, administer the second dose at least 4 weeks later and a third (and final) dose at age 12 through 15 months or 8 weeks after second dose, whichever is later, regardless of Hib vaccine used for first dose.
   - If first dose is administered at younger than 12 months of age and second dose is given between 12 through 14 months of age, a third (and final) dose should be given 8 weeks later.
   - For unvaccinated children aged 15 months or older, administer only 1 dose.
   - For other catch-up guidance, see Figure 2. For catch-up guidance related to MenHibrix, please see the meningococcal vaccine footnotes and also *MMWR* March 22, 2013; 62(RR02);1-22, available at http://www.cdc.gov/mmwr/pdf/rr/rr6202.pdf.

   Vaccination of persons with high-risk conditions:
   - Children aged 12 through 59 months who are at increased risk for Hib disease, including chemotherapy recipients and those with anatomic or functional asplenia (including sickle cell disease), human immunodeficiency virus (HIV) infection, immunoglobulin deficiency, or early component complement deficiency, who have received either no doses or only 1 dose of Hib vaccine before 12 months of age, should receive 2 additional doses of Hib vaccine 8 weeks apart; children who received 2 or more doses of Hib vaccine before 12 months of age should receive 1 additional dose.
   - For patients younger than 5 years of age undergoing chemotherapy or radiation treatment who received a Hib vaccine dose(s) within 14 days of starting therapy or during therapy, repeat the dose(s) at least 3 months following therapy completion.
   - Recipients of hematopoietic stem cell transplant (HSCT) should be revaccinated with a 3-dose regimen of Hib vaccine starting 6 to 12 months after successful transplant, regardless of vaccination history; doses should be administered at least 4 weeks apart.
   - A single dose of any Hib-containing vaccine should be administered to unimmunized* children and adolescents 15 months of age and older undergoing an elective splenectomy; if possible, vaccine should be administered at least 14 days before procedure.
   - Hib vaccine is not routinely recommended for patients 5 years or older. However, 1 dose of Hib vaccine should be administered to unimmunized* persons aged 5 years or older who have anatomic or functional asplenia (including sickle cell disease) and unvaccinated persons 5 through 18 years of age with human immunodeficiency virus (HIV) infection.

   ** Patients who have not received a primary series and booster dose or at least 1 dose of Hib vaccine after 14 months of age are considered unimmunized.*

6. **Pneumococcal vaccines. (Minimum age: 6 weeks for PCV13, 2 years for PPSV23)**

   Routine vaccination with PCV13:
   - Administer a 4-dose series of PCV13 vaccine at ages 2, 4, and 6 months and at age 12 through 15 months.
   - For children aged 14 through 59 months who have received an age-appropriate series of 7-valent PCV (PCV7), administer a single supplemental dose of 13-valent PCV (PCV13).

   Catch-up vaccination with PCV13:
   - Administer 1 dose of PCV13 to all healthy children aged 24 through 59 months who are not completely vaccinated for their age.
   - For other catch-up guidance, see Figure 2.

   Vaccination of persons with high-risk conditions with PCV13 and PPSV23:
   - All recommended PCV13 doses should be administered prior to PPSV23 vaccination if possible.
   - For children 2 through 5 years of age with any of the following conditions: chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure); chronic lung disease (including asthma if treated with high-dose oral corticosteroid therapy); diabetes mellitus; cerebrospinal fluid leak; cochlear implant; sickle cell disease and other hemoglobinopathies; anatomic or functional asplenia; HIV infection; chronic renal failure; nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin disease; solid organ transplantation; or congenital immunodeficiency:
     1. Administer 1 dose of PCV13 if 3 doses of PCV (PCV7 and/or PCV13) were received previously.
     2. Administer 2 doses of PCV13 at least 8 weeks apart if fewer than 3 doses of PCV (PCV7 and/or PCV13) were received previously.

6. **Pneumococcal vaccines (cont'd)**
     3. Administer 1 supplemental dose of PCV13 if 4 doses of PCV7 or other age-appropriate complete PCV7 series was received previously.
     4. The minimum interval between doses of PCV (PCV7 or PCV13) is 8 weeks.
     5. For children with no history of PPSV23 vaccination, administer PPSV23 at least 8 weeks after the most recent dose of PCV13.
   - For children aged 6 through 18 years who have cerebrospinal fluid leak; cochlear implant; sickle cell disease and other hemoglobinopathies; anatomic or functional asplenia; congenital or acquired immunodeficiencies; HIV infection; chronic renal failure; nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin disease; generalized malignancy; solid organ transplantation; or multiple myeloma:
     1. If neither PCV13 nor PPSV23 has been received previously, administer 1 dose of PCV13 now and 1 dose of PPSV23 at least 8 weeks later.
     2. If PCV13 has been received previously but PPSV23 has not, administer 1 dose of PPSV23 at least 8 weeks after the most recent dose of PCV13.
     3. If PPSV23 has been received but PCV13 has not, administer 1 dose of PCV13 at least 8 weeks after the most recent dose of PPSV23.
   - For children aged 6 through 18 years with chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure), chronic lung disease (including asthma if treated with high-dose oral corticosteroid therapy), diabetes mellitus, alcoholism, or chronic liver disease, who have not received PPSV23, administer 1 dose of PPSV23. If PCV13 has been received previously, then PPSV23 should be administered at least 8 weeks after any prior PCV13 dose.
   - A single revaccination with PPSV23 should be administered 5 years after the first dose to children with sickle cell disease or other hemoglobinopathies; anatomic or functional asplenia; congenital or acquired immunodeficiencies; HIV infection; chronic renal failure; nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin disease; generalized malignancy; solid organ transplantation; or multiple myeloma.

7. **Inactivated poliovirus vaccine (IPV). (Minimum age: 6 weeks)**

   Routine vaccination:
   - Administer a 4-dose series of IPV at ages 2, 4, 6 through 18 months, and 4 through 6 years. The final dose in the series should be administered on or after the fourth birthday and at least 6 months after the previous dose.

   Catch-up vaccination:
   - In the first 6 months of life, minimum age and minimum intervals are only recommended if the person is at risk for imminent exposure to circulating poliovirus (i.e., travel to a polio-endemic region or during an outbreak).
   - If 4 or more doses are administered before age 4 years, an additional dose should be administered at age 4 through 6 years and at least 6 months after the previous dose.
   - A fourth dose is not necessary if the third dose was administered at age 4 years or older and at least 6 months after the previous dose.
   - If both OPV and IPV were administered as part of a series, a total of 4 doses should be administered, regardless of the child's current age. IPV is not routinely recommended for U.S. residents aged 18 years or older.
   - For other catch-up guidance, see Figure 2.

8. **Influenza vaccines. (Minimum age: 6 months for inactivated influenza vaccine [IIV], 2 years for live, attenuated influenza vaccine [LAIV])**

   Routine vaccination:
   - Administer influenza vaccine annually to all children beginning at age 6 months. For most healthy, nonpregnant persons aged 2 through 49 years, either LAIV or IIV may be used. However, LAIV should NOT be administered to some persons, including 1) those with asthma, 2) children 2 through 4 years who had wheezing in the past 12 months, or 3) those who have any other underlying medical conditions that predispose them to influenza complications. For all other contraindications to use of LAIV, see *MMWR* 2013; 62 (No. RR-7):1-43, available at http://www.cdc.gov/mmwr/pdf/rr/rr6207.pdf.

   For children aged 6 months through 8 years:
   - For the 2013–14 season, administer 2 doses (separated by at least 4 weeks) to children who are receiving influenza vaccine for the first time. Some children in this age group who have been vaccinated previously will also need 2 doses. For additional guidance, follow dosing guidelines in the 2013-14 ACIP influenza vaccine recommendations, *MMWR* 2013; 62 (No. RR-7):1-43, available at http://www.cdc.gov/mmwr/pdf/rr/rr6207.pdf.
   - For the 2014–15 season, follow dosing guidelines in the 2014 ACIP influenza vaccine recommendations.

   For persons aged 9 years and older:
   - Administer 1 dose.

Figure 115.2 (*continued*)

9. **Measles, mumps, and rubella (MMR) vaccine. (Minimum age: 12 months for routine vaccination)**
Routine vaccination:
- Administer a 2-dose series of MMR vaccine at ages12 through 15 months and 4 through 6 years. The second dose may be administered before age 4 years, provided at least 4 weeks have elapsed since the first dose.
- Administer 1 dose of MMR vaccine to infants aged 6 through 11 months before departure from the United States for international travel. These children should be revaccinated with 2 doses of MMR vaccine, the first at age 12 through 15 months (12 months if the child remains in an area where disease risk is high), and the second dose at least 4 weeks later.
- Administer 2 doses of MMR vaccine to children aged 12 months and older before departure from the United States for international travel. The first dose should be administered on or after age 12 months and the second dose at least 4 weeks later.

Catch-up vaccination:
- Ensure that all school-aged children and adolescents have had 2 doses of MMR vaccine; the minimum interval between the 2 doses is 4 weeks.

10. **Varicella (VAR) vaccine. (Minimum age: 12 months)**
Routine vaccination:
- Administer a 2-dose series of VAR vaccine at ages 12 through 15 months and 4 through 6 years. The second dose may be administered before age 4 years, provided at least 3 months have elapsed since the first dose. If the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid.

Catch-up vaccination:
- Ensure that all persons aged 7 through 18 years without evidence of immunity (see *MMWR* 2007; 56 [No. RR-4], available at http://www.cdc.gov/mmwr/pdf/rr/rr5604.pdf) have 2 doses of varicella vaccine. For children aged 7 through 12 years, the recommended minimum interval between doses is 3 months (if the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid); for persons aged 13 years and older, the minimum interval between doses is 4 weeks.

11. **Hepatitis A (HepA) vaccine. (Minimum age: 12 months)**
Routine vaccination:
- Initiate the 2-dose HepA vaccine series at 12 through 23 months; separate the 2 doses by 6 to 18 months.
- Children who have received 1 dose of HepA vaccine before age 24 months should receive a second dose 6 to 18 months after the first dose.
- For any person aged 2 years and older who has not already received the HepA vaccine series, 2 doses of HepA vaccine separated by 6 to 18 months may be administered if immunity against hepatitis A virus infection is desired.

Catch-up vaccination:
- The minimum interval between the two doses is 6 months.

Special populations:
- Administer 2 doses of HepA vaccine at least 6 months apart to previously unvaccinated persons who live in areas where vaccination programs target older children, or who are at increased risk for infection. This includes persons traveling to or working in countries that have high or intermediate endemicity of infection; men having sex with men; users of injection and non-injection illicit drugs; persons who work with HAV-infected primates or with HAV in a research laboratory; persons with clotting-factor disorders; persons with chronic liver disease; and persons who anticipate close, personal contact (e.g., household or regular babysitting) with an international adoptee during the first 60 days after arrival in the United States from a country with high or intermediate endemicity. The first dose should be administered as soon as the adoption is planned, ideally 2 or more weeks before the arrival of the adoptee.

12. **Human papillomavirus (HPV) vaccines. (Minimum age: 9 years for HPV2 [Cervarix] and HPV4 [Gardasil])**
Routine vaccination:
- Administer a 3-dose series of HPV vaccine on a schedule of 0, 1-2, and 6 months to all adolescents aged 11 through 12 years. Either HPV4 or HPV2 may be used for females, and only HPV4 may be used for males.
- The vaccine series may be started at age 9 years.
- Administer the second dose 1 to 2 months after the first dose (minimum interval of 4 weeks), administer the third dose 24 weeks after the first dose and 16 weeks after the second dose (minimum interval of 12 weeks).

Catch-up vaccination:
- Administer the vaccine series to females (either HPV2 or HPV4) and males (HPV4) at age 13 through 18 years if not previously vaccinated.
- Use recommended routine dosing intervals (see above) for vaccine series catch-up.

13. **Meningococcal conjugate vaccines. (Minimum age: 6 weeks for Hib-MenCY [MenHibrix], 9 months for MenACWY-D [Menactra], 2 months for MenACWY-CRM [Menveo])**
Routine vaccination:
- Administer a single dose of Menactra or Menveo vaccine at age 11 through 12 years, with a booster dose at age 16 years.
- Adolescents aged 11 through 18 years with human immunodeficiency virus (HIV) infection should receive a 2-dose primary series of Menactra or Menveo with at least 8 weeks between doses.
- For children aged 2 months through 18 years with high-risk conditions, see below.

Catch-up vaccination:
- Administer Menactra or Menveo vaccine at age 13 through 18 years if not previously vaccinated.
- If the first dose is administered at age 13 through 15 years, a booster dose should be administered at age 16 through 18 years with a minimum interval of at least 8 weeks between doses.
- If the first dose is administered at age 16 years or older, a booster dose is not needed.
- For other catch-up guidance, see Figure 2.

Vaccination of persons with high-risk conditions and other persons at increased risk of disease:
- Children with anatomic or functional asplenia (including sickle cell disease):
  1. For children younger than 19 months of age, administer a 4-dose infant series of MenHibrix or Menveo at 2, 4, 6, and 12 through 15 months of age.
  2. For children aged 19 through 23 months who have not completed a series of MenHibrix or Menveo, administer 2 primary doses of Menveo at least 3 months apart.
  3. For children aged 24 months and older who have not received a complete series of MenHibrix or Menveo or Menactra, administer 2 primary doses of either Menactra or Menveo at least 2 months apart. If Menactra is administered to a child with asplenia (including sickle cell disease), do not administer Menactra until 2 years of age and at least 4 weeks after the completion of all PCV13 doses.
- Children with persistent complement component deficiency:
  1. For children younger than 19 months of age, administer a 4-dose infant series of either MenHibrix or Menveo at 2, 4, 6, and 12 through 15 months of age.
  2. For children 7 through 23 months who have not initiated vaccination, two options exist depending on age and vaccine brand:
     a. For children who initiate vaccination with Menveo at 7 months through 23 months of age, a 2-dose series should be administered with the second dose after 12 months of age and at least 3 months after the first dose.
     b. For children who initiate vaccination with Menactra at 9 months through 23 months of age, a 2-dose series of Menactra should be administered at least 3 months apart.
     c. For children aged 24 months and older who have not received a complete series of MenHibrix, Menveo, or Menactra, administer 2 primary doses of either Menactra or Menveo at least 2 months apart.
- For children who travel to or reside in countries in which meningococcal disease is hyperendemic or epidemic, including countries in the African meningitis belt or the Hajj, administer an age-appropriate formulation and series of Menactra or Menveo for protection against serogroups A and W meningococcal disease. Prior receipt of MenHibrix is not sufficient for children traveling to the meningitis belt or the Hajj because it does not contain serogroups A or W.
- For children at risk during a community outbreak attributable to a vaccine serogroup, administer or complete an age- and formulation-appropriate series of MenHibrix, Menactra, or Menveo.
- For booster doses among persons with high-risk conditions, refer to *MMWR* 2013; 62(RR02);1-22, available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6202a1.htm.

Catch-up recommendations for persons with high-risk conditions:
1. If MenHibrix is administered to achieve protection against meningococcal disease, a complete age-appropriate series of MenHibrix should be administered.
2. If the first dose of MenHibrix is given at or after 12 months of age, a total of 2 doses should be given at least 8 weeks apart to ensure protection against serogroups C and Y meningococcal disease.
3. For children who initiate vaccination with Menveo at 7 months through 9 months of age, a 2-dose series should be administered with the second dose after 12 months of age and at least 3 months after the first dose.
4. For other catch-up recommendations for these persons, refer to *MMWR* 2013; 62(RR02);1-22, available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6202a1.htm.

For complete information on use of meningococcal vaccines, including guidance related to vaccination of persons at increased risk of infection, see *MMWR* March 22, 2013; 62(RR02);1-22, available at http://www.cdc.gov/mmwr/pdf/rr/rr6202.pdf.

Figure 115.2 (*continued*)

United States in recent years, ACIP now recommends expanded use of Tdap. Tdap vaccine may be given regardless of interval since the last tetanus-toxoid- or diphtheria-toxoid-containing vaccine, it may be used in undervaccinated children aged 7 through 10 years, and it may be used in certain adults aged 65 years and older according to current ACIP recommendations.

The human papillomavirus vaccine (HPV) should also be considered at the pre-adolescent health visit at 11 to 12 years old according to ACIP recommendations. There are two licensed HPV vaccines, one bivalent (HPV2) and the other quadrivalent (HPV4). HPV4 (Gardisil, Merck) vaccine is directed against two oncogenic types (HPV 16 and 18) and two nononcogenic types (HPV 6 and 11) associated with genital warts. HPV4 was originally licensed in 2006 for use in females 9 to 26 years old. HPV2 (Cervarix, GlaxoSmithKline) directed against the two oncogenic types (HPV 16 and 18) was licensed in 2009 for use in females 10 to 25 years old. Both HPV vaccines consist of a series of three doses given by intramuscular injection. The vaccines are composed of virus-like particles (VLPs) prepared from recombinant L1 capsid protein of human papillomavirus together with an adjuvant, and are not live vaccines.

ACIP recommends routine HPV vaccination of females aged 11 or 12 years old, catch-up vaccination for females aged 13 to 26 years old, and administration as early as 9 years old if the girl is at risk of exposure. HPV vaccine is contraindicated in pregnancy, but may be used in lactating women.

In 2009, the FDA expanded licensure for use of HPV4 in males 9 to 26 years old based on risk. In 2011, ACIP issued recommendations for routine HPV4 vaccination of males aged 11 to 12 years, and males 13 to 21 years not vaccinated previously. HPV4 vaccination may decrease the likelihood of genital warts. Additionally, the ACIP recommends routine HPV4 vaccination through the age of 26 years for men who have sex with men (MSM) because of increased risk for disease associated with HPV types 6, 11, 16, and 18, and for immunocompromised males (including those with HIV infection).

Although clinical trials of concomitant administration of HPV vaccine with the other vaccines recommended for adolescents have not been performed, there are no theoretical reasons not to administer the first dose of HPV during the same clinic visit as MCV4 and Tdap vaccines, with the vaccines being administered at different anatomic sites.

Table 115.1 Selected licensed combination vaccines[a]

Vaccine product	Age range
DTaP-IPV-HepB (Pediarix®, GlaxoSmithKline)	6 weeks through 7 years
DTap-IPV/Hib (Pentacel®, sanofi pasteur)	2 months through 5 years
DTaP-IPV (Kinrix®, GlaxoSmithKline)	4 through 6 years
HepA-HepB (Twinrix®, GlaxoSmithKline)	18 years or older
Hib-HepB (Comvax®, Merck)	6 weeks through 5 years
MMR-Var (ProQuad®, Merck)	12 months through 12 years

[a] Consult the package insert for details of licensed use for each combination vaccine.

COMBINATION VACCINES

The number of recommended early childhood immunizations creates issues of compliance and scheduling for parents, patients, and healthcare providers. Depending on the availability and use of existing combination vaccines and new vaccines presently under development, the number of immunization injections per clinic visit can be decreased. Several commercially prepared combination vaccines are available for pediatric use (Table 115.1) and their use is encouraged to promote patient (parent) compliance. However, additional care must be taken in terms of scheduling missed doses, completing a vaccine series with a different vaccine product than originally used, and recognizing differences in antigen content and dose scheduling between monovalent vaccines and corresponding combination vaccines.

ADULT IMMUNIZATIONS

Recommendations for adult immunizations are based on the history of immunizations received in the past and on the need to give booster doses for certain vaccines. A detailed review of the personal immunization history is indicated for international travelers, healthcare workers, and other persons who have risks of exposure related to occupational activities, advanced age, or compromised immune status due to disease (HIV), medications, cancer, or other chronic medical conditions.

The immunization history should be updated and documented at the time of initial intake into a primary care practice, during interim health maintenance visits, on employment in one of the healthcare or social services professions, and/or prior to international travel. Travel immunizations will be covered in Chapter 116, Advice for travelers. If the immunization history of the

person is uncertain or unknown, a conceptual framework of the prevalent practices pertaining to childhood, school, military service, and occupational immunization programs and standards will be helpful for assessing the current immunization status. The recommended adult immunization schedule is given in Figure 115.3.

ROUTINE IMMUNIZATIONS FOR ADULTS

Tetanus and diphtheria and acellular pertussis vaccine

The combined diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP) series is a routine immunization of childhood. A formulation of the tetanus and diphtheria vaccine (Td) with reduced content of diphtheria toxoid is used to boost immunity in persons 7 years of age or older, and booster doses of Td are recommended every 10 years throughout adult life.

Poor control of pertussis in the United States has been noted since the late 1990s and epidemiologic studies suggest that waning immunity to pertussis over time following childhood DTaP immunization contributes to this. In partially immune adolescents and adults, pertussis often causes a prolonged respiratory illness without the characteristic "whooping cough" and thus may not be recognized as such. Adolescents and adults with undiagnosed pertussis may transmit the infection to infants at highest risk of serious complications from the infection. ACIP currently recommends that a single dose of Tdap vaccine (tetanus toxoid with reduced diphtheria toxoid and acellular pertussis content) be used to replace the next booster dose of Td vaccine among persons 19 to 64 years of age to boost levels of pertussis immunity in the adult population. Depending on community outbreaks of pertussis, occupational exposures, and/or personal health risks, Tdap vaccine may be administered with no minimal interval from the last Td vaccine dose based on current vaccine safety data.

HEALTHCARE WORKERS

Healthcare workers exposed to patients with confirmed pertussis infections may warrant antimicrobial prophylaxis and should consult the facility's infection control or occupational health consultant. ACIP recommends the use of Tdap vaccine as a one-time substitute for a Td vaccine booster among healthcare workers, especially for those providing care to pediatric patients.

Measles, mumps, and rubella

The measles, mumps, and rubella vaccines are usually given as a combination vaccine (MMR) in early childhood, at 12 to 15 months of age. However, up to 5% of vaccine recipients may fail to respond to primary immunization and have inadequate or waning immunity to measles by adulthood. For this reason, the ACIP and AAP recommend that a second dose of measles vaccine (as a component of MMR) be given in childhood on school entry. In many American colleges and universities, documentation of receipt of a second dose of measles vaccine or of immunity as evidenced by serum testing for measles antibodies is required for registration. There is no contraindication to using the MMR vaccine to boost measles immunity, even if the recipient is already immune to mumps and rubella. Monovalent measles, mumps, and rubella vaccines are commercially available but are not commonly recommended, stocked, and/or used in vaccine immunization programs.

Potential vaccine adverse reactions include the rare occurrence of usually transient, but occasionally prolonged, arthralgias and arthritis attributed to the rubella component of the MMR vaccine in nonimmune women of reproductive age – the very group most likely to benefit from immunization against rubella. As with any vaccine, the potential risks versus benefits of immunization with MMR vaccine should be discussed with potential vaccine recipients, along with the VIS statements.

CONTRAINDICATIONS

MMR vaccine is a live-virus combination vaccine. Women of childbearing age should not be pregnant at the time of receiving MMR vaccine and should defer pregnancy for 3 months after MMR immunization.

HIV-INFECTED PERSONS

MMR immunization is recommended for use in susceptible persons with asymptomatic HIV infection, as the potential benefits of immunization appear to outweigh the serious course of natural measles infections in this population.

HEALTHCARE WORKERS

People born before 1957 are generally considered immune to measles, mumps, and rubella by virtue of having had the natural infectious diseases in the pre-MMR vaccine era. However, because a small percentage in this group did not acquire lasting immunity from historical accounts

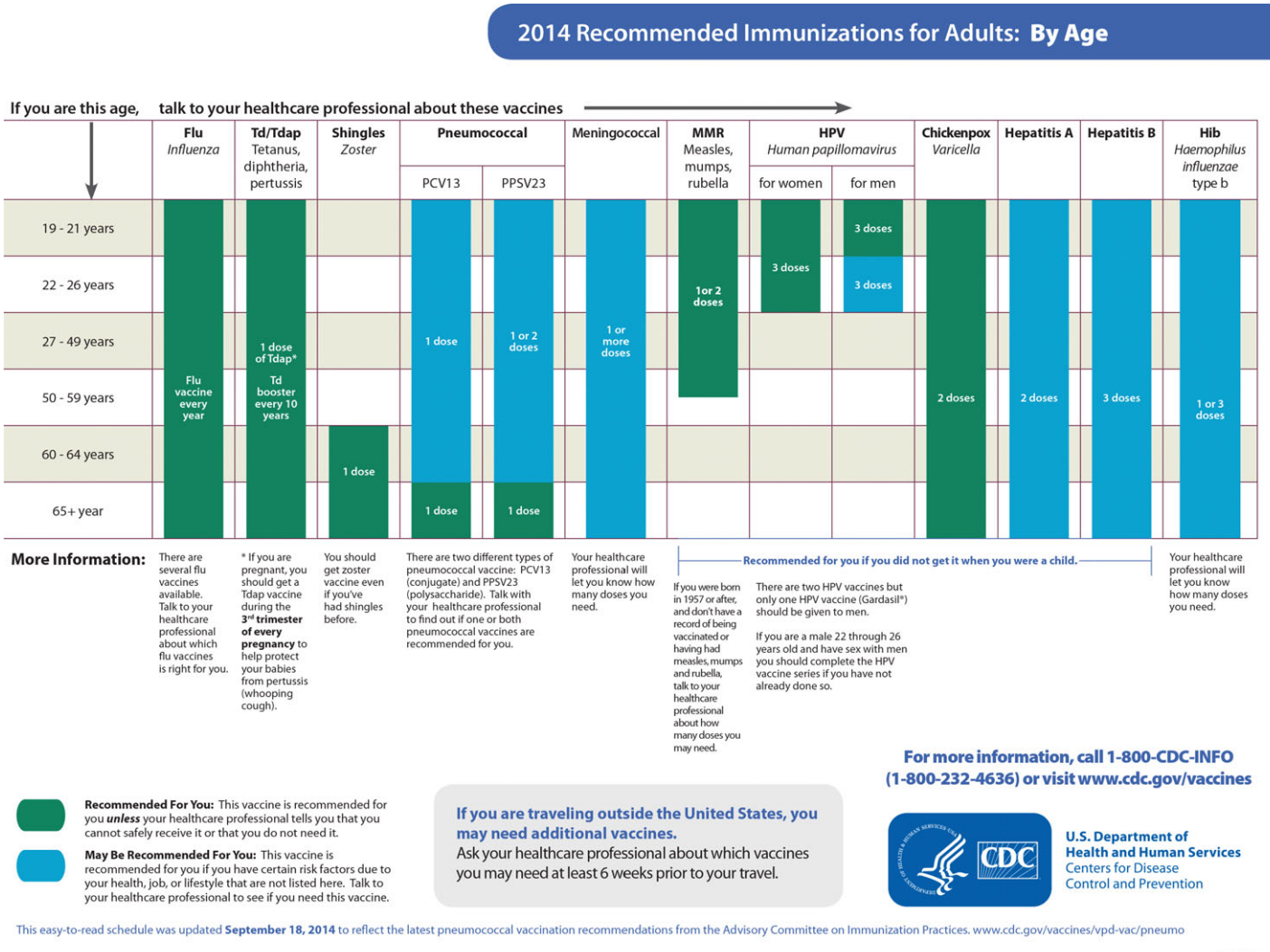


Figure 115.3 Recommended adult immunization schedule by age – United States – 2014. Source: http://cdc.gov/vaccines/schedules. Accessed December 7, 2014.

of diagnosed/presumed infections, and because healthcare workers may be at increased risk of acquiring measles and mumps infections and transmitting them to other patients/clients, healthcare workers should provide proof of prior receipt of two doses of MMR vaccine or serologic immunity to measles and mumps.

Varicella vaccine and zoster (shingles) vaccine

Varicella (chickenpox) infections are more likely to result in severe disease among adults compared to children, often accompanied by complications such as varicella pneumonia. A live attenuated viral vaccine against varicella (VAR: Varivax, Merck) was released in the mid 1990s. The primary series for young people 12 years of age or older and adults consists of two doses given by injection 1 month apart.

Varicella-zoster virus (VZV) causes varicella (chickenpox) and becomes dormant within the nerves following exposure but can reactivate later in life, usually around 50 years old. The risk of virus reactivation increases with age, causing herpes zoster or "shingles," a condition characterized by a vesicular rash that follows a dermatomal distribution that is often associated with debilitating chronic pain. The ACIP recommends that zoster vaccine (Zostavax, Merck) be given to all people 60 years of age and older, including those who have had a previous episode of shingles. The zoster vaccine is a live attenuated virus vaccine and should be used with caution in adults younger than 60 years of age and in adults with immunocompromised status.

CONTRAINDICATIONS

Varicella vaccine and zoster vaccine are live-virus vaccines and contraindicated in pregnant women. Women of childbearing age should not be pregnant at the time of receiving varicella vaccine and should defer pregnancy for 3 months after varicella immunization. Varicella vaccine and zoster vaccine are contraindicated in persons with compromised immunity, including individuals with HIV infection. Some experts suggest that zoster vaccine may be considered for off-label use in immune-competent persons of any age who anticipate treatments or advancing illness that will result in immunocompromised status and in HIV-infected persons with CD4 lymphocytes $\geq$15% (CD4 $\geq$200 mm) on a stable antiretroviral drug regimen for $\geq$3 months, because the potential benefit would outweigh the potential risks.

HEALTHCARE WORKERS

Current occupational health recommendations for healthcare workers include documentation of varicella immunity or varicella immunization as a condition for working in certain clinics and hospitals.

Polio vaccine

Immunization against polio is a part of the routine childhood immunization program, and booster doses are not given routinely in adulthood in the Western Hemisphere (North and South America) and Western Europe, where polio is considered eradicated. Current pediatric regimens use the enhanced inactivated polio vaccine (IPV: Ipol, sanofi pasteur) administered by injection for primary immunization. A single dose of IPV is recommended as a booster in adults when there is imminent risk of exposure, such as travel to certain regions of Africa and Asia where polio is still transmitted, or for occupational exposure (e.g., work in certain research laboratories).

Hepatitis B vaccine

Hepatitis B immunization has been included as one of the regular immunizations in the United States since 1991. Hepatitis B vaccine should be considered a "catch-up" immunization among young adults born before the hepatitis B vaccine was incorporated into the routine childhood immunization programs. Hepatitis B immunization should also be recommended to individuals at risk of exposure to hepatitis B virus through occupational risk; treatment with blood products; contact with infected family, friends, or others; or international travel.

The primary series for hepatitis B immunization consists of three doses given by intramuscular injection into the deltoid muscle at 0, 1, and 6 months (HepB: Recombivax HB, Merck; Engerix-B, GlaxoSmithKline). An accelerated schedule consisting of three doses of hepatitis B vaccine given at 0, 1, and 2 months, with a booster dose at 12 months, has FDA approval (Engerix-B).

A combination vaccine against hepatitis A plus hepatitis B (HepA-HepB: Twinrix, GlaxoSmithKline) has been licensed for 18 years of age and older and is given on a standard schedule of 0, 1, and 6 months. An accelerated schedule for HepA-HepB has received FDA approval. The accelerated dosing schedule of three doses given on 0, 7, and 21 to 28 days, followed by a fourth dose at

12 months, produces protective immunity against hepatitis A and hepatitis B following the first three doses. The fourth dose is given to assure long-lasting immunity. The accelerated schedule will be useful for international travelers with <1 month's time before departure, and for healthcare workers who need rapid protection before duty assignments.

The antibody response to hepatitis B is enhanced when A and B antigens are given simultaneously in the same syringe or concomitantly when monovalent hepatitis A and hepatitis B vaccines are given at the same time but at separate sites. The adjuvant effect of hepatitis A has possible implications for hepatitis B-susceptible adults aged 30 years or older, who tend to respond with lower antibody levels to monovalent hepatitis B vaccine compared with younger hepatitis B vaccine recipients. The utility of combination hepatitis A plus hepatitis B immunization in other groups of hepatitis B vaccine low responders or nonresponders (e.g., obese, cigarette smokers, male) needs further investigation.

HEALTHCARE WORKERS

Hepatitis B immunization or immunity is required for work in certain occupations, including healthcare workers, policemen, firemen, morticians, and others who are likely to have work-related contact with human blood and other bodily substances.

Pneumococcal vaccine

As of 2014, the ACIP recommends that all adults 65 years of age and older receive both PCV13 (pneumococcal conjugate vaccine 13-valent: Prevnar 13, Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc.) and PPSV23 (pneumococcal polysaccharide vaccine 23-valent: Pneumovax 23, Sanofi Pasteur). If not previously vaccinated with a pneumococcal vaccine, PCV13 should be administered first, followed by a dose of PPSV23 6–12 months later. If PPSV23 was previously received, then PCV13 should be administered 12 months or more after PPSV23.

The FDA licensed the 13-valent pneumococcal conjugate vaccine (PCV13) in 2010, and the ACIP recommended PCV13 for children ages six weeks through 71 months to prevent invasive pneumococcal disease. In 2011, the FDA expanded the licensure of PCV13 to include adults aged 50 years and older, and in 2012, the ACIP recommended routine use of PCV13 in adults aged ≥19 years with immunocompromising conditions, functional or anatomic asplenia, cerebrospinal fluid leaks (CSF), or cochlear implants. In pneumococcal vaccine-naïve persons in the 19–64-year age group, it is preferable to administer PCV13 first, followed by PPSV23 at least 8 weeks later if additional immunization is desirable. If one or more PPSV23 doses have been previously received, the PCV13 should be given ≥1 year after the last PPSV23 dose was received. Any additional dose of PPSV23 should be separated by at least 5 years from the most recent dose of PPSV23.

Viral influenza vaccine

Viral influenza vaccine is reformulated annually based on recent worldwide epidemiology of influenza viruses according to World Health Organization data. Annual immunization with the "flu" vaccine is recommended for all persons 6 months of age and older, with rare exception, with priority given to infants aged 6–59 months and adults aged 50 years and older in case of vaccine shortage.

The flu vaccine distributed for a given season may not be totally protective against all strains of influenza viruses in circulation following the annual flu vaccine formulation, thus anti-flu medications may be considered. Chemoprophylaxis or prompt treatment after onset of symptoms with oseltamivir (Tamiflu, Genentech) or zanamivir (Relenza, GlaxoSmithKline) during outbreaks of influenza A or B may prevent or ameliorate illness in breakthrough attacks.

Vaccines include inactivated influenza vaccine quadrivalent (IIV4); inactivated influenza vaccine trivalent (IIV3) standard dose, high dose, and intradermal dose; cell-cultured inactivated influenza vaccine trivalent (ccIIV3); recombinant influenza vaccine trivalent (RIV3) and live attenuated influenza vaccine quadrivalent (LAIV4). LAIV4 (FluMist, Medimmune) administered by a nasal spray is licensed for recipients aged 2–49 years. Intradermal IIV3 (Fluzone Intradermal, Sanofi Pasteur) is licensed for use in persons aged 18–64 years, and high dose IIV3 (Fluzone High Dose, Sanofi Pasteur) is licensed for persons 65 years and older. Current information on brands, manufacturers, dosage and age range are posted on the CDC web site http://www.cdc.gov/flu.

Hepatitis A vaccine

The conditions allowing transmission of hepatitis A are ubiquitous, although the relative risk appears to be highest in countries where sanitation and hygiene are suboptimal and there is widespread fecal contamination of food and water supplies. In areas of low endemicity for hepatitis A virus (HAV), outbreaks of the disease are related to contamination of food during preparation by infected food handlers and to ingestion of fresh or frozen fruits and vegetables imported from areas highly endemic for hepatitis A, contaminated during cultivation or processing. Shellfish from sewage-contaminated beds are another source of foodborne transmission.

In the United States, adults identified by the CDC as being at increased risk for hepatitis A or severe outcomes include travelers, MSM, users of injecting and non-injecting drugs, persons who have clotting-factor disorders, persons working with nonhuman primates, and persons with chronic liver disease.

Children can serve as a significant reservoir of HAV in outbreaks and in endemic communities. Hepatitis A infections are mild and often anicteric in young children, so infected children are not detected. Fecal–oral transmission to other children and family members, as well as adult teachers or caretakers, can easily occur in household, day-care, and institutional settings, especially if children in diapers are present. It is important to note that HAV case-fatality rates in healthy individuals rise with age, so although the rate is 0.1% from younger than 1 to 14 years of age, it is 0.4% in those from 15 to 39 years of age, 1.1% in those older than 40 years, and 2.7% in persons older than 49 years.

A safe and highly efficacious inactivated hepatitis A vaccine became available with the 1994 release of Havrix (Smithkline Beecham; now, GlaxoSmithKline), an inactivated HAV vaccine derived from the HM-175 viral strain. VAQTA (Merck), an inactivated HAV vaccine derived from the CR-326 F strain, was licensed a few years later. Havrix and VAQTA are available in the United States and Canada, as well as worldwide. Other hepatitis A vaccine products are also in use in Europe and Asia.

The immunization schedules for both hepatitis A vaccines licensed in the United States consist of a single primary dose given by intramuscular (IM) injection into the deltoid muscle, resulting in protective antibody titers within 4 weeks that confer protection for 6 months up to 1 year. The first vaccine dose is followed by a booster dose 6 to 12 months later, producing levels of antibody predicted by mathematical modeling to give protection up to 10 years or more. Vaccine protection against hepatitis A may also be obtained by receipt of the combined hepatitis A and B vaccine (HepA-HepB: Twinrix, GlaxoSmithKline) (see above).

Immunoglobulin

Immunoglobulin (IG) is purified human immunoglobulin used to provide protection against HAV infection through the passive transfer of preformed antibodies against HAV present in the IG (at least 100 IU/μL). IG is recommended for prevention of hepatitis A following known exposure to a confirmed case of HAV (0.02 mL/kg) and in nonimmune travelers going to HAV-endemic areas when there is <2 weeks remaining before departure (0.02 mL/kg to 0.06 mL/kg).

SPECIAL CONSIDERATIONS

Attenuated live viral or bacterial vaccines are generally contraindicated for pregnant women and patients with compromised immunity. Exceptions are the recommendations for giving the MMR vaccine to children with HIV infection and giving the yellow fever vaccine to a pregnant female traveler with imminent departure to a high-risk destination in a foreign country. In these cases, the theoretical risk of serious adverse vaccine complications may be outweighed by the anticipated benefits of vaccine-elicited protection.

Vaccine efficacy can be affected by various conditions (including age) and therapies that lead to compromise of the immune system. In persons older than 65 years, the high-dose IIP vaccine is used to elicit improved immunoprotection against influenza compared to the standard dose. In patients receiving hemodialysis, the suboptimal immune response to hepatitis A and B vaccines may necessitate higher-than-standard antigen doses, given as a special vaccine formulation or as additional doses after the standard series has been administered.

Limited data suggest that administration of toxoid, killed virus, and purified derivative vaccines to HIV patients as appropriate may elicit protective immunity in the vaccine recipient if the CD4 count is greater than 200/mm^3. An observed rise in viral loads in some HIV patients following vaccination has been of some concern,

but the phenomenon is thought to be frequently transient. The current consensus is that a severe infection with a given vaccine-preventable pathogen is more likely to be associated with a more detrimental rise in viral load than that seen secondary to the corresponding immunization. High-dose vaccine formulations or additional doses in certain vaccine series may be used in off-license protocols to improve vaccine efficacy in this group of patients.

The conjugate vaccines against encapsulated bacteria (*H. influenzae* type b, pneumococcal, and meningococcal vaccines) are recommended for persons who have a history of functional or anatomic asplenia because of the risk of overwhelming sepsis associated with infections from these agents, although data on protective efficacy of these vaccines in this patient group are incomplete. The new meningococcal Group B vaccine (Trumenba, Wyeth Pharmaceuticals Inc) is covered on page 940 (Chapter 143).

TRAVEL IMMUNIZATIONS

The patient seeking vaccine advice for international travel presents an opportunity to review and update routine immunizations as well as assess the risk of exposure to exotic diseases during the trip (see Chapter 116, Advice for travelers).

DISCLAIMER

The use of trade names and commercial sources in this chapter is for identification only and does not imply endorsement and is not meant to constitute a comprehensive listing.

SUGGESTED READING

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PART XVI

Travel and recreation

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116. Advice for travelers

Henry M. Wu and Jessica K. Fairley

Whether for business, tourism, study, or aid work, more individuals are traveling to more parts of the world. The World Tourism Organization estimates that in 2011, there were 990 million international tourist arrivals worldwide. Health problems associated with travel are common, especially in developing countries where as many as 22% to 64% of travelers self-report a travel-associated health problem and 8% seek healthcare while traveling or after return. Healthcare providers can play a critical role in minimizing the risk of illness and injury during travel.

GENERAL APPROACH

While administration of travel-related vaccinations and malaria prophylaxis remain cornerstones of the pre-travel consultation, providing advice on managing chronic medical conditions, food and water hygiene, physical safety, and disease vector avoidance is also important. Noninfectious causes of morbidity and mortality such as injury and exacerbation of chronic illness are typically the most common health issues travelers encounter. Important considerations include:

- Pre-existing medical conditions, current medications, and allergies
- Itinerary, including details of travel within countries, duration of stay, and sequence of countries visited
- Purpose of travel, accommodations, and activities
- Previous vaccination history and recommended vaccines for the itinerary
- Need for prophylactic and self-treatment medications, including those for malaria prevention, treatment of travelers' diarrhea, and altitude sickness.

Referral to a travel health specialist should be considered, particularly for medically complex travelers, for those traveling to developing nations, and when travel-specific vaccines are indicated. Since vaccines typically take 10 to 14 days to elicit full immune responses, and some require a primary series to become effective, travelers should ideally be evaluated in a travel clinic at least 4 to 6 weeks prior to departure. However, when this is not possible travelers should still be seen, even when travel is imminent.

Pre-existing medical conditions

International travel is increasingly common among individuals of all ages and health statuses, including those with medical conditions that predispose to infection or injury. Exacerbations of underlying conditions are a common cause of morbidity; furthermore, individuals in these groups can be at increased risk for complications from infections including travelers' diarrhea, influenza, and malaria. Current medications should be reviewed for drug interactions or contraindications with travel-related medications or vaccinations. Immunocompromising conditions are generally contraindications to live vaccine administration. Pregnancy presents a particular challenge for travel to malarious areas, as pregnancy is a risk factor for severe infection and a contraindication to some of the commonly used prophylaxis medications. The physical ability of the traveler to withstand environmental conditions at their destinations should also be considered. For example, travel involving high altitude, difficult terrain, and even commercial flying may be inappropriate for some. When risks of travel are significant, advising against nonessential travel can be important. When needed, travelers should be advised to seek the best quality medical care available, and providing information on reliable sources of care as well as medical evacuation insurance (see below) can be very helpful.

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Table 116.1 Sources of information for travel health advisers

1. Centers for Disease Control and Prevention (CDC) Travelers' Health website. Provides country-specific immunization and malaria prophylaxis recommendations. The *Health Information for International Travel 2014* is also available online here. Website: www.cdc.gov/travel
2. Global Polio Eradication Initiative. Provides updated information on polio cases worldwide. Website: www.polioeradication.org/Dataandmonitoring/Poliothisweek.aspx
2. U.S. Department of State. Provides updated travel advisories and alerts, as well as country-specific advice for US travelers. Web site: www.travel.state.gov
3. International Association for Medical Assistance to Travelers (IAMAT). Provides travel health advice and listing of international clinics. Website: www.iamat.org
6. International Society of Travel Medicine (ISTM). Association of travel health advisors and publisher of the *Journal of Travel Medicine*. Provides a listing of travel clinics. Website: www.istm.org
7. Shoreland, Inc. Medical publishing company providing tools for travel health advisors. Website: www.shoreland.com
8. SOS International. Company providing tools for travel health advisors. Also provides medical evacuation and health insurance for travel. Website: www.internationalsos.com

Itinerary and purpose of travel

Review of the traveler's itinerary is important to determine the specific infectious, environmental (e.g., altitude, climate, etc.), and public safety risks that will be encountered. Country-specific health advisories, vaccine recommendations, and malaria prophylaxis recommendations are available from the Centers for Disease Control and Prevention (CDC) Travelers' Health website and other resources (Table 116.1). Notably, countries can have unique yellow fever vaccination requirements, and timing and duration of travel is also important to consider when prescribing malaria prophylaxis (see Chapter 200, Malaria).

The purpose of the trip, accommodations, and likely activities are essential considerations when providing individualized advice. Tourist and business travelers typically take short-term trips to visit major cities and stay in better accommodations, while long-term travelers (e.g., missionaries, aid workers, business expatriates, students, etc.) are more likely to eat, sleep, and travel in conditions closer to that of locals and stay for durations that make health problems more likely. Immigrants visiting friends and relatives in their countries of origin (VFRs) can be unique. While this group shares some risk factors with the long-term travelers, they might not have the financial resources to afford travel vaccinations, and many do not recognize the importance of malaria prophylaxis when visiting their countries of origin.

The usual activities of the business, tourist, and adventure travelers are very different, and each traveler should be counseled about the infections, injuries, and exposures that are most likely. For example, popular freshwater activities in Africa, such as whitewater rafting in the Nile River in Uganda or swimming in East African Rift Valley Lakes can result in schistosomiasis infection. Rural itineraries and direct animal contact can be risk factors for various vaccine-preventable (e.g., rabies, Japanese encephalitis) and nonvaccine preventable (e.g., avian influenza, African tick-bite fever) infections.

Travelers should be aware that blood- and bodily fluid-borne infections such as HIV, hepatitis B, and hepatitis C are more prevalent in much of the world, and routine advice of avoiding unprotected sexual contact and percutaneous exposures (e.g., tattooing, piercings) is prudent. All travelers are potentially at some risk of bloodborne infections when seeking medical care, especially in areas where unsafe injection practices occur or when administration of unscreened blood products occurs. Those working in healthcare settings (i.e., medical missionaries, healthcare trainees, etc.) should be advised to investigate the availability of reliable HIV postexposure prophylaxis medications should an occupational percutaneous bodily fluid exposure occur.

IMMUNIZATIONS

When providing pre-travel advice, it is important to review both routine immunizations as well as those that are particularly recommended or required for the particular itinerary. Travelers should be up to date on routine vaccinations (see Chapter 115, Immunizations). On the other hand, for US residents, indications for yellow fever, typhoid, and Japanese encephalitis vaccination are almost exclusively limited to international travel. Some vaccinations, such as polio or meningococcal vaccination, are routinely administered to children and adolescents in the United States, while adult boosters are recommended for travel to specific areas. Two rarely indicated vaccines are bacille Calmette–Guérin (BCG) and cholera, of which the latter is not available in the United States. Table 116.2 lists the immunizations of special importance for travel and their schedules.

Immunizations should generally be recommended according to risk of disease and not

Table 116.2 Immunizations for foreign travel

Vaccine	Adult dosage	Duration of efficacy
Live attenuated		
Yellow fever	1 (0.5 mL) SC 10 days before travel	Booster q10yr
Typhoid	1 enteric-coated capsule taken on alternate days for 4 doses with cool liquid 1 h before a meal[a]	Booster series q5yr
Inactivated		
Typhoid	1 dose (0.5 mL) IM	Booster q2yr
Rabies pre-exposure	3 doses (1.0 mL) IM on days 0, 7, and 21 or 28	No boosters recommended for most travelers at routine exposure risk
Meningococcal (quadrivalent A/C/Y/W-135) (conjugate[b] or polysaccharide)	1 dose (0.5 mL) IM (conjugate vaccines) or SC (polysaccharide)	Reimmunization recommended q5yr[c]
Japanese encephalitis, inactivated Vero cell culture-derived	2 doses (0.5 mL) IM days 0 and 28	Booster recommended at 1 yr; data on timing and need for further boosters unavailable
Hepatitis A	2 doses, at 0 and 6–12 mo (HAVRIX) or 0 and 6–18 mo (VAQTA)	Probable lifelong immunity
Passive prophylaxis		
Immunoglobulin for protection against hepatitis A[d]	0.02 mL/kg for travel $\leq$3 mo 0.06 mL/kg for travel >3 mo (repeat if travel >5 mo)	

Abbreviations: SC = subcutaneous; IM = intramuscular.

[a] Must not be taken while taking antibiotics, including doxcycycline malaria prophylaxis.

[b] Approved for use in adults up to 55 years old.

[c] For participation in Hajj pilgrimage vaccination within previous 3 years and $\geq$10 days prior to arrival required.

[d] Must be administered at least 2 weeks after or 3 months prior to administration of measles or varicella vaccination.

according to the country visited. The risk of specific infections can vary significantly in different areas within a country; furthermore, infection risk can vary with different activities, accommodations, and eating habits. Trip duration is also important to consider due to the increased risk of infection exposure over time, and some vaccinations such as Japanese encephalitis, hepatitis B, or rabies vaccination, are of higher priority in long-term travelers.

Most vaccines can be administered simultaneously at separate sites, and this is often necessary when multiple are indicated. However, immunologic response to live-virus vaccines (i.e., MMR, varicella, yellow fever, or intranasal live attenuated influenza vaccines) might be attenuated when administered within 30 days of another live-virus vaccine. Therefore, live-virus vaccines should be administered on the same day or spaced apart at least 30 days.

Tetanus, diphtheria, and pertussis

All travelers should be up to date with tetanus, diphtheria, and pertussis vaccination as per routine. Diphtheria continues to be endemic in many countries outside the United States and Western Europe. Pertussis is increasingly recognized worldwide, including in the United States. Adult travelers who have not previously received the combined tetanus/diphtheria/acellular pertussis vaccine (Tdap) should receive one dose of Tdap regardless of the interval since the last Td booster.

Polio

Infants and children should be current on routine polio immunizations prior to travel. Adults aged 18 years and older who are travelling to an endemic or epidemic area should complete a primary series prior to travel if they have never received one. Furthermore, as a precaution, all adults who have received the routine childhood series should also receive a single booster dose of the inactivated polio vaccine before travel to polio endemic or epidemic countries, defined as those that have had wild poliovirus circulation in the preceding 12 months. A single booster dose might also be recommended for adults working in healthcare settings, refugee camps, or other humanitarian aid settings in certain countries that share a border with endemic and epidemic

countries. Long-term travelers staying over 4 weeks in certain polio-affected countries may also be subject to recent requirements for proof of polio vaccination 1–12 months prior to departure from the affected country. Readers are encouraged to refer to the CDC Travelers' Health website for updated country-specific recommendations (Table 116.1). Oral polio vaccine is no longer available in the United States. If time permits, infants and children younger than 2 years should receive at least three doses of polio vaccine. Intervals between doses may be reduced to 4 weeks to optimize immunization status before departure.

Measles, mumps, rubella, and varicella

Measles continues to be a major cause of morbidity and mortality in the developing world, and outbreaks in the United States have been linked to imported cases. Although mumps and rubella are less of a health threat to travelers, both infections can have serious complications. For international travelers, two doses of the MMR vaccine are recommended for those without contraindications, unless there is serologic evidence of immunity, prior history of disease, or birth prior to 1957. Of note, children between 1 and 4 years old may have only had one MMR dose. It is recommmended that they get their second dose prior to travel (as long as it is administered at least 4 weeks after the first dose), and additional doses are unnecessary. For those under 1 year of age, immunization may be given between 6 and 12 months of age and is recommended for international travel. Two doses after age 12 months are still indicated in this circumstance. The combination MMRV vaccine (measles, mumps, rubella, and varicella), can be used when needed, although it is not licensed in the United States for infants less than 1 year old.

Varicella does present a health risk to nonimmune individuals. International travelers should have evidence of immunity, which can include: age-appropriate vaccination (one dose of varicella vaccine for children aged 1 to 4 years and two doses for individuals aged $\geq$4 years), history of chickenpox or zoster, serologic evidence of immunity, or birth before 1980 (not a criterion for healthcare workers, pregnant women, or immunocompromised individuals).

Influenza and pneumococcus

Though many travelers and physicians underrecognize the importance of influenza vaccination prior to travel, influenza is the most common vaccine-preventable illness seen in travelers, and vaccination is recommended for all travelers age 6 months and older. Influenza occurs year-round in the tropics and from May through November in the southern hemisphere. For these reasons vaccine should be administered in the United States to all travelers until the vaccine expiration date (usually in May–June of the year following its availability). The southern hemisphere vaccine is not available in the United States. As per routine guidelines children and those at risk for severe pneumococcal infection, including those older than 65 years, should receive pneumococcal vaccinations prior to travel.

Hepatitis B

Although hepatitis B vaccination is now recommended in the United States for all infants, children, and adolescents, many adults have not been vaccinated. Among travelers, hepatitis B vaccination has typically been reserved for persons at higher risk of exposure, such as healthcare workers, those that may have casual sex, and for long-term travelers to high-prevalence countries. However, all travelers to developing countries are potentially at risk when seeking healthcare, due to potentially unsafe injection practices and inadequately screened blood products. A combined hepatitis A and B vaccine is available in the United States. For those traveling on short notice, an accelerated regimen for both the combined and single hepatitis B vaccines (0, 7, 21–30 days) is approved. When using the accelerated schedule, a booster dose should be given at 1 year to provide long-term immunity.

IMMUNIZATIONS OF SPECIFIC IMPORTANCE FOR THE INTERNATIONAL TRAVELER

Hepatitis A and immunoglobulin

Hepatitis A is one of the most common vaccine-preventable infections in travelers. While risk is higher in rural areas or those with adventurous eating habits, many travel-related cases have occurred with typical tourist itineraries, and hepatitis A vaccination is strongly recommended for all travelers. Although vaccination is now routine for US children, many adults have not been vaccinated. Prior to the availability of the hepatitis A vaccine, immunoglobulin (IG), was used for protection. Though IG protects travelers

immediately, its duration of protection is short and its availability is limited. IG is still recommended for travelers less than 12 months old or those with vaccine contraindications. IG can also be given with the vaccine to older and immunocompromised travelers when travel is imminent (in less than 2 weeks) for optimal protection.

Typhoid

Although *Salmonella enterica* serotype Typhi is prevalent in many countries in Africa, Asia, and Central and South America, typhoid fever is not common in travelers. However, given the serious nature of the infection and availability of well-tolerated vaccines, live Ty21a oral capsular vaccine or the injectible inactivated vaccine should be considered in travelers to endemic areas. Immunocompromised travelers should receive the inactivated vaccine. While those traveling off usual tourist routes or adventurous eaters are at highest risk, long-term and frequent short-term travelers to developing countries are also at increased risk. Vaccine recipients should be aware that the vaccines are only 50% to 80% effective and do not prevent typhoid fever caused by *S. enterica* serotype Paratyphi; therefore, vaccination alone can not be relied upon to prevent typhoid fever.

Yellow fever

Yellow fever is a viral illness transmitted by mosquitoes in tropical Africa and South America. It is rare in travelers, but because of its high mortality, vaccination is recommended for individuals visiting endemic areas. Some countries have specific yellow fever vaccination entry requirements, including some that require documentation of vaccination for all visitors, and others that require vaccination only when arriving from an endemic country. Country-specific entry requirements (available from the CDC Travelers' Health website and country embassies) should be reviewed for each international traveler. In the United States vaccination is available only at approved yellow fever vaccination clinics (see the CDC Travelers' Health website for a listing). Vaccination is valid for 10 years from 10 days after administration, and vaccination is documented on an International Certificate of Vaccination card, which should be carried by the traveler.

Yellow fever vaccine is a live-virus vaccine and is contraindicated in infants less than 6 months of age and individuals with thymus disorders or immunodeficiencies (including AIDS and those receiving immunosuppressive or immunomodulatory therapies for transplanted organs, malignancies, autoimmune disorders, or other conditions). Precautions to vaccination include ages between 6 and 9 months or above 60 years, pregnant or breastfeeding women, and HIV-infected individuals without AIDS. Following yellow fever vaccination, rare cases of encephalitis or autoimmune neurologic disease have been reported, as well as multiorgan system illness similar to yellow fever illness. Although severe adverse events occur with an overall frequency of only 4.7 per 100 000 doses they are more likely among older vaccinees. Individuals with vaccine contraindications who travel to countries with entry requirements must carry a waiver on a physician's letterhead to avoid vaccination upon arrival.

Meningococcal meningitis

Quadrivalent meningococcal vaccines protect against *Neisseria meningitidis* serogroups A, C, Y, and W-135. Routine vaccination in the United States is recommended for adolescents and other groups with increased risk of infection. Travelers to countries that are hyperendemic or epidemic are considered at increased risk, including travelers to the African "meningitis belt" during the dry season (December through June). Vaccination is also required by the Saudi Arabia government for those attending the Hajj pilgrimage in Mecca.

Japanese encephalitis

From 1973 to 2011, there were 58 reports of Japanese encephalitis (JE) infection among travelers from nonendemic countries. JE transmission occurs in Asia during the summer to autumn in temperate regions, and during the rainy season or potentially year-round in the subtropics and tropics. JE is transmitted by night-biting *Culex* mosquitoes, typically in rural areas with rice cultivation and pig-farming. Up to 30% of symptomatic infections are fatal, and 30% to 50% of survivors have neurologic sequelae. Short-term urban travelers are at minimal risk; however, travelers on prolonged itineraries to rural areas can have similar risks as that of the local population. Therefore, vaccination should be particularly considered in travelers with extensive overnight rural exposures and long-term expatriates. The inactivated Vero cell culture-derived vaccine (Ixiaro), given in a two-dose

series (28 days apart), is licensed in the United States for individuals aged 2 months and older. This vaccine has replaced the inactivated mouse brain-derived JE vaccine, which was associated with rare but severe hypersensitivity reactions.

Rabies

The decision to administer rabies pre-exposure vaccination should be based on various considerations including endemicity of rabies in the countries visited, exposure risk, duration of stay, and availability of postexposure biologics. Rabies is transmitted through inoculation of saliva from an infected mammal, typically resulting from a bite, though non-bite exposures can occur via mucous membranes or open wounds. All travelers should avoid contact with wild and feral mammals, as well as unvaccinated domesticated dogs and cats. Children are of particular exposure risk, given their small size, curiosity with animals, and potential to not report exposures. Any possible exposure should be washed immediately with soap and water, and medical care should be sought immediately for postexposure prophylaxis. Although individuals who have received pre-exposure vaccinations do not need rabies immunoglobulin (RIG) following an exposure, booster doses of vaccine are still needed, so all travelers should be advised to seek urgent care following potential exposures.

OTHER ADVICE

Malaria prophylaxis

Because malaria infection represents a significant risk to nonimmune travelers, prescription of malaria prophylaxis can be a critical part of the pre-travel consultation. For details, see Chapter 200, Malaria.

Food and water hygiene

Prevention of travelers' diarrhea and other food and waterborne gastrointestinal infections requires careful selection of food and beverages while traveling in the developing world. Foods that are well-cooked and still hot are safest. Fruits washed and peeled by the traveler are safe. Raw salads, salsas, and fruits eaten whole are risky. Commercially bottled carbonated beverages, alcohol, hot tea, and coffee are generally safe. Tap water consumption is generally unsafe, and only boiled, bottled (from reliable sources), or disinfected water should be consumed. Ice cubes are typically made from untreated tap water. Milk and dairy products should be pasteurized, cooked, or avoided. For more details on the treatment and prevention of travelers' diarrhea, see Chapter 121, Travelers' diarrhea.

Altitude illness

Acute mountain sickness (AMS) can occur with rapid ascent to altitudes above 8000 ft (2500 m), and symptoms can include headache, fatigue, nausea, and loss of appetite. Symptoms usually resolve with acclimatization in 1 to 3 days or descent; however, progressive ascent (e.g., in mountain climbing) can cause persistent symptoms or increase the risk of high-altitude cerebral edema or high-altitude pulmonary edema. Since many popular high-altitude destinations such as Cusco, Peru are reached by direct flight, travelers visiting these areas might be at particular risk for AMS. Susceptibility to AMS is unpredictable; therefore, prophylaxis medication such as acetazolamide should be considered for travelers going to these areas.

Injuries

Accidents can be the cause of nearly half of fatalities among international travelers. These can include traffic accidents, drownings, and other injuries resulting from outdoor activities. Travelers should be aware that traffic laws, road quality, fire codes, and other safety regulations in the developing world are typically at much lower standards, or nonexistent. Alcohol consumption is a signficiant risk factor for travel-related injury, and individuals often consume more during travel. Crimes such as robberies, sexual assault, and homicide are worldwide problems. Politically unstable countries or those in the midst of social unrest can be particularly dangerous for travelers. The US State Department provides updated travel alerts and country-specific safety advice (www.travel.state.gov).

Jet lag

Travel across several time zones typically results in disrupted sleep as the traveler's internal body clock adjusts to the local time, a process that takes about 1 day for each time zone crossed. Adequate hydration, resting after arrival, and judicious use of sedatives can help with adjustment or symptom management. Bright light exposure can help

reset the internal clock. For travel eastward, it is recommended that travelers seek bright light in the early morning, and for westward travel, exposure should be in the late afternoon. There are data supporting the efficacy of melatonin for jet lag; however, its use is controversial as supplements are unregulated and may contain contaminants.

Insect avoidance

Mosquito and other arthropod avoidance measures such as insect repellents, bednets, and permethrin-treated clothing can be important, particularly when visiting areas endemic for dengue, malaria, and other arthropod-borne infections. See Chapter 200, Malaria, for insect avoidance recommendations.

Travelers' health kit

A travel health kit can be important and might include prescription medications, over-the-counter medications (analgesics and fever medications, antidiarrheals, anti-nausea medications, antihistamines, topical medications for insect bites and rashes, etc.), a digital thermometer, oral rehydration solution packets, and first-aid supplies. Travelers should anticipate airline security regulations that restrict carry-on items. Some over-the-counter or prescription medications may be subject to more strict regulations overseas (e.g., diphenhydramine is considered a controlled substance in Zambia). Prescription medications are best carried in the original containers with the patient's name and prescribing physician information. Carrying a physician's letter that lists medical conditions and medications (with generic names and dosages) is advised.

Health and evacuation insurance

Travelers should be aware that health care obtained overseas might not be covered by their usual health insurance, and supplemental insurance might be prudent. Furthermore, medical evacuation by air ambulance is typically not covered, and travelers should consider purchasing evacuation insurance when traveling to countries where standards of care are significantly lower.

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117. Fever in the returning traveler

Alimuddin Zumla

GENERAL CONSIDERATIONS

Fever is a frequent problem in travelers, returning from holidays, business trips, or employment, outside their country of residence. In 2010, an estimated 940 million tourists arrived at international destinations and half of international travelers to developing countries become ill during their trip with approximately 8% seeking medical care for a travel-associated illness either during or after travel. A wide range of infectious and parasitic diseases can cause fever, some of which can be rapidly fatal if not detected and treated early. For example *Plasmodium falciparum* malaria is a medical emergency and prompt diagnosis and treatment is essential. All patients should be assessed for risk of malaria or viral hemorrhagic fever.

Fever in a traveler may not be specifically related to travel and may be related to more universal causes such as common cold, viral pharyngitis, sinusitis, influenza (Flu A and Flu B), bacterial pneumonia, otitis media, or urinary tract infections. The subject of this chapter is fever related to more "imported" diseases acquired during travel to which the physician practicing in the west may be unfamiliar (see Table 117.1). With the great increase in volume and speed of travel between developed and developing countries, physicians in the United States, Europe, and other developed countries are seeing more patients with imported infections.

Careful assessment of travelers with fever must involve a detailed history, a thorough examination, and targeted laboratory investigations. The following are essential in the clinical management of fever in the returning traveler:

1. A comprehensive history:
   a. Symptoms, time of onset, duration and progression and evolution of symptoms over time. Try and localize symptoms to organ systems.

Table 117.1 Causes of tropical fevers in travelers

Most common
Cosmopolitan infections (common cold, sinusitis, upper respiratory tract infections, urinary tract infections, etc.)
Malaria
Enteric fever (typhoid and paratyphoid)
Atypical pneumonia, acute respiratory tract infections (bacterial and viral pneumonia)
Hepatitis (hepatitis A, hepatitis E)
Rickettsial infections
Arboviral infections (dengue, chikungunya, yellow fever, Western equine encephalitis [WEE], Eastern equine encephalitis [EEE], and others)
Bacterial diarrhea or dysentery
Viral gastroenteritis
Protozoal diarrhea (giardiasis or amebiases)
Amebic liver abscess
Sexually transmitted diseases
Less common
African trypanosomiasis
Tuberculosis
Human immunodeficiency virus (HIV)
Brucellosis
Leptospirosis
Histoplasmosis
Atypical pneumonia (Legionnaires' disease, pulmonary histoplasmosis, psittacosis)
Acute schistosomiasis (Katayama fever)
Leptospirosis
Filariasis
Drug fever
Uncommon
Visceral leishmaniasis (kala-azar)
Cutaneous leishmaniasis
Lyme disease
Relapsing fever (borreliosis)
Melioidosis
Viral hemorrhagic fevers
Tropical pulmonary eosinophilia
Cutaneous larva migrans
Endocarditis
Noninfectious causes (malignancy, autoimmune)

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   b. Travel history – destinations, type of accommodation, prophylaxis measures taken, activities (e.g., game viewing, camping, farms, caves, swimming in lakes/rivers, sex, drug abuse, consumption of uncooked or semi-cooked food, and water source), bites (insects, ticks, fleas, lice, mites, animal, other).
2. A complete physical examination of all systems:
   Clinical features to look for are: skin rash (maculopapular, petechiae, ecchymosis), skin lesions (eschars, insect bites, erythema nodosum, boils, erysipelas), lymphadenopathy, hepatomegaly, splenomegaly, jaundice, wheeze, crackles, crepitations, joint or muscle involvement, stiff neck, photophobia, conjunctivitis, neurologic signs, or evidence of bleeding.
3. Urgent investigations:
   a. Full blood count
   b. Malaria thin and thick blood films including rapid malaria diagnostic test
   c. Blood culture
   d. Urine culture and dipstix analysis (blood, protein, sugar)
   e. Stool – bacteriology, virology, and parasitology (ova, cysts, and parasites)
   f. Blood biochemistry (C-reactive protein, urea, electrolytes, creatinine, and liver function tests)
   g. Chest x-ray
   h. Specific PCR tests on clinical specimens for those suspected of having rapidly fatal diseases e.g., arboviruses, viral hemorrhagic fevers (VHF), Middle East respiratory syndrome (MERS)-coronavirus.
4. Other investigations in persisting fever:
   a. Serology – bacterial, viral, fungal, spirochetal (save serum for paired serology)
   b. Bone marrow and/or lymph node aspirates – microscopy and culture may be required if fever persists without localizing signs.
   c. Further imaging – CT scan, PET, PET/CT scans.

The most common tropical fevers in travelers are malaria, enteric fever, hepatitis, amebic liver abscess, and rickettsial and arboviral infections.

MALARIA

Malaria is the most important potentially fatal cause of fever in travelers returning from the tropics. Thus, all febrile travelers returning from malaria endemic areas must be evaluated for malaria, even those who have taken appropriate malaria chemoprophylaxis. Antimalarial prophylaxis regimens cannot be considered fully protective.

Nearly all malaria due to *Plasmodium falciparum* present with fever within 4 weeks of returning but could present several months after leaving a malarious area. *Plasmodium vivax* and *Plasmodium ovale* malaria may occur up to 3 years after exposure due to persistence of hypnozoites (latent parasites) in the liver. *Plasmodium malariae*, which does not have a latent liver phase, is the least common species causing fever in travelers, but may present up to a year or longer (up to 20 years) after first infection. Typical symptoms are high fever, shaking, chills, sweats, headache, and myalgias. Symptoms may be modified or masked according to the immune status, as in an immune native of an endemic area, or by the use of prophylactic antimalarial drugs. Severe *Plasmodium falciparum* infections can rapidly lead to such lethal complications as cerebral malaria, renal failure, severe hemolysis, and adult respiratory distress syndrome.

Diagnosis is by appropriately prepared and carefully examined Giemsa-stained thin and thick malaria smears. A single negative set of smears cannot rule out malaria; smears should be repeated at 6-hour intervals for at least 24 hours. Rapid malaria antigen detection tests are now available. Specific prophylaxis and therapy for malaria is discussed in Chapter 200, Malaria.

ENTERIC FEVER (TYPHOID AND PARATYPHOID)

Typhoid and paratyphoid fevers can be contracted from contaminated food or water where the prevalence of these bacteria is high. Typhoid vaccines offer protection to no more than 70% of recipients. Enteric fever should be suspected in travelers returning from an endemic area with fever, headaches, abdominal pain, diarrhea, or cough. Symptoms may not develop until several weeks after return. Diagnosis is confirmed by positive blood, stool, or urine culture. The agglutinin test (Widal) lacks sensitivity and specificity and is not recommended. Newer rapid serologic tests that detect IgM antibodies to *Salmonella typhi* antigens are available. Blood and bone marrow cultures have the highest yield within 1 week of symptoms and urine and stool cultures become positive after the first week. *Salmonella typhi*

worldwide have developed multiple antibiotic resistance, including to fluoroquinolines. See Chapter 150, *Salmonella*, for specific therapy details.

HEPATITIS

Travelers to the developing world who have not received hepatitis A vaccine or immune serum globulin (ISG) run a significant risk of contracting hepatitis A from ubiquitously contaminated water or food. Rare cases of hepatitis E have been contracted in South Asia and elsewhere, and this type of hepatitis may not be prevented by ISG. Hepatitis B is usually contracted from sexual contact and is uncommon in travelers. In the preicteric phase of acute hepatitis, fever, chills, myalgias, and fatigue may occur, and this syndrome can mimic malaria and other acute tropical fevers. Hepatitis serologic testing can confirm the type of infection, but when these tests are negative in a patient with apparent hepatitis, cytomegalovirus or infectious mononucleosis (Epstein–Barr virus [EBV]) should be considered.

AMEBIC LIVER ABSCESS

A period of acute diarrhea often precedes development of an amebic liver abscess. A returned traveler with fever and right upper quadrant pain should be suspected of this infection. Stools are positive for *Entamoeba histolytica* in only 10% to 15%. Sonography or computed tomography (CT) of the liver will show a filling defect, and an amebic serology test will confirm infection. Needle aspiration is seldom required for diagnosis or treatment. There is very rapid clinical response to metronidazole, 750 mg three times daily for 10 days, followed by a luminal drug such as paromomycin (Humatin), 500 mg three times daily for 7 days.

RICKETTSIAL INFECTIONS

Tick typhus can be contracted in West, East, and South Africa and in the Mediterranean littoral. Infection typically begins with a skin eschar at the tick-bite site; fever, chills, and headache; and in a few days, a diffuse papular rash can develop. Epidemic, scrub, and murine typhus and Q fever are much less commonly contracted by travelers. Diagnosis is made by indirect fluorescent antibody tests or PCR of eschar and skin lesion for specific rickettsial organisms. Tetracycline is highly effective, and response is generally rapid. A single 200-mg dose of doxycycline may be adequate, but 100 mg twice a day for 5 to 7 days may be required for some *Rickettsia* species.

VIRAL FEVERS

Dengue fever, endemic in most parts of the tropical world, especially Asia, Africa, and the Indian subcontinent, is the most commonly imported arbovirus infection. Symptoms include fever, fatigue, headache, body and bone aches, and eye pain. Typically, a diffuse rash appears on the third to fifth day as other symptoms abate. Chikungunya virus is a mosquito-borne disease that has similar clinical symptoms to dengue but differs in causing severe joint pains rather than deep bone pain. A recent outbreak of chikungunya in islands of the Indian Ocean has led to numerous imported cases into Europe, North America, and parts of Asia. Japanese B encephalitis is a rare infection of travelers to rural areas of the Far East. A number of other rarer acute viral illnesses have been imported from endemic areas, including lethal Lassa and Marburg fever viruses from West and Central Africa. Diagnosis is usually confirmed serologically, there is no specific treatment and management is generally supportive. (See Chapter 183, Dengue, and Chapter 194, Viral hemorrhagic fevers.)

LESS COMMON FEBRILE ILLNESSES IN TRAVELERS

African trypanosomiasis is uncommon in American travelers, although it has been reported from travelers to East Africa. Even short-term travelers to game parks of East and Central Africa should take precautions against tsetse fly bites. Travelers should inform their physician of exposure if symptoms such as trypanosomal chancre at a bite site, fever, evanescent rash, headache, and lethargy develop up to 4 weeks after returning home. (See Chapter 202, Trypanosomiases and leishmaniases.)

Tuberculosis (both drug-sensitive and drug-resistant) remains a threat worldwide. Any returnee with fever, cough, and chest radiography evidence suggestive of pulmonary disease should be screened for tuberculosis. Screening with the IGRA test (interferon-gamma release assay) before and after travel is recommended.

Brucellosis is contracted from contaminated raw goat or cow milk or soft cheese. Presentation

can be with fever, chills, sweats, body aches, headache, monoarticular arthritis, weight loss, fatigue, or depression. Diagnosis is by blood culture and/or specific agglutination tests. Treatment is with a tetracycline plus streptomycin or rifampin.

Leptospirosis is common in the tropics but is rarely contracted by travelers. Infection is acquired through direct or indirect contact (such as contaminated water) with infected animals. Recreational activities, such as water sports and adventure travel, are emerging as important risk factors for this infection. Most infections are anicteric and mild. Initial symptoms may include high remittent fever, chills, headache, myalgias, nausea, and vomiting. No more than 10% of patients develop jaundice. Diagnosis is usually made with serology. Early therapy with penicillin or tetracycline is usually beneficial.

Histoplasmosis, a cosmopolitan disease, has rarely infected travelers to Latin America. Visitors to caves contaminated with bat droppings are at particular risk. Consideration should be given to histoplasmosis in a returned traveler with fever and pulmonary or, less likely, disseminated disease. Ketoconazole or itraconazole given for 3 to 6 weeks is effective treatment.

Visceral leishmaniasis (kala-azar) is extremely rare in American tourists, although European travelers have been infected around the Mediterranean littoral. Symptoms include fever, hepatosplenomegaly, and wasting. Diagnosis is confirmed by demonstrating leishmanial organisms in a biopsy specimen of liver, spleen, or bone marrow or detection of parasite DNA by PCR test. Pentavalent antimonial compounds (sodium stibogluca-mate [Pentostam] and meglumine antimoniate [Glucantime]) are first-line drugs. Second-line drugs are amphotericin B and pentamidine.

Classically associated with tick bites during visits to forests, Lyme disease occurs in Europe and the United States and may also be present in other parts of the world. Hikers in particular should take precautions against tick bites in any recognized endemic area.

Relapsing fever is caused by a spirochetal organism of the *Borrelia* spp. and occurs in a louse-borne, primarily epidemic form, and in a more widely scattered tick-borne, endemic form. The latter form is present in the western United States and has been diagnosed in returnees from that area to the eastern United States. Imported relapsing fever is uncommon, but cases have been contracted in West Africa, Spain, and Central America. Diagnosis is by finding the spirochetes in a thick or thin Giemsa-stained blood smear. Treatment is with a tetracycline.

Legionnaires' disease cases in travelers have continued to rise since its first identification in Philadelphia in 1976. Many cases are associated with travel on cruise ships, hotels, and aircraft within and outside Europe. Infection is acquired from contaminated air conditioning systems, whirlpool spas, or swimming pools. Whilst diagnosis in suspected cases can be confirmed from culture, seroconversion, and urinary antigen detection, the mainstay of clinical management for Legionnaires' disease is prompt empiric administration of *Legionella*-specific antibiotic treatment for community-acquired pneumonia and *Legionella* spp. with azithromycin, levofloxacin, or tetracyclines.

Melioidosis is endemic primarily in Southeast Asia and sporadically occurs in other areas. The majority of imported cases are seen in refugees from Southeast Asia, in returned servicemen from that area, and occasionally in tourists. An asymptomatic form of infection is most common, but acute pneumonic and septicemic forms may occur. Chronic suppurative forms may also develop in various organs. These forms can lie dormant for many years and have the capacity to flare into acute fulminant symptoms. Any patient with a pneumonic process who is returning from rural areas of Southeast Asia should be considered to have possible melioidosis. Diagnosis is by special culture techniques or by serology. The most effective treatment is with intravenous ceftazidime or imipenem or meropenem. Oral therapy is with trimethoprim–sulfamethoxazole or doxycycline.

Human immunodeficiency virus (HIV) infection is a particular hazard from sexual contact, blood transfusion, or contaminated needle or syringe contact worldwide. A number of disposable syringes and needles should be carried by the traveler who may need injection while traveling in areas where only nondisposable products are used. HIV serology screening should be done on any traveler with such exposure. Postexposure prophylaxis (PEP) involves taking anti-HIV medications as soon as possible after exposure to HIV.

Most viral and bacterial causes of diarrhea, amebic dysentery, and occasionally parasitic diarrhea due to *Giardia lamblia* may often present as intermittent diarrhea, nausea, headache, and fatigue and also cause fever, which may precede diarrhea by some hours or days. Acute schistosomiasis, acute fascioliasis, and acute bancroftian filariasis are uncommon causes of fever in travelers.

Drugs used for prophylaxis or treatment of travel-related infections may themselves be a cause of fever. These include sulfonamide-containing drugs such as trimethoprim–sulfamethoxazole and pyrimethamine with sulfadoxine (Fansidar) (used for malaria treatment). Quinine and doxycycline may rarely cause fever. Drugs obtained abroad, often in combinations and without prescription, may cause a cryptic fever. It is worthwhile to stop all nonessential medications pending an etiologic diagnosis in febrile travelers.

Whilst some illnesses with fever may begin during travel, others may occur days, weeks, or even years after return from travel. Thus travel history must be part of the routine medical history for every ill patient. Furthermore, clinicians should consider the public health implications of certain infections (such as drug-resistant tuberculosis, influenza, measles, viral hemorrhagic fever, and newer viral threats (such as the Middle East respiratory syndrome coronavirus [MERS-CoV] and H7N9 influenza) and notify appropriate public health authorities in their home countries.

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118. Systemic infection from animals

David J. Weber, Jonathan J. Juliano, and William A. Rutala

INTRODUCTION

Zoonoses are defined as diseases and infections that are transmitted between vertebrate animals and humans. Currently there are more than 200 recognized zoonotic diseases, and 75% of emerging infectious diseases fit into this category. Zoonotic diseases can be transmitted to humans through bites and scratches, direct contact, aerosols, arthropod vectors, or contamination of food or water. There are many reasons for the increased impact of zoonotics in current times. Contact with domestic animals continues to be frequent, even in urban centers. Pets are a major reservoir and source of zoonoses, especially for children. In 2011–2012, 62% of US households, or approximately 72.9 million total households, owned a pet: 39% of households owned a dog, 33% owed a cat, 5% owned a pet bird, and 4% owned a reptile. The total number of animals owned was 78 million dogs, 86 million cats, 16 million birds, and 4.6 million reptiles. Other common pets include fish, rabbits, hamsters, gerbils, mice, and farm animals such as horses.

Recent factors that have had a substantial impact on emergence of zoonotics are human encroachment on wildlife habitat, wildlife trade and translocation, the ownership of exotic pets, petting zoos, and ecotourism. The epidemics of severe acute respiratory syndrome (SARS), West Nile virus, and monkeypox in North America have demonstrated the role of wildlife and exotic pets in the emergence of zoonotic diseases in industrialized nations. Traditional leisure pursuits such as hunting, camping, and hiking are increasingly common and continue to bring people into close contact with wild animals, arthropods, and sometimes contaminated water. Occupational exposures to domestic animals or animal products, especially in backyard operations, remain a leading cause of zoonotic disease exposure.

For all of the reasons described above, it is increasingly important for physicians, veterinarians, and public health professionals to work together in recognizing and controlling zoonotic diseases. The Centers for Disease Control and Prevention (CDC) has become a World Organization for Animal Health (OIE) Collaborating Center for Emerging and Remerging Zoonoses and now dedicates an entire issue of the *Emerging Infectious Disease* journal to zoonotics. The key to controlling zoonoses continues to lie with the astute clinician diagnosing and reporting these diseases, and the goal of this chapter is to assist in these efforts.

CLINICAL APPROACH

Zoonoses are caused by a diverse group of microorganisms. Infectious syndromes caused by zoonotic pathogens are equally diverse. Hence, classification of zoonoses is difficult for the clinician. Diseases may be classified by the nature of the pathogen, animal host, mode of transmission from animal to human, geographic range of host, or clinical syndrome (i.e., systemic disease or specific organ system of infection). Although most zoonoses are relatively unusual, they must be included in the differential diagnosis of many clinical syndromes. All patients with an infectious syndrome whose cause is not apparent after a standard history and physical examination should be questioned to assess the possibility of a zoonosis. First, the clinician should question patients about exposure to pets and ask whether they own or have had recent contact with a dog, cat, bird, fish, reptile, or rodent. If contact may have occurred, the clinician should ask about a history of bites or scratches. Second, the patient should be asked about exposure to farm animals (which may also be pets) such as horses, pigs, cattle, and fowl (i.e., chickens and turkeys). The clinician should determine the amount and degree of exposure. Third, patients should be asked about leisure pursuits such as hunting, fishing, hiking, and camping. The clinician should assess specific animal contacts such as

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dressing or skinning animals, ingestion of water from streams and lakes, and bites by arthropods such as ticks (see also Chapter 119, Tick-borne disease). Fourth, the clinician should obtain a careful travel history to determine the risks of exposure to geographically limited zoonoses. In particular, it is important to ascertain whether a patient has had an animal bite or scratch while visiting an area endemic for rabies. Because the incubation period for rabies may extend for years, persons bitten or scratched by dogs or other possible rabid hosts should be considered for postinjury prophylaxis. In general, evaluation for specific zoonoses should be based on the possibility of exposure (Table 118.1).

A brief description of the approach to possible systemic infections caused by animals is provided in subsequent paragraphs. More detailed information may be found in specific chapters in this book or in the Suggested Reading at the end of this chapter.

ZOONOTIC DISEASES ACQUIRED BY ANIMAL BITE OR SCRATCH

Dog bites account for 70% to 90% of animal bites and cat bites account for 3% to 15%. Bites from wild animals constitute <1% of bite wounds. The infection rate from penetrating dog bites is approximately 3% to 12%. Cat bites are much more likely to become infected. Most dog and cat bites occur on the extremities. Males are more likely to be bitten by a dog than are females, whereas the opposite is true for cat scratches and bites. The highest incidence of dog bites is in children ages 5 to 9 years and the highest incidence of cat bites/scratches is now in adults >75 years of age. Approximately 1% of rodent bites become infected.

Although infections following animal bites may be caused by various flora, some generalizations can be made. The most common pathogen to cause infection following feline bites is *Pasteurella multocida* (see Chapter 23, Animal and human bites), which generally results in rapid progressive cellulitis similar to that caused by *Streptococcus pyogenes*. Occasionally sepsis may result, especially in the immunocomprised host. The agents of rat-bite fever, *Streptobacillus moniliformis* and *Spirillum minus*, may be transmitted by several small rodents, including the rat, mouse, and gerbil. Both agents cause a systemic illness. Infections with *Aeromonas hydrophila* may follow bites inflicted in fresh or brackish water or by aquatic animals such as snakes and alligators. Severe local infection progressing to crepitant cellulitis with systemic toxicity may occur. Although most cases of tularemia follow the handling of rabbits, infection may be transmitted by animal bites or scratches, especially domestic cats (other animals include the coyote, pig, and squirrel). *Capnocytophaga canimorsus* is an unusual systemic infection strongly associated with dog bites. More than 50% of patients have reported dog bites before clinical infection, although infection has also been reported following scratches from dogs, cat bites or scratches, and contact with wild animals. Approximately 80% of patients reported in the literature have a predisposing condition, most commonly splenectomy. Other predisposing conditions have included Hodgkin's disease, trauma, idiopathic thrombocytopenia purpura, alcohol abuse, steroid therapy, and chronic lung disease. Bites from seals, whales, and walruses may transmit a murine mycoplasma. *Erysipelothrix rhusiopathiae* is carried most commonly by swine but is also found in sheep, horses, cattle, chickens, crabs, fish, dogs, and cats. A local infection, erysipeloid, may result from bites or injury with these animals usually during occupational exposure. Thus, abattoir workers, butchers, fishermen, farmers, and veterinarians are at risk for infection with *E. rhusiopathiae*. Sepsis and endocarditis may result from local infection.

ZOONOTIC DISEASES ACQUIRED BY ARTHROPOD BITES

Due to major changes in the environment the incidence of zoonotic diseases vectored by arthropods has increased dramatically in recent years. The most significant of these diseases are vectored by ticks and include Rocky Mountain spotted fever (RMSF), Lyme disease, ehrlichiosis, and anaplasmosis. RMSF is caused by the rickettsial agent *Rickettsia rickettsii* and is the most severe rickettsial disease occurring in the United States. This disease is characterized with an acute onset of fever, malaise, headaches, chills, and in most cases a maculopapular rash. The rash of RMSF typically appears between the third and fifth days of illness but is absent in 5% to 15% of patients. Initially maculopapular, it begins on extremities, often around the wrist and ankles. As the rash progresses, it spreads centripetally to the trunk and characteristically involves the palms and/or soles. As it evolves, it becomes

Table 118.1 Infectious diseases acquired from animals

Disease	Persons at risk[a]	Birds, fowl	Cats, dogs	Farm animals	Fish, reptiles,[b] water	Rabbits	Rodents	Arthropod vectors	Wild animals
Viral									
Avian influenza (H5N)	I, V, VI	+++							
Bovine papular stomatitis	I, II			+					
California encephalitis	III, rural, public							+++	
Colorado tick fever	III							+++	
Eastern equine encephalitis	III, public							+++	
Hantavirus pulmonary syndrome	I, III, public						+++		
B virus (*Herpesvirus simiae*)	IV, V								Macaca monkeys
Lymphocytic choriomeningitis	III, IV, V, public						+++		
Milker nodule (pseudocowpox)	I, II			+					
Newcastle disease	I, II, IV, V	++							
Orf (contagious ecthyma)	I, II			+					
Powassan encephalitis	I, III, public							+++	
Rabies	III, VI, public		++	+					+++
Rotavirus	I, III, IV, public			++					
SARS-coV	I, II, IV, V								+
St. Louis encephalitis	I, III, public							+++	
Venezuelan encephalitis	I, III, public							+++	
Western equine encephalitis	I, III, public							+++	
Yellow fever	III, VI							+++	
Bacterial									
Aeromonas	III, IV, VIII, public				+++				
Anthrax (wool sorter disease)	I, II, IV, X		+	+++					
Brucellosis	I, II, III, V		+	+++					
Campylobacteriosis	I, II, III, IV	+	++	+++	++		++		
Capnocytophaga canimorsus sepsis	III, IV, IX, public		+++						

Disease	Persons at risk[a]	Birds, fowl	Cats, dogs	Farm animals	Fish, reptiles,[b] water	Rabbits	Rodents	Arthropod vectors	Wild animals
Cat scratch fever	III, IV, IX, public		+++						
Edwardsiella tarda infection	IV, VIII				++				
Ehrlichiosis	I, III, IV, VI, IX, public							+++	
Erysipeloid	I, II, III, VIII	++	+	+	++		++		
Leptospirosis	I, III, IV, V	++	+	++	+		++		
Listeriosis	IX, public	+	+	+++		+			
Lyme disease	I, III, IV, VI, public							+++	+
Murine typhus	I, III, VI						(Vector)	+++	
Mycobacteriosis (*M. marinum*)	VIII				+++				
Pasteurellosis	III, IV, public	+++	+++			++			++
Plague	III, IV, V, VII, X		+				++		
Plesiomonas infection	VIII				+++				
Psittacosis	I, II, III, IV, V, VI	+++							
Q fever	I, II, V		++	+++					++
Rat-bite fever	I, III, IV						++		
Relapsing fever	I, III, IV							+++	(Vector)
Rhodococcus	I, II, IV			++					
Rocky Mountain spotted fever	I, III, IV, IX, public		(Vector)					+++	
Salmonellosis	I, II, III, IV, VIII, IX	+++	+	+++	+++	+++	+++	+	+++
Staphylococcus aureus infection	I, II, IV, V, IX		+	++					
Group A streptococcal infection	I, II, IV, public		+	+					
Tuberculosis	I, V, IX	+	+			+			
Tularemia	I, III, IV, X		++	++		+++	++	+++	++
Vibriosis	III, VIII					++			
Vibrio vulnificus infection	VIII, IX					+++			
Yersiniosis	I, II, III, IV, VIII	+	+	++	+	++	++		
Fungi									
Ringworm	I, II, III, IV, V, VI		++						

Table 118.1 *(continued)*

Disease	Persons at risk[a]	Birds, fowl	Cats, dogs	Farm animals	Fish, reptiles,[b] water	Rabbits	Rodents	Arthropod vectors	Wild animals
Parasites									
Babesiosis	III, IV, IX							+++	
Cryptosporidiosis	I, II, III, IV, VI, IX	+	++	+++	++	+	+		
Cystircercosis	Public		++						
Dipylidiasis	IV		++						
Dirofilariasis	III		(Vector)					+++	
Echinococcosis	I		+	++					
Giardiasis	I, III, IV	+			++		+		+++
Toxocariasis	IV		++						
Toxoplasmosis	IV, IX		+++	+					
Trichinosis	Public			+					++

Abbreviation: SARS-coV = severe acute respiratory syndrome-coronavirus.

+, Rare source; ++, occasional source; +++, most-common source; (vector), not spread directly by animal but always via vector.

[a] Persons at risk: Group I (agriculture), farmers and other people in close contact with livestock and their products; group II (animal-product processing and manufacture), all personnel of abattoirs and of plants processing animal products or by-products; group III (forestry, outdoors), persons frequenting wild habitats for professional or recreational reasons; group IV (recreation), persons in contact with pets or wild animals in the urban environment; group V (clinics, laboratories), healthcare personnel who attend patients and healthcare workers, including laboratory personnel, who handle specimens, corpses, or organs; group VI (epidemiology), public health professionals who do field research; group VII (emergency), public affected by catastrophes, refugees, or people temporarily living in crowded or highly stressful situations; group VIII (fisherman), people catching or cleaning fish or engaging in recreational activities in the water; group IX (immunocompromised hosts), people who are immunocompromised because of immunodeficiency, cancer chemotherapy, organ transplants, immunosuppressive medications, liver and/or renal disease; group X (disaster responders, public), potential bioterrorist agent.

[b] Reptiles include lizards, snakes, and turtles.

[c] Rodents include hamsters, mice, and rats.

more clearly defined and more petechial and may rarely progress to skin necrosis and gangrene. RMSF has a case-fatality rate of 13% to 25% when untreated. Lyme disease has been reportable since 1992, and almost 10 000 cases were reported that year. In 2011 there were approximately 24 000 definite and 9000 probable cases of Lyme disease reported in the United States. Lyme disease is characterized by a distinctive circular rash, called erythema migrans (EM). Erythema migrans is characteristically an expanding annular erythematous plaque with central clearing, most commonly seen in the axilla, thigh, and groin. Color varies from pink to violaceous. Erythema migrans may last up to 4 weeks and may recur during the secondary stage of infection. Ehrlichiosis is a tick-borne disease caused by *Ehrlichia chaffeensis*, *E. ewingii,* and *E muris*-like which is characterized by fever, headache, malaise, mylagias, nausea/vomiting/diarrhea, and conjunctival injection and rash (in up to 60% of children, less than 30% of adults). It is a serious disease with a case-fatality rate of 1.8%. Anaplasmosis is a tick-borne disease caused by *Anaplasma phagocytophilum*. Symptoms are similar to ehrlichiosis but rash is rare.

Mosquito-borne zoonotic diseases are common and significant throughout much of the world but play only a minor role domestically. The most common in the United States is West Nile virus. The vast majority of infected have subclinical or mild disease, whereas 1 in 150 infected will develop encephalitis. A unique feature is the ascending paralysis ("West Nile polio"). Other mosquito-borne zoonotics that occur in the United States are western equine encephalitis (WEE), eastern equine encephalitis (EEE), St. Louis encephalitis, and Lacrosse encephalitis. Other than EEE, these agents generally cause mild disease but can occasionally cause severe encephalitis in immunocompromised patients. EEE is rare but has a case-fatality rate of about 33%.

Plague, caused by *Yersinia pestis*, persists in wild rodents in the western half of the United States and is vectored by rodent fleas. Tularemia, caused by *Francisella tularensis*, occurs throughout the entire United States and is vectored by

ticks, deer flies, and other insects. Tularemia also has several reservoirs such as rabbits, voles, and badgers. Both plague and tularemia may cause local skin and soft-tissue infection and serious systemic illness.

ZOONOTIC DISEASES ACQUIRED BY INHALATION

Although community-acquired pneumonia (CAP) is a common disease, few cases of pneumonia are due to zoonotic agents. Lower respiratory infection due to zoonotic agents generally causes an "atypical" pneumonia and may be mistaken for infection caused by *Legionella* spp., *Mycoplasma pneumoniae*, or *Chlamydia pneumoniae*. Zoonotic diseases that may be acquired in the home include *P. multocida* infection (cats and dogs), psittacosis (birds), and Q fever (parturient cats). Hunting or hiking in the United States may bring people into contact with animals capable of transmitting brucellosis (farm animals), plague (rodents, ground squirrels, prairie dogs), Q fever (farm animals, cats), tularemia (rabbits), and RMSF (ticks). The hantavirus cardiopulmonary syndrome (HCPS) due to Sin Nombre virus (SNV) results from inhalation of aerosols of excreta from infected rodents and is characterized by fever, headache, myalgias, and respiratory failure with a mortality rate of ~40%. In 2012 there was an outbreak in people visiting Yosemite National Park. Persons engaged in processing animal products such as hides are at risk for brucellosis and anthrax.

Few zoonotic pneumonias are capable of being transmitted from person to person. However, person-to-person transmission has been reported of avian influenza (H5N1 strain), *Coxiella burnetii* (Q fever), *Mycobacterium bovis*, and *Y. pestis* (plague). Avian influenza (H5N1) and pneumonic plague represent potentially serious nosocomial pathogens, and patients with these diseases should be placed on isolation precautions. Several zoonotic agents acquired via the respiratory route are potential agents of bioterrorism, including anthrax, brucellosis, plague, Q fever, and tularemia. Because of transmissibility and global migration, zoonotic pneumonias have the potential to cause significant epidemics across continents. A worldwide epidemic of SARS occurred in 2003 due to a novel coronavirus (SARS-coV). Molecular epidemiology suggested transmission from the palm civet and that the ultimate reservoir for the virus was bats. In 2009 a variant H1N1 triple assortment strain (human, avian, pig) led to a worldwide pandemic of influenza.

ZOONOTIC DISEASES ACQUIRED VIA INGESTION

Zoonotic diseases acquired through ingestion are the most commonly acquired zoonotic diseases in the world. The main category is bacterial diarrhea, with fever and abdominal cramps. *Campylobacter* is the most common agent and is normally found in the intestines of birds. Birds are also the primary reservoir of *Salmonella*, but it can also be found in many reptiles and mammals. The main reservoir of *Escherichia coli* O157:H7 is cattle and similar ungulates. One possible consequence of infection with *E. coli* O157:H7, especially in children and the elderly, is hemolytic-uremic syndrome (HUS), with hemolysis and renal failure. Brucellosis and listeriosis are bacterial foodborne zoonotic diseases of increasing importance in the United States due to the consumption of unpasteurized dairy products, causing a generalized febrile illness. Pregnant women are at higher risk for severe listeriosis.

There are also zoonotic agents that are transmitted via contaminated water. The most common disease is cryptosporidiosis, a protozoal disease spread by drinking and recreational water throughout the entire United States. Cryptosporidiosis generally causes a self-limited mild diarrheal illness. Giardiasis is also a protozoal waterborne zoonotic disease that is common and causes a mild diarrheal illness. Leptospirosis is generally transmitted through contaminated water. Although not common in the United States, there are sporadic outbreaks. Most cases produce a febrile illness that may progress to severe hepatic, renal, or neurologic disease. The reservoirs for leptospirosis are rodents, cattle, pigs, and small mammals (e.g., raccoons, opossums).

SYSTEMIC INFECTIONS RESULT FROM ZOONOTIC DISEASES

Many zoonoses cause severe systemic symptoms. The range of possible pathogens can often be narrowed if the patient manifests specific organ involvement. Diseases to consider in patients with fever without focal signs on initial history and

physical examination include *Aeromonas* sepsis, babesiosis, brucellosis, *C. canimorsus* sepsis, ehrlichiosis, cat scratch disease, leptospirosis, listeriosis, plague, Q fever, rat-bite fevers, relapsing fever, RMSF and other rickettsial infections, salmonellosis, tularemia, and viral hemorrhagic fevers.

Zoonoses may be associated with skin lesions. A generalized maculopapular rash may accompany cat scratch fever, Colorado tick fever, ehrlichiosis, leptospirosis, lymphocytic choriomeningitis, psittacosis, RMSF and other rickettsial infections (exceptions include Q fever and trench fever), rat-bite fever resulting from *Spirillum minus*, relapsing fever, and salmonellosis. Most rashes associated with zoonoses are too nonspecific to be of significant clinical utility. Crepitant or gangrenous lesions may complicate *Aeromonas*, *C. canimorsus*, or *Vibrio vulnificus* and related species. Petechial and purpuric lesions may occur with viral hemorrhagic fevers (e.g., dengue, yellow fever, Ebola, Lassa), RMSF, *Rickettsia prowazekii* infection, rat-bite fever resulting from *Streptobacillus moniliformis*, relapsing fever, and *C. canimorsus* sepsis. A local eschar often occurs with *Rickettsia conorii*, *Rickettsia australis*, *Rickettsia sibirica*, *Rickettsia akari*, and *Rickettsia tsutsugamushi*. Local skin lesions with or without lymphangitis may occur with cat scratch fever, rat-bite fever resulting from *Spirillum minus*, and tularemia.

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119. Tick-borne disease

Steven C. Buckingham

Ticks can transmit numerous bacterial, parasitic, and viral pathogens to humans, and the secretions of some species can induce allergic reactions or cause paralysis. This chapter aims to provide a broad overview of tick-borne infections endemic to North America and to discuss general principles regarding their epidemiology, therapy, and prevention. Details about each of these infections are provided in their respective chapters.

EPIDEMIOLOGY

Tick-borne infections occur most often in the spring and summer, when ticks are most active, but are reported in colder months as well. Some patients with tick-borne infections will recall a recent tick bite, and many, but not all, report having spent time in a rural or wooded area within 2 to 4 weeks before the onset of illness. Frequently, however, patients are unaware of their recent tick exposure, for several reasons: Tick bites are usually painless, ticks may attach in sites covered by hair or clothing, and ticks in their larval and nymphal stages are very small but still capable of transmitting infection. Tick-borne infections have been reported in urban areas and, in endemic areas, among patients whose only outdoor exposures occurred in their own backyards. Thus the historical findings of tick bite or outdoor exposure may provide useful diagnostic clues, but their absence never excludes the possibility of a tick-borne illness.

Clinicians must understand the epidemiology of tick-borne infections to make presumptive diagnoses. The geographic distributions of tick-borne infections (listed in Table 119.1) correspond to the distributions of their associated tick vectors; thus, patients' geographic residence and travel history are keys to deciding which tick-borne illnesses are possible or likely.

CLINICAL MANIFESTATIONS

Most tick-borne infections present with nonspecific signs and symptoms, similar to those observed in viral syndromes (e.g., fever, malaise, headache, and myalgias). Sometimes, certain constellations of symptoms suggest a specific diagnosis. For example, the combination of erythema migrans, arthritis, and neurologic abnormalities suggests Lyme disease, whereas a cutaneous ulcer with associated regional adenopathy suggests tularemia.

Some of the typical physical and laboratory findings associated with specific tick-borne infections endemic to the United States are listed in Table 119.1. It must be emphasized, however, that not all patients with these illnesses will have all of their typical findings; for example, fewer than two-thirds of patients with Rocky Mountain spotted fever (RMSF) have the "classic triad" of fever, rash, and headache. Moreover, these illnesses have broad differential diagnoses; for example, the symptoms and signs of RMSF overlap considerably with those of ehrlichiosis, brucellosis, salmonellosis, Q fever, numerous viral infections (e.g., Epstein–Barr virus, cytomegalovirus, and enterovirus) and many other illnesses.

THERAPY

Tick-borne infections should, in general, be diagnosed presumptively, based on clinical findings and epidemiologic history. Because most specific tests yield negative results in early disease or must be sent out to a reference laboratory, the clinician often must prescribe antibiotics empirically (i.e., before a diagnosis is confirmed by laboratory testing). This is particularly true with regard to RMSF, in which mortality rates are significantly higher among patients who receive antirickettsial therapy on the fifth day of illness or later.

Details regarding the treatment of specific tick-borne infections are provided in the respective

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Table 119.1 Principal tick-borne diseases of the United States

Disease	Organism	Geographic distribution and vector	Typical clinical findings[a]
Rocky Mountain spotted fever (RMSF)	*Rickettsia rickettsii*	Eastern United States: *Dermacentor variabilis* (dog tick) Mountain West: *Dermacentor andersoni* (wood tick) Southwestern deserts: *Rhipicephalus sanguineus* (brown dog tick)	Fever, headache, petechial rash, hyponatremia, thrombocytopenia
Rickettsia parkeri infection	*Rickettsia parkeri*	Southeastern United States: *Amblyomma maculatum* (Gulf Coast tick)	Similar to RMSF, but with eschar at inoculation site; rash may be vesicular or pustular; gastrointestinal symptoms less prominent
Human monocytotropic ehrlichiosis (HME)	*Ehrlichia chaffeensis*	Southeastern and southcentral states: *Amblyomma americanum* (Lone Star tick)	Similar to RMSF, but rash less common; leukopenia, thrombocytopenia, elevated transaminases
Human granulocytotropic anaplasmosis (HGA)[b]	*Anaplasma phagocytophilum*	Northeast and upper Midwest: *Ixodes scapularis* (blacklegged tick) Pacific coast: *Ixodes pacificus*	Similar to HME, but rash is rarely present
Ehrlichia ewingii infection	*Ehrlichia ewingii*	Southeastern and southcentral states: *A. americanum*	Same as HGA
Lyme disease	*Borrelia burgdorferi*	Northeast and upper Midwest: *I. scapularis* Pacific coast: *I. pacificus*	First stage: fever, erythema migrans Second stage: multiple skin lesions, conjunctivitis, arthralgias, myalgias, headache, cranial nerve palsies Third stage: arthritis; encephalopathy, dementia, peripheral neuropathy
Southern tick-associated rash illness	*Borrelia lonestari*	Southeastern and southcentral states: *A. americanum*	Rash similar to erythema migrans
Endemic relapsing fever	*Borrelia hermsii* *B. turicatae* *B. parkeri*	Western mountains and deserts: *Ornithodoros* species	Fever, chills, relapsing course
Tularemia	*Francisella tularensis*	Eastern United States: *D. variabilis* Mountain West: *D. andersoni* Southeastern and southcentral states: *A. americanum*	Fever, cutaneous eschar, lymphadenopathy, pulse–temperature dissociation
Babesiosis	*Babesia microti*	Northeast, Midwest, and West Coast: *I. scapularis*, other *Ixodes* species	Fever, malaise, headache, hepatosplenomegaly, thrombocytopenia, hemolytic anemia
Colorado tick fever	Coltivirus	Mountain West: *D. andersoni*	Fever, headache, leukopenia, thrombocytopenia; biphasic course
Powassan encephalitis	Powassan virus	Northeastern, north-central United States: *Ixodes* species, *D. andersoni*	Headache, seizures, altered sensorium, focal neurologic signs, meningismus
Tick paralysis[c]	Neurotoxin	Widespread: *Dermacentor* species, others	Ascending flaccid paralysis

[a] Not all patients will have all of the "typical" findings for these diseases. Many cases present simply with fever and vague constitutional symptoms.
[b] Formerly termed *human granulocytic ehrlichiosis*.
[c] Tick paralysis is not caused by an infection, but its epidemiology is similar to that of tick-borne infections.

chapters. Generally speaking, doxycycline is appropriate for treatment of most tick-borne infections endemic to North America. At one time, chloramphenicol was advocated for use in children younger than 8 years, owing to concerns over doxycycline's perceived potential to stain permanent teeth. Now, however, doxycycline is recognized as the drug of choice for the treatment of all suspected rickettsioses or ehrlichioses in North America, regardless of the patient's age. The principal reason for this change is that doxycycline treatment achieves superior outcomes in patients with RMSF

or human monocytic ehrlichiosis, compared to chloramphenicol. Moreover, doxycycline does not penetrate teeth as well as tetracycline does; whereas repeated administrations of tetracycline to young children certainly can cause unsightly tooth discoloration, there is no evidence that a single course of doxycycline will do so.

PREVENTION OF TICK-BORNE DISEASES

Prevention of tick-borne diseases consists of avoidance of tick bites and prompt removal of attached ticks. During spring and summer months, it is prudent to examine persons and pets that have been outdoors at least daily for attached ticks. Wearing light-colored clothing will facilitate the identification of ticks. Nymphs and larvae are very small and may hide in areas such as the head, neck, axillae, belt line, or scrotum; thus, these areas must be scrutinized closely.

Attached ticks should be removed by grasping with tweezers close to the skin and pulling gently with steady pressure; the bite site should then be washed with soap and water. Attempts to detach ticks by applying petroleum jelly, fingernail polish, isopropyl alcohol, or a hot, extinguished kitchen match are discouraged, as these methods are both ineffective and potentially dangerous.

The repellant *N,N*-diethyl-*meta*-toluamide (DEET) is very effective for preventing tick, mosquito, chigger, and fly bites. Because protection increases with increasing concentrations, repellants containing 20% to 30% DEET are currently recommended for adults and children. When used appropriately, DEET is quite safe; concerns over its toxicity have been vastly overstated. Nevertheless, a few cautionary statements are in order. DEET must not be ingested and should be applied only to exposed, intact skin, or to clothing. It should not be introduced to the mouth, eyes, or other mucous membranes (and thus should not be applied to the hands of children). Children should not apply DEET-containing products to themselves, and DEET is not recommended for use on children younger than 2 months. DEET should not be overused; in most cases, one application per day is adequate. Treated skin should be washed with soap and water after coming indoors.

Permethrin is an insecticide that may be sprayed on clothing, providing an additional layer of protection against tick bites (and those of other arthropods). Clothes should be sprayed on each side of the fabric for 30 to 45 seconds and allowed to dry for 2 to 4 hours before wearing. Permethrin maintains potency for at least 2 weeks after application, even if clothes are washed. Although permethrin is occasionally associated with skin erythema or edema, systemic adverse effects have not been noted.

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120. Recreational water exposure

Andrea K. Boggild and Mary Elizabeth Wilson

Many common forms of recreation involve water exposure. Pathogens in water infect susceptible humans by multiple routes: through skin and mucous membranes, via inhalation of aerosols, aspiration, and ingestion. Clinical manifestations of these infections range from superficial skin lesions to fatal, systemic infections. The survival of many water-associated pathogens is influenced by climate, season, other environmental conditions, and the level of sanitation. The types and abundance of organisms vary depending on the salinity, pH, temperature, and other characteristics of the water. Hence, many are found only or primarily in certain geographic regions or during some seasons of the year. The risk of infection by waterborne pathogens is a function of the duration and type of exposure, concentration density of organisms in water, and host immunity. This chapter describes the types of pathogens, geographic distribution, sources and routes of transmission, clinical presentations, and management of water-associated infections. Water can also be a source of toxins, including heavy metals. Oceans and beaches are the sites of marine envenomations. These topics are beyond the scope of this chapter.

Visits to recreational water venues are common, as are outbreaks of infections related to them. In the United States in 2007–2008, for example, 134 waterborne disease outbreaks in 38 states were reported to the Centers for Disease Control and Prevention (CDC). Almost 14 000 persons were affected by these outbreaks, with at least 74 associated hospitalizations and 17 deaths. Over the past 20 years, the number of reported diarrheal illnesses following recreational water exposure has steadily increased. Of the 134 outbreaks reported in 2007–2008, more than half ($n = 81$) were outbreaks of gastroenteritis, whereas dermatitis, acute respiratory illness, meningoencephalitis, and mixed infections accounted for smaller respective percentages. Cryptosporidiosis, giardiasis, *Escherichia coli* O157:H7 gastroenteritis, norovirus, shigellosis, leptospirosis, and *Pseudomonas* dermatitis have been the most commonly reported infections related to recreational water exposures in the United States in recent years. Outbreaks of adenovirus 3 (causing pharyngitis), cercarial dermatitis, and hepatitis A (public swimming pool) have also been reported. Chlorinated swimming pools, water parks, lakes, ponds, and whirlpools have been common sources. Although outbreaks related to recreational water use can occur throughout the calendar year, most occur in the summer months, with 62% of recreational water outbreaks in 2007–2008 beginning in June, July, or August.

Table 120.1 Types of activities associated with water exposure

Swimming, wading, diving
Near-drowning events
Fishing, hunting
Rafting, boating, kite sailing, sailing, surfing, windsurfing, water-skiing
Water parks (wave pools and water slides)
Sitting in hot tubs, whirlpools
Showering and bathing, ritual washing
Drinking water and water-containing beverages (untreated surface water consumed during hiking, camping)
Care of fish tanks, aquaria

Patients typically do not volunteer specific descriptions of water exposures, as they may not recognize their relevance. Table 120.1 lists several sources of water exposures that have been associated with infections and can be used as a checklist to help the clinician obtain relevant history. Most water-associated infections will become apparent within hours to days (usually $\leq$14 days) of exposure. An important exception is schistosomiasis, which may first manifest months or longer after exposure. Relevant history includes types of exposures; dates, duration, and location of exposures; and type of water (e.g., mountain stream, lake, hot tub, chlorinated pool, salt water). During

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Table 120.2 Clinical manifestations of infections related to recreational water exposure

Skin and mucosal surface exposure
Conjunctivitis
Keratitis
Otitis externa
Dermatitis (including folliculitis)
Mastitis
Cellulitis
Fasciitis
Endometritis (reported after intercourse in water)
Systemic infection
Aspiration, inhalation, ingestion
Pharyngitis
Sinusitis
Meningoencephalitis
Pneumonitis
Gastroenteritis, colitis
Systemic infection

participation in water sports, people commonly ingest water and inhale aerosols.

Ingestion of contaminated water, whether during swimming, showering, or drinking often causes infections manifested by diarrhea. Some pathogens have the capacity to cause systemic infection after ingestion. Fecally contaminated water may contain a potpourri of microbes – bacteria, viruses, protozoa, and helminths – causing a variety of illnesses with differing manifestations and incubation periods. Swimming at beaches near a sewage outlet, for example, leads to increased rates of conjunctivitis, otitis externa, skin and soft-tissue infections, as well as gastrointestinal infections. Interactive fountains are known to be particularly vulnerable to contamination as they are open to young children, the homeless, and animals, and recirculate potentially contaminated water back onto users.

Recreational water activities are often group activities, so contaminated water may be associated with outbreaks, sometimes involving dozens or even hundreds of people. In addition to caring for the acutely ill patient, the clinician must consider the public health implications and alert the appropriate authorities. Early interventions may slow or halt an outbreak and allow early recognition of other cases. In many instances, outbreaks are the result of inadequate operation or maintenance procedures. For example, in a recent US-wide inspection of >5000 spas, nearly 3000 were found to be in violation of water quality and other maintenance parameters, resulting in the immediate closure of 11% of those inspected. As further illustration of this point, in August 2003, inadequate disinfection of an athletic facility spa resulted in an outbreak of methicillin-resistant *Staphylococcus aureus* (MRSA) skin infections among college football players, thus establishing this emerging pathogen as one with potential for waterborne transmission. A review of 18 outbreaks of *Pseudomonas* from spas implicated substandard levels of chlorination in each case.

The route of entry may influence the clinical findings for several of the water-associated pathogens, with skin penetration causing local wound infections and ingestion causing diarrheal infections. Table 120.2 lists the range of clinical manifestations of infections that follow water exposure. With some of the more virulent organisms or in the setting of immune compromise, infection may enter the bloodstream after any one of several entry points. Minor trauma, cuts, bites, and breaks in the skin can provide the portal of entry for many water-dwelling microbes. Table 120.3 summarizes infections and infestations that enter through the skin. Table 120.4 lists specific infections acquired via aspiration, inhalation, and ingestion.

Several water-associated infections and intoxications can be rapidly progressive or can lead to serious complications. Because some of these are infrequent or rare, they may be unfamiliar to most physicians. The following section provides a brief summary of each. More common infections, such as shigellosis, campylobacteriosis, salmonellosis, and *E. coli* O157:H7 that can be acquired through water exposure are covered in more detail in other chapters of this book. Table 120.5 lists the recommended treatment for the less familiar water-associated infections and ones that are not covered in other chapters of the text.

ACQUIRED BY PENETRATION THROUGH SKIN

Pseudomonas dermatitis or folliculitis

Use of hot tubs and whirlpools (spas), and occasionally swimming pools and water slides, has been associated with development of a characteristic diffuse rash caused by the aerobic, gram-negative organism *Pseudomonas aeruginosa*. The rash, which is maculopapular or vesiculopustular and usually pruritic, develops within 48 hours of exposure and typically resolves within a week. Lesions are more prominent in areas covered by a bathing suit or clothing. Associated findings may include otitis externa, mastitis (in men and women), conjunctivitis, and lymphadenopathy.

Table 120.3 Infections and infestations acquired via percutaneous and permucosal recreational water exposure

Pathogen or disease	Source
Bacteria	
Aeromonas hydrophila[a,b]	Freshwater streams, lakes, soil
Burkholderia pseudomallei (melioidosis)[a,b]	Fresh water, soil (tropics, subtropics)
Chromobacterium violaceum[a,b]	Freshwater rivers, soil (tropics, subtropics)
Leptospirosis[b]	Fresh water contaminated with animal urine (especially tropics, subtropics)
Mycobacterium marinum[a]	Fish tanks, swimming pools
Pseudomonas aeruginosa[a]	Hot tubs, whirlpools, swimming pools
Vibrio vulnificus, other vibrios[a,b]	Seawater
Tularemia[a,b,c] (*Francisella tularensis*)	Fresh water contaminated by infected animal; inoculation of skin, conjunctiva, oropharyngeal mucosa
Helminths	
Schistosomiasis[a,b]	Freshwater streams, lakes (focal in Asia, Africa, South America, parts of Caribbean)
Cercarial dermatitis (avian schistosomes)[a]	Fresh and salt water (worldwide)
Protozoa	
Acanthamoeba species[a,b] (keratitis); *Naegleria fowleri*[b]; *Balamuthia mandrillaris*[a,b]	Fresh water, especially stagnant ponds during hot summers; hot tubs, swimming pools, thermal springs
Viruses	
Adenovirus[a,b] (swimming pool conjunctivitis)	Swimming pools; likely other freshwater sites
Coxsackieviruses[a,b]	Fresh water
Other	
Seabather's eruption[a]	Seawater

Note: *Pseudomonas* dermatitis and *M. marinum* are rarely associated with systemic infection, primarily in compromised hosts.

[a] Skin and soft tissue.

[b] Systemic infection.

[c] Conjunctivitis.

Infection is typically self-limited in healthy hosts; immunocompromised persons may develop hemorrhagic bullae, pneumonia, and bacteremia. In 2007–2008, four outbreaks caused by *Pseudomonas* were linked to hotel/motel pools or spas, and led to 52 cases of skin- or ear-related disease. Infections can be prevented if water is maintained at a pH of 7.2 to 7.8 with adequate chlorination (free, residual chlorine levels should be in the range of 2.0 to 6.0 mg/L), with levels <0.5 mg/L consistently detected in outbreak situations.

OTITIS EXTERNA (SWIMMER'S EAR)

Infection of the external ear canal, otitis externa, is common in swimmers. Usual symptoms are mild pain and pruritus around the ear. Pain may become more severe if infection progresses to involve deep tissues and bone, as more commonly occurs in patients with underlying medical conditions, such as diabetes mellitus. Common organisms are *S. aureus* and *P. aeruginosa*; multiple bacterial species are often recovered from cultures. Purulent drainage and local lymphadenopathy may develop. Occasionally infections progress to cellulitis that requires systemic antibiotic therapy. Topical therapy can be effective in early infections. See Chapter 6, Otitis media and externa, for treatment.

Cercarial (schistosome) dermatitis

Cercarial dermatitis, also known as swimmer's or clam digger's itch, is caused by an allergic response to penetration of skin by cercariae of nonhuman larval trematodes of the genus *Schistosoma* (often avian schistosomes). A pruritic, maculopapular rash develops in water-exposed areas of the body (Figure 120.1). Both total duration of exposure and duration of exposure to shallow water correlate with increased likelihood of developing cercarial dermatitis. Shallow water exposure is a particular risk factor as this is where snail beds are most dense and cercarial accumulation is greatest. In 2007–2008, four outbreaks of cercarial dermatitis in the United States were linked to recreational water exposure.

Lesions appear hours to a day or more after water exposure and are often less prominent in areas covered by a bathing suit or other protective clothing. Papules may become vesicular. Secondary bacterial infection may result from scratching-related skin abrasions. Lesions peak in 2 to 3 days and typically resolve over 1 to 2 weeks without specific therapy. In persons with previous exposures lesions may develop sooner and may be more severe. Treatment is symptomatic and may include antihistamines and topical steroids. Systemic steroids have been used in severe cases. Nonhuman schistosomes are widely distributed, including in temperate areas, and may contaminate fresh, brackish, and seawater.

Schistosomiasis

Penetration of the skin by human schistosomes (e.g., *Schistosoma mansoni*, *Schistosoma haematobium*, *Schistosoma japonicum*, *Schistosoma mekongi*)

Table 120.4 Specific infections or toxins acquired via inhalation, aspiration, or ingestion during recreational water exposure

Disease or pathogen	Main clinical finding
Adenovirus 3	Pharyngitis, fever, conjunctivitis
Amebiasis (*Entamoeba histolytica*)	Colitis, liver abscess
ARTRI (aerosolized red tide respiratory irritation)	Rhinorrhea, cough, bronchospasm
Balantidiasis (*Balantidium coli*)	Diarrhea or dysentery
Campylobacteriosis	Diarrhea
Cholera (*Vibrio cholerae*)	Diarrhea, dehydration
Coxsackieviruses	Diarrhea
Cryptosporidiosis	Diarrhea, fever, nausea, vomiting
Cyclospora	Diarrhea, fever, nausea, vomiting
E. coli O157:H7	Bloody diarrhea
Free-living amoebae (especially *Naegleria fowleri*)	Meningoencephalitis
Giardiasis	Subacute diarrhea, fever, nausea, vomiting
Hepatitis A virus	Acute hepatitis
Hepatitis E virus	Acute hepatitis (potentially fatal in pregnancy)
Legionnaires' disease (*Legionella*)	Pneumonia
Leptospirosis	Fever, severe myalgia, conjunctival suffusion; may cause severe icterohemorrhagic fever
Melioidosis	Pneumonia, sepsis, skin lesions; protean manifestations
Norovirus ("Norwalk-like viruses")	Diarrhea, vomiting
Pfiesteria (possible estuary-associated syndrome)	Eye irritation, cough, rash, vomiting, abdominal cramps, neurocognitive changes
Poliovirus	Nonspecific febrile illness; flaccid paralysis $\leq$1%
Pontiac fever (*Legionella*)	Fever (self-limited)
Primary amebic meningoencephalitis (PAM)	See Free-living amoebae
Rotavirus	Watery diarrhea
Salmonellosis	Diarrhea; extraintestinal manifestations if bacteremic diarrhea; dysentery
Shigellosis	Diarrhea, dysentery
Toxoplasmosis	Fever, lymphadenopathy, lymphocytosis
Tularemia	Fever, lymphadenopathy, pneumonia; manifestations depend on route of transmission
Typhoid/paratyphoid fever (enteric fever due to *Salmonella enterica* serotype Typhi or Paratyphi)	Fever, systemic infection, gastrointestinal sequelae
Vibrio parahaemolyticus	Watery diarrhea; occasionally dysentery
Vibrio vulnificus	Sepsis, bullous skin lesions; high rate of hospitalization and mortality
Yersinia enterocolitica	Fever, diarrhea, acute mesenteric lymphadenitis

may cause redness, urticaria, and pruritic papules, typically less severe than the cercarial dermatitis described above. Systemic manifestations of schistosomiasis may develop months or years later. Among 28 travelers who developed schistosomiasis after water exposure in Mali, 36% gave a history of schistosomal dermatitis. Infection can follow even brief water exposure, including river rafting. Attack rates have often been high in travelers who swim, wade, or bathe in infested water. An acute illness characterized by fever, malaise, and eosinophilia (Katayama syndrome) may develop 2 to 6 weeks after exposure and corresponds to larval migration following initial skin penetration. Dry cough, dyspnea, and pulmonary infiltrates may be present. Neurologic complications (including transverse myelitis) can occur early or late. Clinical findings vary with the species of schistosome and are related to granulomatous reactions to eggs in tissue (Figure 120.2). Maps showing the geographic distribution of schistosomiasis are found on World Health Organization (WHO) and CDC websites and in the CDC reference.

Seabather's eruption (also marine dermatitis or sea lice)

Seabather's eruption is caused by penetration of the skin by *Linuche unguiculata*, *Edwardsiella lineata*, and other larvae of the phylum Cnidaria. Characteristic findings include an intensely pruritic, papular rash that begins 4 to 24 hours after swimming in the ocean. The lesions are found in areas covered by a bathing suit and at points of contact (e.g., flexural areas, wristbands of diving suits). The tiny larvae are entrapped by the bathing suit, which acts as a mechanical stimulus for the release of nematocysts and injection of toxin by the larvae. Outbreaks are sporadic. Persons with extensive involvement may have systemic symptoms, including fever. Lesions usually clear within 10 days. Antihistamines and topical steroids may provide symptomatic relief. Systemic steroids have been used in severe cases.

Table 120.5 Diagnosis and treatment of selected infections

Pathogen or disease	Diagnosis[a]	Treatment
Aeromonas hydrophila	C	TMP–SMX or FQ[b,c] (third-generation cephalosporins; AG; imipenem)
Burkholderia pseudomallei	C	Ceftazidime[b,c] (imipenem[b,c] or meropenem; TMP/SMX + doxycycline[c])
Chromobacterium violaceum	C	Limited clinical data; may be sensitive to FQ, TMP–SMX, tetracyclines, AG, extended-spectrum penicillins
Francisella tularensis (tularemia)	S, C	Gentamicin,[b] streptomycin,[b] or tobramycin[b] (doxycycline or ciprofloxacin; chloramphenicol)
Leptospirosis	S, C	Penicillin G[b,c] or doxycycline[b]
Mycobacterium marinum	C (at 30°C), M	Minocycline or clarithromycin (TMP–SMX; rifampin + ethambutol; doxycycline)
Primary amebic meningoencephalitis (due to free-living amoebae)	Visualization of trophozoites in CSF; C, M	*Naegleria*[d]: amphotericin B IV and IT *Acanthamoeba* : itraconazole, TMP–SMX, rifampin; pentamidine *Balamuthia*: pentamidine + fluconazole + sulfadiazine + flucytosine ± clarithromycin
Schistosomiasis	Demonstration of eggs in tissue, urine, or stool; S	Praziquantel[b,c]
Vibrio vulnificus	C	Doxycycline + ceftazidime[b] (cefotaxime; ciprofloxacin; doxycycline + AG [FQ])

Abbreviations: AG = aminoglycoside; CSF = cerebrospinal fluid; FQ = fluoroquinolone; IT = intrathecal; IV = intravenously; TMP–SMX = trimethoprim–sulfamethoxazole.

[a] Method of diagnosis: C = culture, M = molecular testing (such as PCR), S = serology.

[b] Considered first-line therapy at time of printing.

[c] Randomized controlled trial level of evidence for therapy.

[d] Reports of treatment success are scant.

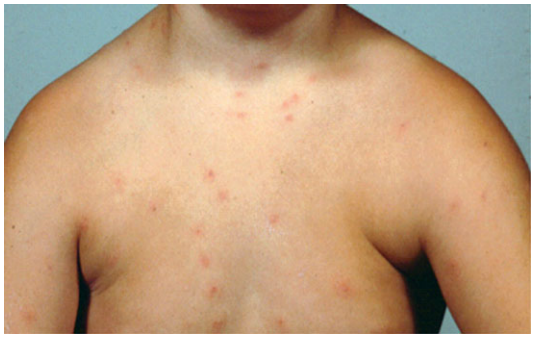

Figure 120.1 Skin lesions of cercarial dermatitis. (Courtesy of Jay Keystone, MD.)

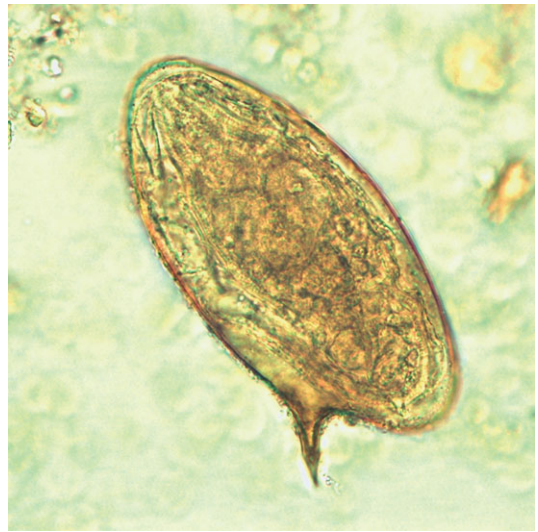

Figure 120.2 Egg of *Schistosoma mansoni* from stool.

Vibrio soft-tissue infections

As resident marine flora, *Vibrio vulnificus*, *Vibrio parahemolyticus*, *Vibrio alginolyticus*, and other *Vibrio* species can cause soft-tissue infections through recreational water exposure. In 2007–2008, 236 cases of vibrioses linked to recreational water exposure were reported from 25 states, which represents one-fifth of the total cases of vibrioses in the country over that period of time. Almost one-third required hospitalization, and nine patients died. Organisms can be introduced by injuries (often on the lower extremity) that break the skin during swimming in the ocean or walking on beaches or can enter via pre-existing open skin lesions. After trauma, *V. vulnificus* can cause pustular lesions, lymphangitis, and cellulitis, which may be mild or rapidly progressive, causing pain, myositis, skin necrosis, and gangrene. Surgical debridement (or amputation) in addition to antibiotic therapy and general support may be necessary. Of all *Vibrio*-associated illnesses

secondary to recreational water exposure reported to the CDC in 2007–2008, *V. vulnificus* carried the highest rate of hospitalization and mortality.

Vibrio soft-tissue infections, including necrotizing fasciitis, can also follow ingestion of contaminated food (commonly raw shellfish). Many vibrios, in addition to *V. cholerae*, can cause diarrheal illness, and gastroenteritis may be associated with high-grade bacteremia and high mortality. Large bullous skin lesions may occur with primary *Vibrio* bacteremia (especially *V. vulnificus*). Severe infections are more common in persons with chronic liver disease or other underlying diseases that compromise immune function.

Vibrios are found in seawater or brackish water and are part of the usual bacterial flora of coastal waters in the United States and elsewhere. They are more abundant in warmer months, and most reported infections occur in the summer. Rising water temperatures in the Baltic Sea over the past three decades have led to an increase in the number of outbreaks due to *Vibrio* spp. in countries that have been historically protected from these organisms due to their cooler climate.

Treatment of soft-tissue and systemic infections following seawater exposure should include coverage for *Vibrio* species.

Aeromonas hydrophila

Aeromonas hydrophila is a non-spore-forming, motile, facultatively anaerobic gram-negative organism found in freshwater lakes, streams, and soil. Puncture wounds or soft-tissue injury in contaminated water may lead to cellulitis that can resemble acute streptococcal infection with lymphangitis and fever. If not treated with effective drugs, it can progress to bullae formation and necrotizing myositis with gas in soft tissues. Findings can mimic gas gangrene. Soft-tissue infections may require local debridement along with systemic antibiotic therapy.

Ingestion of *Aeromonas* may cause diarrhea. Although *Aeromonas* is frequently isolated from environmental waters, evidence of clearly defined outbreaks of diarrhea attributable to aeromonads is lacking. Aspiration of *Aeromonas*-contaminated water may lead to *Aeromonas* pneumonia and bacteremia.

Melioidosis (*Burkholderia pseudomallei*)

This water- and soil-associated gram-negative organism, found especially in tropical and subtropical areas, is a common cause of pneumonia, skin lesions, and sepsis predominantly in Southeast and South Asia and Australia, though also in Oceania, the Caribbean, and South America. The organism can be acquired through minor skin wounds or via aspiration or ingestion. Infection can be acute, subacute, or chronic and has protean manifestations, including cavitary lung disease, splenic abscesses, and osteomyelitis. The organism can persist silently in the human host and reactivate decades after acquisition, mimicking tuberculosis.

Acanthamoeba infections, including primary amebic meningoencephalitis

Free-living amebae of the genus *Acanthamoeba*, found in soil and fresh water, can enter human tissues and cause local or disseminated infection. Several species of *Acanthamoeba* have been reported to cause keratitis and granulomatous inflammation, which may be acute or subacute. Soft-tissue infections have also been reported, although are more likely to result from infection with the related free-living ameba *Balamuthia mandrillaris*. Minor trauma to the cornea, as may occur in persons who wear contact lenses, predisposes to infection. The diagnosis is confirmed by finding *Acanthamoeba* on biopsy, corneal scrapings, or culture (Figure 120.3). Treatment typically requires both debridement and topical therapy (several agents have been tried: combination of miconazole nitrate, propamidine isethionate, and Neosporin; propamidine isethionate and dibromopropamidine; among others, although level of evidence is case series only).

Free-living amebae, including *Acanthamoeba* species, though, usually *Naegleria fowleri*, cause primary amebic meningoencephalitis (PAM), typically in young healthy persons. Trophozoites enter the nasal passages during swimming or diving, penetrate the cribriform plate, and invade the central nervous system via olfactory neuroepithelium, causing rapid destruction of gray and white matter. Symptoms usually begin 3 to 7 days after exposure to water. Infection causes high fever, headache, and stiff neck, resembling bacterial meningitis, which rapidly progresses to coma and, usually, death. Diagnosis is made by finding trophozoites in the cerebrospinal fluid (CSF) (wet mount, Giemsa staining after fixation, or by culture), although in most cases of PAM, diagnosis is postmortem. Infections have followed exposures in lakes, rivers, stagnant ponds, thermal springs, canals, and hot tubs and are more common during

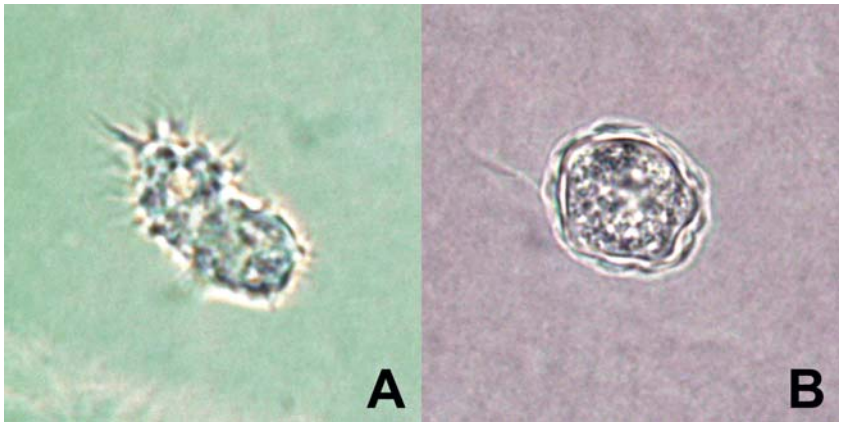

Figure 120.3 (A) Trophozoite and (B) cyst of *Acanthamoeba* spp. from corneal specimen, wet mount.

very warm periods, due to the thermophilic nature of these free-living protozoa. Disruption of lake or riverbed sediment by deep swimming or digging is a particular risk factor for PAM and may therefore serve as an important historical clue for clinicians. Ritualistic washing before prayers, which involves sniffing water to cleanse the nose, has also emerged as a risk factor for PAM in rural Nigeria. In 2007–2008, eight fatal cases of PAM due to *N. fowleri* were reported from Florida, Texas, Arizona, California, and Oklahoma.

Chromobacterium violaceum

This gram-negative organism is found in abundance in tropical and subtropical freshwater rivers and soils. The rarely reported infections have usually followed penetrating skin injury and are typically bacteremic. Persons with chronic granulomatous disease are at risk for severe infection. Clinical data are limited, and evidence to guide management decisions is lacking.

Leptospirosis

Spirochetes of the genus *Leptospira* cause leptospirosis, a zoonosis of global significance. Leptospirosis has caused outbreaks in swimmers (lake, creek, other fresh water), kayakers, whitewater rafters (e.g., in Costa Rica), and, more recently, in 2011, among members of the French Armed Forces training in canyon rescue along the Absalon River of Martinique. Fresh water becomes contaminated with urine of infected domestic and wild animals. Humans become infected when organisms enter through skin (especially if abraded) or mucous membranes, or after ingestion of contaminated water or food. Infections are more common in tropical and subtropical areas and during warm seasons in temperate regions. In the United States, infections have been especially common in Hawaii, although sporadic infections and occasional clusters occur in other areas, primarily in warmer months. In July 1998, an outbreak of leptospirosis occurred in Springfield, Illinois, primarily affecting triathletes who swam in Lake Springfield. Imported cases in travelers, however, can be seen throughout the year in North America. The single outbreak of suspected leptospirosis reported to the CDC in 2007–2008 was related to exposures in a pond.

Infected persons can develop a systemic infection with protean manifestations, commonly including fever, headache, severe myalgia, and conjunctival suffusion. The spectrum of clinical disease can range from asymptomatic or mild infection to the most serious form, Weil's disease, characterized by an icterohemorrhagic fever. A biphasic course is classic, and complications such as aseptic meningitis, pneumonia, and acute renal failure are seen in one-quarter to one-third of all cases of leptospirosis. A large flood in Metro Manila, Philippines, in 2009 led to 471 hospitalizations and 51 deaths, with a case-fatality rate of 8%.

Mycobacterium marinum

Mycobacterium marinum usually invades only superficial tissue after local inoculation. Infection manifests as red plaques, papules, or nodules (sometimes with sporotrichoid or lymphocutaneous spread) (Figure 120.4). The infection is referred to as "swimming pool granuloma" and "fish tank granuloma" because of the associations with fish and water. This subacute infection, most often on

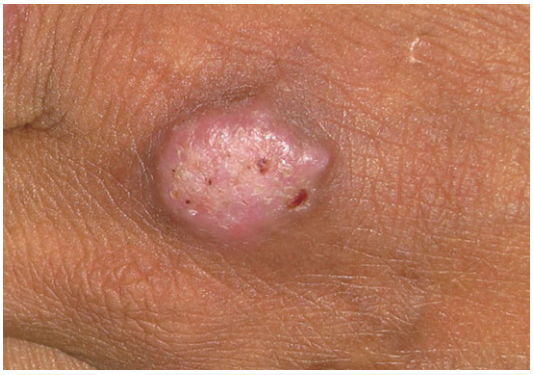

Figure 120.4 Cutaneous nodule of *Mycobacterium marinum* several months after repeated fish tank exposure.

the hand or arm, can occur after exposure to fresh or salt water in aquariums and in swimming pools. Because the organism is relatively chlorine resistant, infection can follow exposures in chlorinated pools.

Tularemia

Tularemia, caused by *Francisella tularensis*, an organism that sometimes contaminates water (from infected animals), can infect via multiple routes, including through conjunctivae, skin, oropharynx, and gastrointestinal tract. Ticks and other arthropods can transmit infection. It is mentioned in this chapter because infection can be severe, even fatal, but does respond to appropriate therapy.

ACQUIRED BY INHALATION, ASPIRATION, OR INGESTION

Legionnaires' disease

Legionella can infect susceptible hosts through inhalation of aerosols generated by showers, whirlpools/spas, and sinks. Temperature is the most important abiotic factor influencing survival and growth of *Legionella*, which proliferates in hot-water tanks and heat-exchanging systems. Several outbreaks of Legionnaires' disease, an acute pneumonic process, have been traced to exposures in resort hotels and to whirlpools on cruise ships. Hence, this is an infection to consider in persons with febrile illness and pneumonia after travel. Pontiac fever results from the aerosolized antigens of *Legionella pneumophila* and is characterized by a self-limited febrile

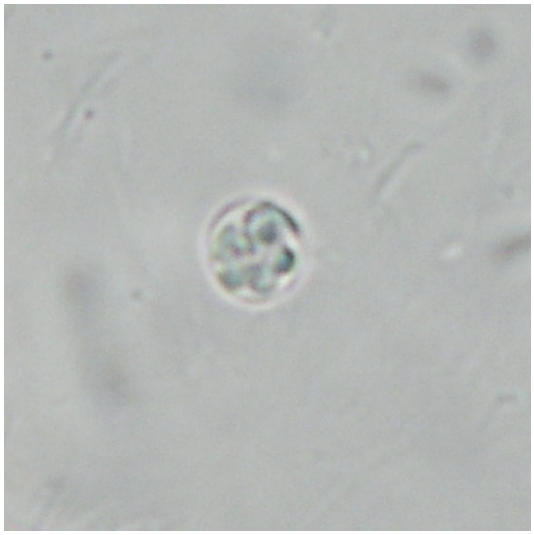

Figure 120.5 Oocyst of *Cryptosporidium* spp. from stool, wet preparation.

illness. In 2007–2008, 10 outbreaks caused by *Legionella* were linked to pools or spas, leading to 122 cases of Pontiac fever or Legionnaires' disease. Randomized controlled trials support the use of either macrolides (clarithromycin, azithromycin) or fluoroquinolones (levofloxacin) for the management of Legionnaires' disease or for empiric coverage of *L. pneumophila* in cases of community-acquired pneumonia.

Cryptosporidiosis

Cryptosporidium, an apicomplexan protozoan, has eclipsed *Giardia* as the most common parasitic cause of gastroenteritis outbreaks following recreational water exposure in the United States. Of 81 gastroenteritis outbreaks reported in the United States in 2007–2008, 58 were caused by *Cryptosporidium*, resulting in 12 137 cases of illness. A single community-wide outbreak in Utah in 2007 accounted for 5697 cases of cryptosporidiosis related to recreational water exposure. Most cases of *Cryptosporidium* occur following exposure at treated water venues, such as swimming pools. A number of factors contribute to the spread and transmission of *Cryptosporidium*, notably the wide range of animal reservoirs, the large number of fully infectious oocysts excreted by human and animal hosts (Figure 120.5), the relative resistance of oocysts to standard disinfection practices, and a low minimum infective dose. Oocysts of *Cryptosporidium* may be difficult to distinguish from those of *Cyclospora cayetanensis*

(Figure 120.6), which causes a similar clinical syndrome to cryptosporidiosis.

Although the clinical course is usually self-limited, severe and prolonged diarrhea may occur in young children and in those who are immunocompromised. Nitazoxanide has recently emerged through randomized controlled trials as an effective agent for the treatment of cryptosporidiosis in both healthy adults and children and in those who are immunocompromised.

Giardiasis

Since the first documented outbreak in 1965, more than 100 waterborne outbreaks have been attributable to the flagellated protozoan *Giardia*. In 2007–2008, four outbreaks reported to the CDC were due to giardiasis acquired from recreational water exposure. Outbreaks of giardiasis have frequently been traced to ingesting unfiltered, unchlorinated, or inadequately chlorinated surface waters. Many infections in campers and hikers have followed drinking from mountain streams, even in remote wilderness areas. Like *Cryptosporidium*, *Giardia* has a broad mammalian host range, and cysts are excreted in fully infectious form (Figure 120.7). There are a number of effective therapeutic options for giardiasis that have been evaluated in randomized controlled trials, including metronidazole, nitazoxanide, tinidazole, mebendazole, albendazole, and furazolidone.

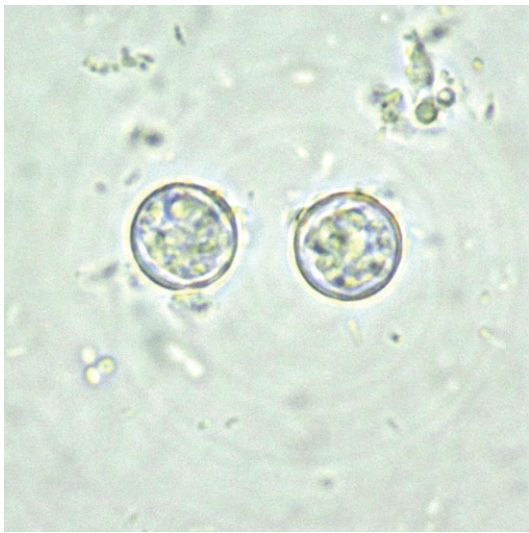

Figure 120.6 Oocyst of *Cyclospora cayetanensis* from stool, wet preparation.

Norovirus ("Norwalk-like viruses")

In the 2007–2008 reporting period, norovirus was responsible for five waterborne disease outbreaks, which caused 121 cases of gastroenteritis, rendering it second only to *Cryptosporidium* in the number of individuals who were sickened by a specific etiologic agent causing gastroenteritis. The majority of individuals were sickened by norovirus following exposure at treated water venues, notably swimming pools. Although community outbreaks of norovirus are often linked to transmission via doorknobs, toilets, and shared utensils, recreational water exposure significantly contributes to the overall case burden. The increasing number of cases reported over the past few years has been attributed to improved awareness and availability of viral detection methods, although diagnostic test underutilization is still likely to result in underreporting of viral agents of gastroenteritis. Visualization of norovirus in stool via electron microscopy is definitive (Figure 120.8). Management is supportive.

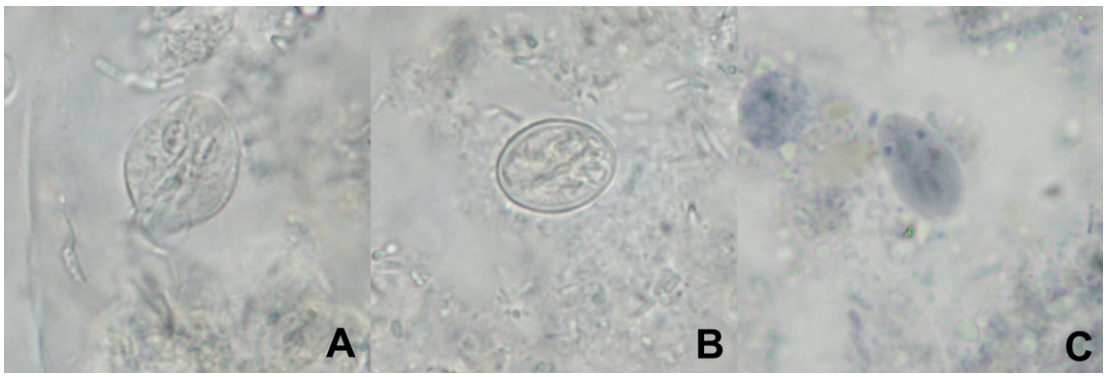

Figure 120.7 Trophozoite and cysts of *Giardia lamblia*, (A) wet preparation trophozoite; (B) wet preparation cyst; (C) iron–hematoxylin stain cyst.

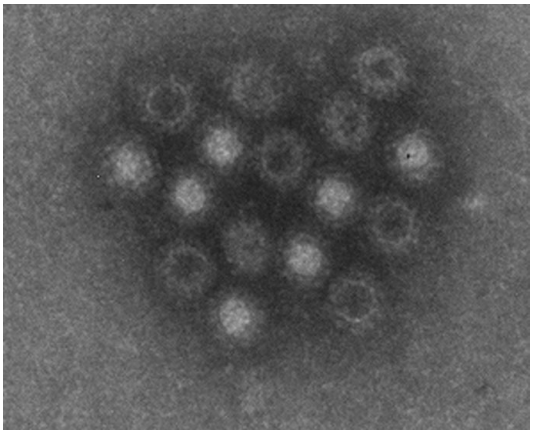

Figure 120.8 Electron micrograph of norovirus isolated from stool of a patient with acute gastroenteritis.

Chemical exposures and intoxications

Recreational use of marine water systems can lead to intoxications including, but not limited to, possible estuary-associated syndrome (PEAS), and aerosolized red tide respiratory irritation (ARTRI), caused by toxins liberated by the species of dinoflagellates, *Pfiesteria* and *Gymnodinium breve*, respectively. PEAS due to *Pfiesteria* leads to respiratory and eye irritation along with rash, vomiting, abdominal cramps, and cognitive changes, all of which appear to be self-limited. ARTRI occurs due to inhalation of brevetoxins present in sea spray during algal blooms, and is characterized by a syndrome of rhinorrhea, cough, and bronchospasm. In both cases, treatment is supportive.

In 2007–2008, nine outbreaks following recreational water exposure to chemicals or toxins sickened 747 individuals. The largest such outbreak was associated with an indoor waterpark in Ohio, led to respiratory and eye symptoms in employees and patrons, and was caused by high trichloroamine and endotoxin levels. Other outbreaks related to recreational water exposure reported in the same time period were due to chlorine gas, muriatic acid, and brevetoxin released by the alga *Karenia brevis*.

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121. Travelers' diarrhea

Karen J. Vigil and Herbert L. DuPont

Diarrhea is the most frequent health problem encountered by persons going from industrialized to developing countries. Of the 100 million people traveling annually from industrialized to developing countries, approximately 40% will suffer from so-called travelers' diarrhea (TD), many more than once.

Classically, TD is defined as the passage of three or more unformed stools within 24 hours in association with at least one of the following symptoms of enteric infection: nausea, vomiting, abdominal pain or cramps, fever, fecal urgency, tenesmus, or the passage of bloody/mucoid (dysenteric) stools. This definition includes illness occurring up to 10 days after travelers return to their home countries.

Cases of TD can be categorized by severity as being mild (no disturbance in normal activities), moderate (modified travel activities required), or severe (illness requires confinement to bed). Fewer than 1% of patients are admitted to a hospital, but almost 40% are required to change their travel schedule.

Acute TD lasts for less than 2 weeks. Illness lasting more than 2 weeks is considered "persistent" and is seen in 2% to 10% of travelers. Possible etiologies of persistent diarrhea include intestinal infection by protozoal parasites, for example, giardiasis or cryptosporidiosis, and occasionally bacterial enteropathogens can cause a more protracted diarrhea. Unmasked gastrointestinal disease is seen in this setting occasionally, including irritable bowel syndrome, inflammatory bowel disease, and malabsorptive syndromes. Postinfectious irritable bowel syndrome, a recognized complication of bacterial enteric infection, has been shown to occur in as many as 10% of people after an episode of TD.

Food is the most important source of bacterial enteropathogens, which explains a majority of cases of TD. Water, which becomes more contaminated during rainy seasons, is often the source of viral gastroenteritis. Genetic factors contribute significantly to susceptibility to enteric infections. Fecal levels of inflammatory cytokines, including interleukin (IL)-8 and IL-1β, are often elevated in people who developed bacterial diarrhea. Host polymorphisms in the IL-8, IL-10, CD14, osteoprotegerin and lactoferrin genes were found to be associated with an increased susceptibility to TD.

ETIOLOGY

Bacterial enteropathogens cause up to 80% of TD cases. There is a relationship between geographic areas and the enteropathogens responsible for illness. For example, the diarrheagenic *Escherichia coli*, particularly enterotoxigenic *E. coli* (ETEC) and enteroaggregative *E. coli* (EAEC), are the major etiologic organisms in most areas of the developing world, responsible for ~50% to 60% of cases. Invasive pathogens, such as *Shigella*, *Salmonella*, and *Campylobacter*, represent 10% to 15% of cases but may account for up to 30% of cases in Asia, of which ciprofloxacin-resistant *Campylobacter* is of the greatest concern as it may not respond to customary self-treatment. Noncholera vibrios are found to cause TD in coastal areas of the world in a small number of cases. *Vibrio cholerae*, the causative agent of cholera, is a rare but serious cause of TD. *Klebsiella oxytoca, Laribacter hongkongensis*, enterotoxigenic *Bacteroides fragilis*, and *Arcobacter* have also been described as less frequent causes of TD.

Other than bacterial pathogens, parasites and viruses also cause TD. *Giardia* is an important pathogen in mountainous areas of North America and Russia. *Cryptosporidium* spp. are an important cause of diarrhea in travelers to Russia. *Cyclospora cayetanensis* has been found to be a causative organism of TD in Nepal, Haiti, and Peru. Rotavirus and norovirus are among the most common viruses described. Noroviruses have been identified in 10% to 20% of TD cases and remain a special problem on cruise ships.

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The causes of TD in some areas of the world are also affected by the regional climate. ETEC was shown to be the major pathogen in the rainy, summer season in Mexico, with emergence of *Campylobacter jejuni* in the dry wintertime. In semitropical Morocco, *C. jejuni* was also found to be the most important pathogen in the dry winter season.

PREVENTION AND CHEMOPROPHYLAXIS

Disease prevention is important to facilitate the purpose of the leisure or business trip and to prevent chronic enteric complications. Prevention measures consist of education for the future traveler on usually safe and occasionally unsafe foods and chemoprophylaxis.

Travelers should be instructed to avoid consuming moist foods served at room temperature and tap water (including ice). Food served steaming hot (>59°C), dry foods (e.g., bread), fruits that can be peeled, and foods with high sugar content (e.g., syrup, honey, or jelly) generally are safe.

Chemoprophylaxis may be used for short-term travel (≤3 weeks) in persons on a tight schedule (musicians, athletes, business persons, tourists, and politicians), in those who have experienced TD before (possibly related to genetic susceptibility), and for those who request it. Additional persons who might routinely employ chemoprophylaxis include those with underlying illness that might predispose them to increased risk of diarrhea or complications of illness, including persons with achlorhydria (from prior gastric surgery or regular use of proton pump inhibitors), inflammatory bowel diseases, human immunodeficiency virus (HIV) infection, transplant recipients or other immunosuppressions.

Bismuth subsalicylate (BSS) is modestly effective in the prevention of TD, with protection rates of approximately 65%. The dosage recommended for prophylaxis is two tablets (262 mg/tablet) orally with meals and at bedtime (eight tablets/day). Quinolones can prevent TD in up to 80% to 100% of cases. The emergence of quinolone-resistant *Campylobacter* spp. in South East Asia precludes their use in some areas of the world. Also, this class of drugs is too important for serious bacterial infection, and use for diarrhea prevention, which could encourage resistance development, cannot be justified. Rifaximin was shown to have a protection rate of 72% to 77% in a study in Mexico where diarrheagenic *E. coli* were the major pathogens. The drug was free of side effects when given for 2 weeks and was associated with minimal changes in fecal flora. We recommend rifaximin as the routine approach when chemoprophylaxis is desired because of its convenience and safety. It should not be given for trips longer than 2 to 3 weeks. The recommended dose is 200 mg (one tablet) with each of the major daily meals (usually two tablets a day) for as long as the person remains in the high-risk region.

Immunologic protection against ETEC diarrhea is feasible. An oral vaccine consisting of cholera toxin B subunit and inactivated whole-cell cholera strains has become available in some parts of the world. This vaccine confers protection against ETEC in up to 67%. However, it only has a 28% prevention rate for TD. A novel transcutaneous patch ETEC vaccine is also in development. Vaccination for TD with an anti-ETEC preparation can offer important protection from the major cause of the illness but cannot be completely protective because TD is a syndrome caused by multiple organisms.

TREATMENT

Hydration and dietary recommendations

Travelers' diarrhea can cause dehydration in infants, the elderly, or persons who have underlying medical illness. Fluids combined with electrolytes are the most important form of therapy. In the nondehydrated person without important underlying medical illness, commercially available sports drinks, diluted fruit juices, and other flavored soft drinks taken with saltine crackers and/or soups are usually enough to meet the fluid and salt needs during TD. Oral rehydration powders or solutions are also commercially available (e.g., CeraLyte).

During the early hours of diarrheal illness, it may be helpful to temporarily withhold solid foods that are complicated to absorb and that act as a stimulant of intestinal motility. In most cases of diarrhea, carbohydrates (noodles, rice, potatoes, oat, wheat, bananas) and steamed or baked white meats (fish and chicken) can be ingested. As illness improves and stools become formed, the diet can return to normal. In general, dairy products should be avoided in adults for the first day or two. It is important to feed patients with diarrhea to facilitate enterocyte renewal.

Nonantimicrobial therapy

Symptomatic therapy can be used in cases of mild TD. BSS is a commonly used antidiarrheal drug.

This agent has antimicrobial, antisecretory, and anti-inflammatory properties. BSS can decrease the number of unformed stools passed in cases of TD by approximately 40%. BSS rarely causes mild tinnitus, and it commonly produces blackening of the tongue and stools from bismuth sulfide, a harmless salt of the nonabsorbed bismuth moiety. If a person is taking antimalarials for malaria prophylaxis, BSS should not be used concomitantly, because it can prevent absorption of the antimalarial drug.

Antimotility agents such as loperamide (Imodium) and diphenoxylate with atropine (Lomotil) are synthetic opioids that have selective effects on the intestine. These agents can improve diarrhea by slowing intestinal transit, leading to greater absorption of fluids and electrolytes. Loperamide is a drug of choice for symptomatic treatment of subjects without fever and not passing bloody stools. This agent will reduce the number of stools passed during a diarrhea episode by approximately 60%.

Antisecretory agents are being developed that work through a variety of pathways including calmodulin inhibition, chloride channel inhibition, and enkephalinase inhibition. In the United States a chloride channel inhibitor, crofelemer, is being developed for acute secretory diarrhea.

Antimicrobial therapy

Antimicrobial therapy in patients with TD shortens the duration of diarrhea and cures the disease. Clinical trials use time from initiation of therapy to passage of the last unformed stool (TLUS) as a primary parameter of efficacy. Antibiotic therapy is indicated in patients with moderate to severe disease because it has been shown to reduce TLUS by 1 to 3 days compared with placebo.

A variety of effective treatments for TD are available (Table 121.1). Rifaximin, 200 mg three times a day (TID) for 3 days, has a TLUS of 25.7 hours and a treatment failure of 10%, similar to ciprofloxacin, 500 mg twice a day (BID) for 3 days (25 hours and 6%, respectively), for treatment of noninvasive forms of the disease. Poorly absorbed (≤0.4%) rifaximin has an advantage for uncomplicated watery diarrhea in its safety profile. Rifaximin is not effective in the treatment of invasive forms of TD, particularly those associated with fever or dysentery.

For febrile dysenteric diarrhea, a systemic antibiotic, including the fluoroquinolones (ciprofloxacin, levofloxacin) or azithromycin, is preferred. Fluoroquinolones should not be used in children and pregnant women because they have been shown to damage articular cartilage in growing animals. These agents may interfere with xanthine metabolism, so patients taking theophylline may need to adjust their dosage of the drug. Fluoroquinolone resistance has become a problem with *Campylobacter* strains seen worldwide, which is a limitation of ciprofloxacin or levofloxacin.

Azithromycin is an azalide antibiotic related to macrolides and is more active than erythromycin against ETEC, *Salmonella* species, *Shigella* species, *V. cholerae*, and *C. jejuni*. In a clinical trial in Thailand, where *Campylobacter* has become resistant to ciprofloxacin, azithromycin was more effective than ciprofloxacin against *Campylobacter*. Azithromycin is effective against most forms of bacterial diarrhea and can be given as a single 1000-mg dose or daily in a lower dose for 3 days (see Table 121.1). Azithromycin may be the drug of choice for some regions of Asia where invasive pathogens are most common and is also the drug of choice for rescue therapy when rifaximin chemoprophylaxis is employed.

Travelers to high-risk areas should be encouraged to take with them an antibiotic for self-treatment of diarrhea that develops. It takes approximately 24 hours for a drug to cure the

Table 121.1 Recommended empiric treatment of travelers' diarrhea in adults

Agent	Dosages	Comments
Loperamide	4 mg initially, then 2 mg after each stool, not to exceed 8 mg/d[a]	Should not be used in patients with fever and dysentery
Bismuth subsalicylate	30 mL or 2 tablets (262 mg/tablet) PO q 30 min up to 8 doses/d[a]	Should not be used with doxycycline when used for malaria prophylaxis Caution in people taking aspirin
Ciprofloxacin	500 mg PO BID or 750 mg PO qd for 1–3 d	Treatment failures most common because of resistant strains of *Campylobacter*
Rifaximin	200 mg PO TID for 3 d	Not recommended for febrile dysenteric diarrhea
Azithromycin	1000 mg single dose or 500 mg PO 1× and then 250 mg qd for 1 or 2 more d	Treatment of choice for febrile dysentery when *Campylobacter* is known to be the causative agent

[a] To be used for no more than 48 h.

diarrhea. The antibiotic can be started after passage of the third unformed stool, to avoid unnecessary exposure to antibiotics for milder self-limiting syndromes. Some travel medicine experts prefer to begin the treatment with passage of the first unformed stool in a diarrheal episode to help reduce the duration of illness.

Combination therapy

Perhaps the optimal approach for empiric treatment of nondysenteric TD is to give the combination of loperamide with an antibiotic to combine a near-immediate effect of the loperamide with a curative effect of the antibiotic. This approach is not appropriate for patients with febrile, dysenteric diarrhea where a systemically absorbed antimicrobial agent alone should be used.

SUGGESTED READING

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PART XVII

Bioterrorism

122. Bioterrorism 815
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122. Bioterrorism

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INTRODUCTION

Bioterrorism (BT), the deliberate use of microbial agents or their toxins as weapons for political gain, continues to represent a persistent global threat due to the widespread availability of these substances and the opportunities for terrorists to deploy them against civilian targets. Although the potential deleterious consequences associated with exposure to biologic threat agents are high, the probability of exposure to these hazards is unknown – it remains in the unpredictable and malicious minds of terrorists. Therefore, a precise calculation of "risk" as it relates to BT is not possible. However, due to the potential for catastrophic sequelae, it is important for clinicians to understand the diagnostic and therapeutic approach to illnesses caused by agents of BT in order to mitigate the effects of an attack.

BT agents are considered weapons of mass terror because of their potential for large-scale morbidity and mortality. For example, one early model predicted nearly 200 000 casualties from a release of 50 kg of aerosolized anthrax spores upwind of a population center of 500 000. Based on more recent experience – the US anthrax attacks of 2001 resulted in 11 cases of systemic disease associated with 5 deaths – it is evident that even relatively small-scale events may cause mass terror.

Unlike conventional, chemical, and nuclear weapons, BT agents are associated with a clinical latency period during which transmission may occur and detection is difficult. The US Centers for Disease Control and Prevention (CDC) has classified BT threats into priority groupings, based on their feasibility for deployment and their potential for mortality, morbidity, and public health impact; this categorization (Table 122.1) has informed current biodefense strategies.

CLINICAL PRESENTATION

The clinical pictures of diseases caused by agents of BT are varied but, with few exceptions among the CDC category A and B threats, can be categorized into a limited number of syndromic presentations (Table 122.2). Unfortunately, there are scant pathognomonic features of BT-related illness, only suggestive ones. For this reason a high index of suspicion among clinicians is necessary to capitalize on subtle clues, many of which may be epidemiologic in nature. Nonetheless, many of these agents demonstrate suggestive clinical and laboratory findings (Table 122.2) that in the appropriate clinical context should prompt further, targeted evaluations and warrant appropriate, empiric management. More detailed clinical information on each agent is covered in organism-specific chapters of this book.

DIAGNOSIS

Rapid detection and accurate identification of BT agents are important not only for confirming that a BT event has occurred but also for treating individual patients and implementing appropriate public health measures. By definition BT is insidious; in the absence of credible advance notification, it is likely that clustered, syndromic, clinical illness will be the initial manifestation of a BT attack. Early recognition, although critical, is problematic for a variety of reasons: (1) targets of BT, especially in an open society, are diverse and unpredictable; (2) the clinical latency of BT agents, discussed above, makes it likely that clusters of symptomatic individuals will present for medical care days to weeks after an "event" and at geographically diverse locations; (3) initial clinical manifestations of many BT-related illnesses are nondiagnostic and may be mistaken for other, more common but less impactful diagnoses; (4) clinicians are inexperienced with the clinical manifestations of these infections; and (5) even if the classic clinical findings are known, because BT agents are manipulated in the laboratory, their associated clinical syndromes may not present in the same manner as those from naturally

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Table 122.1 Agents of concern for use in bioterrorism

Highest priority – Category A

Based upon potential mortality, morbidity, virulence, transmissibility, aerosol feasibility, and psychosocial implications of an attack

Microbe/toxin	Disease
Bacillus anthracis	Anthrax – Inhalational, cutaneous, injection
Variola virus	Smallpox and its variants
Yersinia pestis	Plague – Pneumonic, bubonic, septicemic
Clostridium botulinum	Botulism
Francisella tularensis	Tularemia – Pneumonic, typhoidal
Viral hemorrhagic fevers	
Filoviruses	Ebola, Marburg
Arenaviruses	Lassa fever, South American hemorrhagic fevers
Bunyaviruses	Rift Valley fever, Congo–Crimean hemorrhagic fever

Moderately high priority – Category B

Based upon potential morbidity, aerosol feasibility, dissemination characteristics, and diagnostic difficulty

Microbe/toxin	Disease
Coxiella burnetii	Q fever
Brucella species	Brucellosis
Burkholderia mallei	Glanders
Burkholderia pseudomallei	Melioidosis
Chlamydia psittaci	Psittacosis
Rickettsia prowazekii	Epidemic typhus
Alphaviruses	Viral encephalitides
Ricin	Ricin intoxication
Staphylococcus enterotoxin B	Staphylococcal toxin illness
Salmonella species, *Shigella dysenteriae*, *Escherichia coli* 0157;H7, *Vibrio cholerae*, *Cryptosporidium parvum*	Food- and waterborne gastroenteritis

Emerging threat agents – Category C

Based upon potential for production and dissemination, availability, morbidity/mortality

Microbe/toxin	Disease
Hantaviruses	Viral hemorrhagic fevers
Flaviviruses	Yellow fever
Mycobacterium tuberculosis	Multidrug-resistant tuberculosis
Nipah virus	Systemic, flu-like illness

Miscellaneous

Other examples of candidate threat agents that possess some elements of bioterrorism concern

Genetically engineered vaccine- and/or antimicrobial-resistant Category A or B agents
Human immunodeficiency virus 1
Adenoviruses
Influenza
Rotaviruses
Hybrid pathogens – e. g., smallpox/plague, smallpox/Ebola

occurring infection. Conversely, in the setting of a high level of suspicion, early recognition may be aided by a number of epidemiologic and clinical clues: case clustering, which because of the clinical latency of BT requires attention to geographic surveillance and communications; unusual clinical presentations of common syndromes, such as fulminant pneumonia in otherwise healthy young adults; or unusual disease patterns, such as rare diseases occurring in nonendemic areas or concurrent disease in humans and animal populations.

The CDC has developed a national laboratory response network (LRN) for BT that integrates selected microbiologic laboratories across the United States into a network and mandates uniform practices for specimen collection, processing, shipping, security, and testing. Laboratories within the LRN consortium are designated as having screening, confirmatory, or reference functions. The network of laboratories is connected by a secure communications system, thus ensuring the timely flow of information among the CDC, other governmental agencies, state health authorities, and other laboratories. The mission of the LRN is to enable a rapid and organized response to BT; the CDC routinely audits the performance of network members using panels of unknown pathogens.

Although diagnostic tests are available for most BT agents, many are not readily available in clinical laboratories, are time-consuming, have less than optimal sensitivity and specificity, or cannot test for multiple agents simultaneously. Diagnostic platforms that can assess for the presence of multiple pathogens concurrently, so-called multiplex strategies, offer attractive advantages, especially in the arenas of environmental surveillance and

Table 122.2 Syndromic differential diagnoses and clinical clues for Category A agents of bioterrorism (BT)

Syndrome	Clinical presentation	Differential diagnosis	BT-associated disease	Disease-specific clues
Influenza-like illness	Nonspecific constitutional and upper respiratory symptoms: malaise, myalgias, nausea, emesis, dyspnea, cough +/− chest discomfort, without coryza or rhinorrhea → abrupt onset of respiratory distress +/− shock +/− mental status changes, with CXR abnormalities (wide mediastinum or infiltrates or pleural effusions)	Influenza, community-acquired bacterial pneumonia, viral pneumonia, *Legionella*, Q fever, psittacosis, mycoplasma, *Pneumocystis* pneumonia, tularemia, dissecting aortic aneurysm, bacterial mediastinitis, SVC syndrome, histoplasmosis, coccidioidomycosis, sarcoidosis, ricin, and *Staphylococcus* enterotoxin B (pulmonary edema/ARDS)	Inhalational anthrax	• 3-day average symptom duration before presentation • Abdominal pain, headache, mental status abnormalities, hypoxemia common • Mediastinal adenopathy: ~90% (Figure 122.1) • Hemorrhagic pleural effusions: ~70% • CT more sensitive than CXR in early hemorrhagic mediastinal adenopathy • Meningoencephalitis: possibly ~50% • Blood cultures positive in untreated; pleural fluid cultures or antigen-specific immunohistochemical stain usually positive
Skin lesions	Pruritic, painless papule on exposed areas→vesicle(s)→ ulcer→edematous black eschar +/− massive local edema and regional adenopathy, +/− fever, evolving over 3–7 days	Recluse spider bite, staphylococcal lesion, atypical Lyme disease, Orf, glanders, tularemia, plague, rat-bite fever, ecthyma gangrenosum, rickettsialpox, atypical mycobacteria, cutaneous diphtheria, cutaneous leishmaniasis	Cutaneous anthrax	• Painless; spider bite is painful lesion • Nonpitting local edema may be massive (Figure 122.2) • If untreated, may progress to systemic involvement • Blood cultures, skin biopsy (from vesicular edge or erythema at edge of eschar)
Fulminant pneumonia	Abrupt-onset constitutional symptoms and rapidly progressive respiratory illness with cough, fever, rigors, headache, sore throat, myalgias, dyspnea, pleuritic chest pain, GI symptoms, lung consolidation, +/− hemoptysis, +/− shock; variable progression to respiratory failure	Severe community-acquired bacterial or viral pneumonia, inhalational anthrax, pulmonary infarct, pulmonary hemorrhage, influenza, mycoplasma pneumonia, *Legionella*, Q fever, SARS, tuberculosis	• Pneumonic plague • Pulmonary tularemia	• Lobar or multilobar involvement +/− buboes • Hemoptysis common • Characteristic sputum Gram stain • Cough generally nonproductive • Pulse–temperature dissociation in 40% • Hilar adenopathy, pleural effusions • Ulceroglandular form most common after natural or cutaneous exposures • Erythema multiforme or nodosum in significant minority of systemic disease
Sepsis with bleeding diathesis and capillary leak	Sepsis syndrome, GI symptoms, mucosal hemorrhage, altered vascular permeability, DIC, purpura, acral gangrene, hepatitis, hypotension, +/− CNS findings, multiorgan system failure	Meningococcemia; gram-negative sepsis, streptococcal, pneumococcal, or staphylococcal bacteremia with shock; malaria, leptospirosis, typhoid fever, borrelioses, typhoidal tularemia; overwhelming postsplenectomy sepsis; acute leukemia; Rocky Mountain spotted fever; fulminant hepatitis, TTP, hemolytic-uremic syndrome, SLE, hemorrhagic smallpox; hemorrhagic varicella (in immunocompromised)	• Septicemic plague • Viral hemorrhagic fever	• Occurs in minority of aerosol exposures • Cutaneous findings as late sequelae +/− buboes • High-density bacteremia • Maculopapular rash in Ebola, Marburg • Certain organ systems preferentially involved with specific VHF etiologies

Table 122.2 *(continued)*

Syndrome	Clinical presentation	Differential diagnosis	BT-associated disease	Disease-specific clues
Febrile prodrome with generalized exanthem	Fever, malaise, prostration, headache, myalgias, and enanthema followed by development of synchronous, progressive, centrifugal papular→vesicular→pustular rash on face, mucous membranes, extremities>>trunk→generalization +/− hemorrhagic component, with systemic toxicity	Varicella, drug eruption, Stevens–Johnson syndrome, measles, secondary syphilis, erythema multiforme, severe acne, disseminated herpes zoster or simplex, meningococcemia, monkeypox, generalized vaccinia related to smallpox vaccination, insect bites, Coxsackievirus, vaccine reaction	Smallpox	• Palms and soles involved • Rash is denser peripherally even after fully evolved (Figures 122.3, 122.4) • Lesions are well circumscribed, uniform, and almost nodular (Figure 122.5) • Secondary bacterial infection common • Hemorrhagic variant in pregnant and immunocompromised patients associated with severe systemic toxicity, bleeding diathesis, and early mortality
Progressive weakness	Acute onset of afebrile, symmetric, descending flaccid paralysis that begins in bulbar muscles, dilated pupils, diplopia or blurred vision, dysphagia, dysarthria, ptosis, dry mucous membranes→airway obstruction + respiratory muscle paralysis, clear sensorium and absence of sensory changes	Myasthenia gravis, brainstem CVA, polio, Guillain–Barré syndrome variant, tick paralysis, chemical intoxication	Botulism	• Expect dearth of GI symptoms in aerosol attack as opposed to foodborne botulism • Low-dose inhalation exposure may delay symptom onset • Prominent anticholinergic effects

Abbreviations: CXR = chest x-ray; SVC = superior vena cava; ARDS = acute respiratory disease syndrome; CT = computed tomography; GI = gastrointestinal; SARS = severe acute respiratory syndrome; DIC = disseminated intravascular coagulation; CNS = central nervous system; TTP = thrombotic thrombocytopenic purpura; SLE = systemic lupus erythematosus; VHF = viral hemorrhagic fever; CVA = cerebrovascular accident.

in screening either patients presenting with nonspecific symptoms or asymptomatic individuals who have possible exposure to an unknown agent.

The preferred methods for the laboratory diagnosis of BT agents differ depending on the agent in question. For most bacterial agents the gold-standard diagnostic assay remains standard culture; other supporting assays include modified staining with light microscopy, motility testing, lysis by gamma phage, capsule production staining, hemolysis, wet mounts, staining for spores, slide agglutination, direct fluorescent antibody, enzyme-linked immunosorbent assay (ELISA), and rapid immunochromatography. Routine assays for viral agents include virus isolation through tissue culture or growth in eggs, direct and indirect immunofluorescence, immunodiffusion in agar, electron microscopy, modified staining and light microscopy, plaque reduction neutralization, hemagglutination inhibition, neuraminidase activity, complement fixation, and ELISA. Pathologic examination of tissues and immunohistochemistry also play an important role in diagnosing BT agents.

Molecular assays are becoming the new gold standard for BT detection, with sensitivities and specificities close to 100% when compared with culture or serologic assays. These assays detect infectious agents in humans through target nucleic acid isolation and amplification followed by specific pathogen identification. Several technologies and methods have been used for multiplex detection of different BT agents. Although still in the developmental stages, it is likely that DNA microfluidic devices will be commonly used diagnostic platforms in the future. These methods are sensitive and specific and theoretically can be used on unprocessed specimens in field settings, thus obviating laborious microbial isolation steps. However, several challenges, including sampling issues, data analysis, development of specific probes, quality control, cost containment, automation, performance, and integration, must be addressed before such methods replace the standard ones.

Laboratory diagnosis of specific Category A agents

BACILLUS ANTHRACIS (FIGURES 122.1 AND 122.2)

Presumptive laboratory identification of *Bacillus anthracis* is based on the presence of large gram-positive bacilli in either gram- or

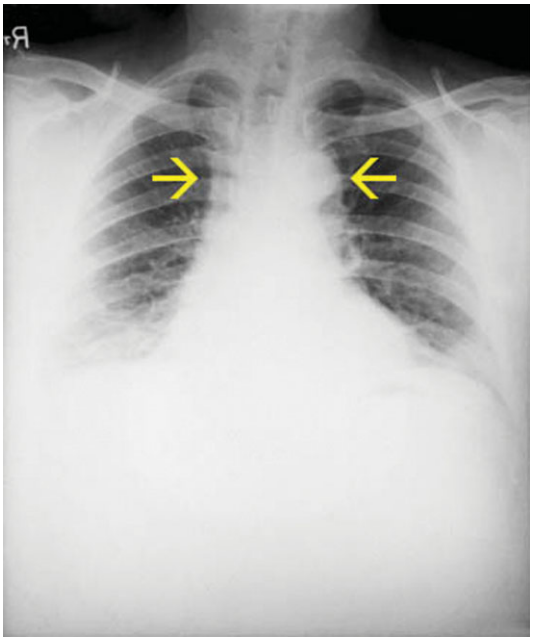

Figure 122.1 Inhalational anthrax. Note widened mediastinum (arrows). (Courtesy of Centers for Disease Control and Prevention.)

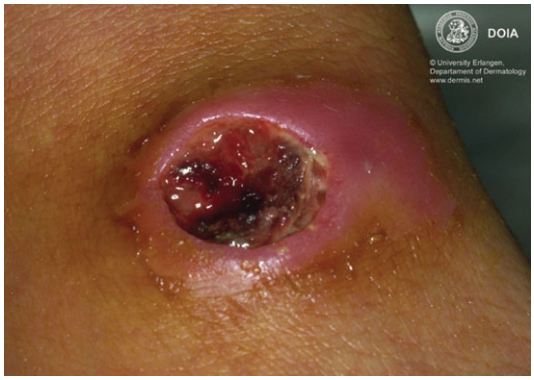

Figure 122.2 Cutaneous anthrax. (Courtesy of University of Heidelberg.)

immunohistochemical-stained material from skin lesions, cerebrospinal fluid, pleural fluid, or blood in an appropriate clinical setting or on the growth of aerobic, nonhemolytic, large, catalase-positive, gray-white colonies on sheep-blood-agar cultures containing nonmotile, nonencapsulated, gram-positive, spore-forming rods. Although the diagnosis may be suspected at the screening laboratory level, confirmatory diagnostic tests must be performed in containment facilities of the LRN. Such tests include susceptibility to lysis by gamma phage and polymerase chain reaction (PCR); the US Food and Drug Administration (FDA) has approved a real-time PCR assay for the diagnosis of anthrax. Although there are no assays that have been rigorously and prospectively validated for the rapid diagnosis of inhalational anthrax during its early, nonspecific clinical stages, the development of assays that detect cell wall and capsular antibodies and anti-protective antigen responses should improve the outlook for early diagnosis of anthrax.

Serologic testing is of little value in the diagnosis of acute disease but may have some use in undiagnosed survivors who demonstrate seroconversion. The use of nasal cultures for detecting *B. anthracis* early after potential exposure may be of some use in defining the epidemiologic parameters of exposure but are not useful in making individual decisions about the use of treatment or prophylaxis.

YERSINIA PESTIS

The gold standard for *Y. pestis* diagnosis remains standard microbiologic techniques such as microscopy of stained specimens and culture applied to expectorated sputum, bronchial washings, blood, or lymph node aspirates. The organism is suggested by its characteristic appearance as small gram-negative coccobacillary forms with bipolar, "safety-pin," uptake of Wright–Giemsa stain. *Y. pestis* grows slowly at routine incubation temperatures and may be misidentified by automated identification systems. Confirmation of the diagnosis requires the deployment of specialized testing: direct fluorescent antibody tests to detect the presence of F1 envelope antigen or PCR. Rapid tests to detect the F1 antigen are under investigation for potential field applicability on direct clinical specimens.

FRANCISELLA TULARENSIS

Francisella tularensis appear as small, intra- and extracellular gram-negative coccobacilli in stains of clinical specimens. Because the organism does not grow readily in standard laboratory media and because it is highly infectious to laboratory personnel, specialized microbiologic and safety procedures must be instituted for this pathogen. For this reason, the diagnosis is usually based on clinical features, and cultures should be pursued in higher-level laboratories of the LRN. Serology is generally useful only in retrospect, as it takes longer than 2 weeks to develop a serologic

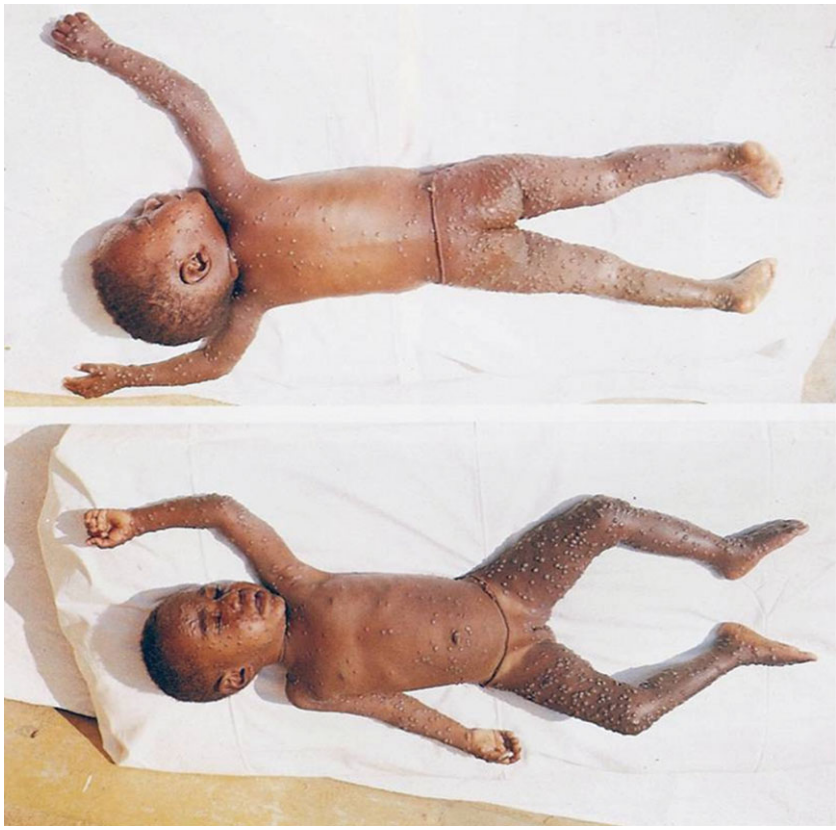

Figure 122.3 Smallpox. Note heavy concentration of lesions on face and extremities compared to trunk. Compare also to the truncal concentration seen in varicella. (Courtesy of World Health Organization.)

response in most individuals. The FDA has approved a real-time PCR assay for the diagnosis of tularemia.

CLOSTRIDIUM BOTULINUM

The diagnosis of botulism is largely based on epidemiologic and clinical features and the exclusion of other possible differential diagnoses. If laboratory diagnosis is necessary, the gold standard currently remains a mouse bioassay at a reference laboratory; PCR may have some utility in detecting *C. botulinum* nucleic acids in environmental samples.

SMALLPOX

The majority of smallpox cases present with a vesicular, centrifugal rash (Figures 122.3, 122.4, and 122.5) that in the appropriate clinical and epidemiologic context should prompt immediate notification of state or local public health authorities; specimens from suspected smallpox patients must be collected and transported under the direction of health authorities and in collaboration with the facilities of the LRN. Laboratory confirmation of the clinical diagnosis, especially in early or atypical cases in a suspected outbreak, is important; clinical diagnosis is probably sufficient in a confirmed outbreak. Infection control measures should be implemented prior to the acquisition of specimens in suspected cases.

Diagnostic assays in smallpox are typically performed on lesion scrapings, vesicular fluid, crusts, blood, or tonsilar swabs. A presumptive poxvirus diagnosis may be obtained by observing brick-shaped virions on electron microscopy of vesicular scrapings or by noting aggregations of virus particles, Guarnieri bodies, on histopathologic examination of tissue specimens. Isolation of variola virus in live cell cultures, followed by nucleic acid identification of specific orthopoxvirus species, is confirmatory but only performed in national reference laboratories with the highest level of biocontainment. The development of standard and multiplexed PCR platforms promises a reliable and less cumbersome way to discriminate between variola and other orthopoxviruses in clinical specimens.

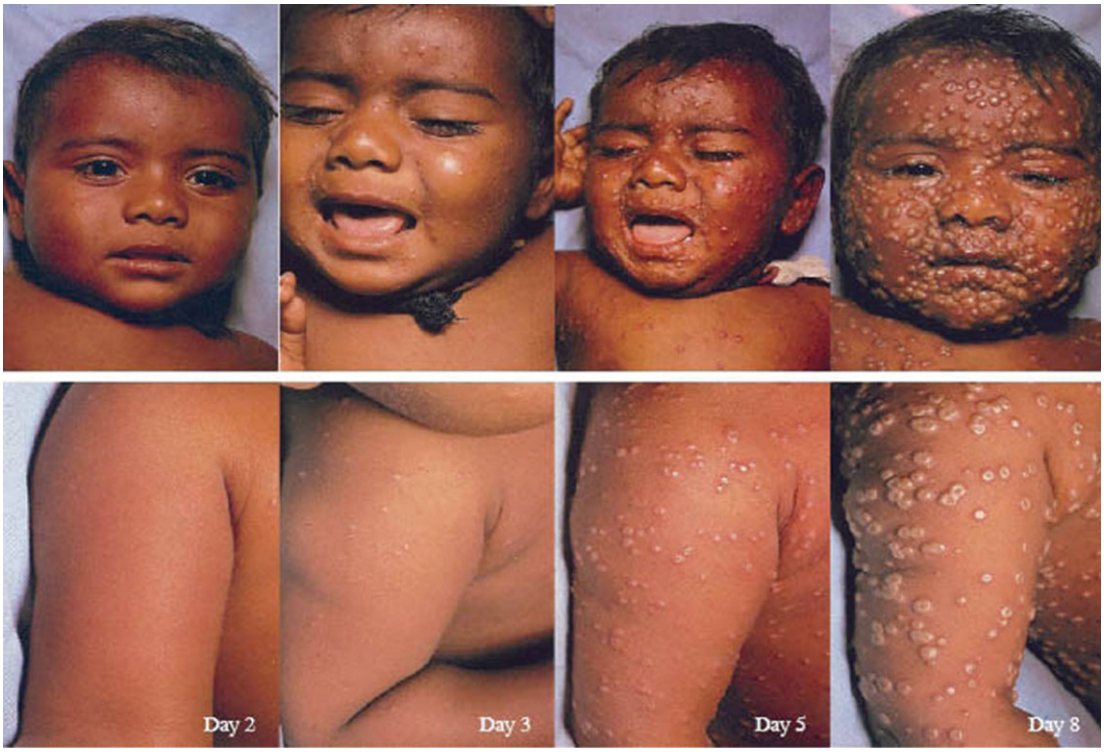

Figure 122.4 Progression of smallpox exanthem over the first eight days of illness. (Courtesy of World Health Organization.)

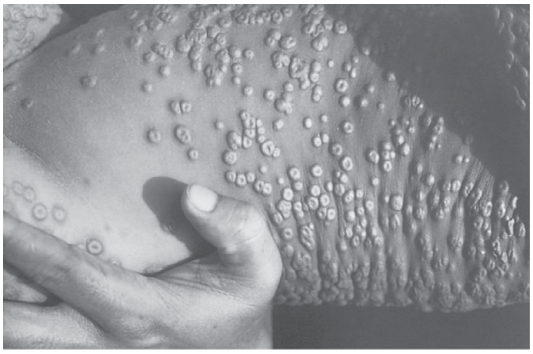

Figure 122.5 Smallpox. Lesions are characteristically round, uniform in size, and at same stage of development. (Courtesy of Centers for Disease Control and Prevention.)

VIRAL HEMORRHAGIC FEVERS

Clinical microbiology and public health laboratories are not currently equipped to make a rapid diagnosis of any of the implicated viruses, and clinical specimens would need to be sent to the CDC or the US Army Medical Research Institute of Infectious Diseases (USAMRIID), the highest-level laboratories in the LRN. Definitive diagnosis depends on identification of a specific viral etiology. Methods of early diagnosis at specialized laboratories include rapid enzyme immunoassays for antigen detection or viral immunoglobulin M (IgM), reverse transcriptase-PCR, and viral isolation in a biosafety level-4 facility. In general, serology is of limited value in early diagnosis because antibodies to these viruses usually do not appear until after the second week of illness.

MANAGEMENT

Once the diagnosis of BT-associated illness is considered, the initial step in the evaluation and management of an individual or group of patients is the immediate implementation of appropriate infection control measures according to the suspected agents (Table 122.3). This will ensure the maximal protection of healthcare workers as well as other patients in the healthcare environment. Empiric antimicrobial therapy of BT-associated illness should be initiated once the diagnosis is

Table 122.3 Epidemiologic characteristics for selected bioterrorism-associated diseases

Disease	Incubation period range (days)	Person-to-person transmission	Infection control precautions for patients	Case-fatality rate
Inhalational anthrax	2–58[a]	No	Standard	Untreated – 100% Treated – 45%
Cutaneous anthrax	1–12	No	Standard	Untreated – 20% Treated – <1%
Botulism	12–72 hours	No	Standard	6%
Primary pneumonic plague	1–6	Yes	Droplet	Untreated – 100% Treated – ~50%
Bubonic plague	2–8	No	Standard	Untreated – 60% Treated – <5%
Smallpox	7–19	Yes	Contact + airborne	Unvaccinated – 30% Vaccinated – 3%
Tularemia pneumonia	1–21	No	Standard	Untreated – 60% Treated – <4%
Viral hemorrhagic fevers	2–21	Yes	Contact + airborne	Marburg – 25% Ebola – 80% Other forms – 2%–30%
Viral encephalitides	1–14	No	Standard	10%–35%
Q fever	2–41	No	Standard	3%
Brucellosis	5–60	No	Standard	Untreated – 5%
Glanders	1–21	Yes	Contact + droplet	Untreated – approaches 100% Treated – low

[a] Based on limited data from human outbreaks and animal aerosol challenges.

seriously considered, as the early institution of appropriate therapy will not only potentially confer outcome advantages but may also potentially limit the spread of transmissible pathogens. The use of prophylactic antimicrobials is warranted for some agents. Recommendations for specific antimicrobial strategies for diseases caused by category A agents of BT are provided in Table 122.4.

Anthrax

Given the rapid clinical progression and attendant high mortality of inhalational anthrax, the early administration of appropriate, combination antimicrobials is essential and is likely to confer a survival advantage, as patients appear to quickly reach a clinical threshold beyond which survival is unlikely. There have been no controlled clinical studies for the treatment of inhalational anthrax in humans because of its rare and sporadic occurrence in nature.

Many patients with cutaneous anthrax can be successfully treated as outpatients; however, those with cutaneous infection involving the head, neck, or upper torso areas or with signs of systemic inflammatory response syndrome or those with inhalational or injection anthrax generally require hospitalization. Although there are different pathophysiologic mechanisms underlying systemic anthrax and traditional severe sepsis, standard guidelines used for hemodynamic support in the latter condition should be followed. Additionally, aggressive and repeated drainage of pleural effusions may improve both ventilation and survival. Limited surgical debridement is indicated in cases of injection anthrax for diagnostic purposes and to debulk potential toxin reservoirs.

During the anthrax attacks in the United States in 2001, the CDC promulgated treatment protocols recommending combination antimicrobials for the initial management of suspected inhalational anthrax; these have recently undergone further refinement (Table 122.4). Reasons to empirically treat with multiple drugs include heightened concerns regarding the deployment of antimicrobial-resistant pathogens by terrorists; the high potential for meningeal involvement in victims of systemic anthrax necessitating the

Table 122.4 Treatment recommendations for bioterrorism Category A agents in adults

	Anthrax-systemic
Treatment	• Initial IV therapy when meningitis possible: ciprofloxacin 400 mg q8h ***and*** meropenem 2 g q8h ***and*** linezolid 600 mg q12h (levofloxacin or moxifloxacin as alternates to ciprofloxacin; imipenem, penicillin G, or ampicillin as alternates to meropenem; clindamycin or rifampin as alternates to linezolid) • If meningitis is excluded, optimal first-line therapy is ciprofloxacin 400 mg q8h ***and*** clindamycin 900 mg q8h (PCN G, levofloxacin, moxifloxacin, ampicillin, or meropenem as alternates to ciprofloxacin; linezolid, doxycycline, or rifampin as alternates to clindamycin) • Oral follow-up therapy using ciprofloxacin 500 mg q12h or doxycycline 100 mg q12h (levofloxacin, moxifloxacin, or clindamycin as alternatives)
Postexposure prophylaxis	• Ciprofloxacin 500 mg orally q12h ***or*** doxycycline 100 mg orally q12h ***plus*** anthrax vaccine (unlicensed indication) • Use levofloxacin or moxifloxacin as alternates • Amoxicillin 500 mg orally q8h for pregnant women
Comments	• IV treatment initially before switching to oral antimicrobial therapy when clinically appropriate; IV treatment should be used for 2 weeks or until patient is stable, whichever is longer • Use of β-lactams should be informed by susceptibility profile • Continue oral treatment to complete total of 60 days • Treatment for immunocompromised individuals and pregnant women as above; recommendation based on life-threatening nature of illness
	Anthrax–cutaneous
Treatment	• Oral therapy: ciprofloxacin 500 mg q12h or doxycycline 100 mg q12h (levofloxacin, moxifloxacin, or clindamycin as alternatives) for 60 days
	Botulism
Treatment	• Early administration of antitoxin • Supportive treatment (hydration, nasogastric suctioning for ileus, mechanical ventilation for respiratory failure)
Postexposure prophylaxis	• Antitoxin administration
	Plague
Treatment	• Preferred: streptomycin 1 g intramuscular twice daily ***or*** gentamicin 5 mg/kg intramuscular or IV once daily or 2 mg/kg loading dose followed by 1.7 mg/ kg intramuscular or IV 3 times daily • Alternative: doxycycline 100 mg IV twice daily or ciprofloxacin 400 mg IV twice daily or chloramphenicol 25 mg/kg IV 4 times daily
Postexposure prophylaxis	• Preferred: doxycycline 100 mg orally twice daily ***or*** ciprofloxacin 500 mg orally twice daily • Alternative: chloramphenicol 25 mg/kg orally 4 times daily
Comments	• 10 days for treatment regimens • 7 days for postexposure prophylaxis
	Smallpox
Treatment	• There is no treatment approved by the Food and Drug Administration for orthopoxviruses, although there are multiple promising agents in animal studies • Treatment is supportive • Antimicrobial agents effective against *Staphylococcus aureus* and streptococci should be used if smallpox lesions are secondarily infected, if bacterial infection endangers the eyes, or if the eruption is very dense and widespread • Adequate hydration and nutrition for substantial fluid and protein losses • Topical idoxuridine should be considered for the treatment of corneal lesions, although its efficacy is unproved for smallpox
Postexposure prophylaxis	• Vaccination within 7 days of exposure unless contraindicated
	Tularemia
Treatment	• Preferred: streptomycin 1 g intramuscular twice daily ***or*** gentamicin 5 mg/kg intramuscular or IV once daily • Alternative: doxycycline 100 mg IV twice daily or ciprofloxacin 400 mg IV twice daily ***or*** chloramphenicol 15 mg/kg IV 4 times daily (not to be used in pregnancy)
Postexposure prophylaxis	• Doxycycline 100 mg orally twice daily or ciprofloxacin 500 mg orally twice daily

	Viral hemorrhagic fevers		
Treatment	• Intensive supportive care • Ribavirin • For confirmed or suspected Bunyaviridae (Old World Hantavirus, Crimean–Congo hemorrhagic fever, Rift Valley fever) and Arenaviridae (Lassa virus) infections under an Investigational New Drug (IND) protocol • Not useful for Ebola or Marburg viral hemorrhagic fevers		
	Ribavirin	**Loading dose**	**Maintenance dose**
	Intravenous	• 30 mg/kg IV (maximum 2 g) once	• 16 mg/kg IV (maximum 1 g per dose) q6h for 4 days followed by 8 mg/kg IV (maximum 500 mg per dose) q8h for 6 days
	Oral	• 2000 mg orally once	• Weight >75 kg: 600 mg orally bid for 10 days • Weight ≤75 kg: 400 mg orally in a.m., 600 mg orally in p.m. for 10 days
	• Convalescent plasma in Argentinian and Bolivian hemorrhagic fevers		
Postexposure prophylaxis	• Prophylactic ribavirin for Bunyaviridae and Arenaviridae infections, under IND status, may be useful		

achievement of adequate drug levels in the central nervous system; and the potential for additive or synergistic effects using multiple therapies with different targets.

Once the antimicrobial susceptibility profile of the organism has been determined and clinical improvement is evident, therapy may be tailored. Isolated cutaneous disease may be managed with single, oral antimicrobials but, as in other forms of anthrax, monotherapy using β-lactam agents is contraindicated due to resistance concerns. The recommended duration of therapy is 60 days for all BT-associated forms of anthrax due to presumed concomitant inhalational exposure to the primary aerosol and experimental animal data supporting a persistent risk of latent infection from delayed germination of spores.

Because anthrax is a toxin-mediated illness, some advocate the use of clindamycin as part of combination therapy despite the dearth of clinical data, citing the drug's theoretical benefit of diminishing bacterial toxin production, a strategy employed in some toxin-mediated streptococcal infections. Central nervous system penetration is another consideration in therapy selection and drives the preferential use of ciprofloxacin over doxycycline, plus augmentation with chloramphenicol, rifampin, or penicillin when meningitis is suspected. Corticosteroids have been used as adjunctive therapy in the setting of meningitis or severe mediastinal or head/neck edema, but there are scant data of their definitive efficacy. In the future it is likely that novel therapies, such as toxin inhibitors or receptor antagonists, will be available, in concert with antimicrobials, to treat systemic anthrax. Anthrax vaccine has been proven to be effective in preventing cutaneous anthrax in human clinical trials and in preventing inhalational disease after aerosol challenge in nonhuman primates. The vaccine, which acts by generating an immune response to protective antigen, a key component of anthrax toxin, has been generally found to be safe and has been recommended, in combination with antimicrobials, in a three-dose regimen as postexposure prophylaxis following exposure to aerosolized spores. Passive immunotherapy with anthrax immunoglobulin may serve an adjunct role to antimicrobials and may provide additional benefit in illness caused by multidrug-resistant pathogens. Raxibacumab, a recently approved, recombinant, fully human, monoclonal antibody targeted against anthrax-protective antigen blocks the formation of anthrax toxins and may have use in advanced disease, drug-resistant cases, or as part of a combination, multifocal approach to therapy.

Plague

Yersinia pestis is typically susceptible in vitro to penicillins, many cephalosporins, carbapenems, aminoglycosides, quinolones, and tetracyclines. It is variably susceptible to trimethoprim, chloramphenicol, and rifampin and is commonly resistant to macrolides and clindamycin. Recommended therapeutic approaches to plague in the BT setting are detailed in Table 122.4.

Naturally occurring antibiotic-resistant strains of *Y. pestis* have been reported in endemic areas of the world and are extremely concerning with respect to the development of biologic weapons.

Production of the currently licensed formalin-inactivated vaccine was discontinued by its

manufacturers in 1999; this product had demonstrated efficacy in preventing or ameliorating bubonic disease but not primary pneumonic plague. A subunit vaccine using a bacterial capsular protein has demonstrated protective efficacy in an animal model of pneumonic plague.

Tularemia

Francisella tularensis is generally susceptible in vitro to aminoglycosides, tetracyclines, rifampin, and chloramphenicol; however, many strains are resistant to β-lactams. Similar to the treatment of plague and lacking contraindications, therapy with streptomycin or gentamicin is preferred although alternatives, such as ciprofloxacin, are effective. Because the use of drug-resistant organisms is possible in a bioterrorist event, empiric therapy should account for this, and antimicrobial susceptibility testing of isolates should be expeditiously accomplished. A live attenuated vaccine derived from the avirulent live vaccine strain has been used to protect laboratorians working with *F. tularensis* but is not approved for commercial use.

Botulism

Supportive medical care, airway protection, and mechanical ventilation represent the primary modes of therapy for botulism. Advancements in these modalities account for the improvements in clinical outcomes observed since the mid 1950s; the mortality rate from foodborne botulism in the United States has decreased from 60% to 6%. Passive immunization with equine antitoxin, early in the course of clinical illness, remains the specific treatment of choice to neutralize circulating toxin. Timely administration of this product may be neuroprotective and mitigate severity of disease but will not reverse extant paralysis. Antitoxin should be given to patients with neurologic symptoms as soon as possible after the diagnosis of botulism is suspected; treatment should not be delayed for definitive diagnosis. In the United States, antitoxin is available only from the CDC via state and local health departments. As with any equine-based antisera, anaphylaxis is a potential risk in allergic individuals. To screen for hypersensitivity, skin testing with escalating challenge doses may be necessary before proceeding to a full dose. Patients responding to intradermal challenge with systemic symptoms or signs of hypersensitivity may be desensitized with expert guidance and ready access to epinephrine and airway protection in the event of an adverse reaction.

Smallpox

A suspected case of smallpox warrants immediate implementation of stringent contact and airborne precautions, in a negative-pressure, respiratory isolation setting, and immediate engagement of public health authorities for diagnostic, forensic, and epidemiologic purposes. Vaccination of potential exposures, so-called ring vaccination and containment, must be expeditiously performed; vaccination of symptomatic individuals is indicated if in the early stages of illness, as this is known to be effective in controlling the spread of disease, may mitigate the individual course of disease, and/or may prevent death. There are no currently approved antiviral treatments for smallpox, although cidofovir, licensed for the treatment of cytomegalovirus, has shown promise in vitro and in animal studies for the prevention of orthopoxvirus infection if given proximate to exposure. Topical idoxuridine may be useful in the setting of ocular involvement. Bacterial superinfection is a common complication of smallpox and a frequent cause of death in infected individuals. Aggressive deployment of penicillinase-resistant antimicrobial agents should be used to manage secondary infections with additional consideration given to the institutional and community prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in specific areas. Vaccinia immune globulin (VIG) is indicated for the management of specific, severe complications of smallpox vaccine; there is no evidence to support the use of VIG in either the treatment or prophylaxis of smallpox infections.

Viral hemorrhagic fevers

The mainstay of treatment for all etiologies of viral hemorrhagic fevers (VHF) is supportive medical care, with special attention paid to hemodynamics, volume status, and respiratory parameters. As many of these agents cause systemic hypotension while at the same time causing capillary leak syndromes, careful monitoring of fluid and electrolyte balance is an important component of patient management. Invasive hemodynamic monitoring, mechanical ventilation, blood product support, dialysis, and neurologic support are often needed.

Although there are no approved antiviral therapies for VHF, the nucleoside analog ribavirin has in vitro and in vivo activity against some arenaviral and bunyaviral etiologies of VHF, such as Rift Valley fever, Lassa fever, and Congo–Crimean hemorrhagic fever. The drug has been shown to reduce morbidity from hemorrhagic fever with renal syndrome, caused by Old World hantaviruses, and to probably reduce morbidity and mortality from Lassa fever. Intravenous ribavirin given within the first 6 days of fever to patients with Lassa fever who had high levels of viremia decreased mortality from 76% to 9%. The drug is available under IND status from the CDC and USAMRIID and is associated with significant hemolysis, cytopenias from marrow suppression, and is teratogenic in animals. Ribavirin appears to have no clinical utility in infections caused by filoviruses, such as Marburg or Ebola, or flaviviruses.

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123. Actinomycosis

Thomas A. Russo and Rajinder P. S. Bajwa

ETIOLOGIC AGENTS

Actinomycosis is an infectious syndrome caused by anaerobic or microaerophilic bacteria, primarily from the genus *Actinomyces*. It is most commonly caused by *Actinomyces israelii*. However, *Actinomyces naeslundii*, *Actinomyces odontolyticus*, *Actinomyces viscosus*, *Actinomyces meyeri*, and *Actinomyces gerencseriae* are less common causes of infection. Advances in microbiologic taxonomy, using genotypic methods such as comparative 16S ribosomal RNA (rRNA) or sequencing of alternative genes, have led to the identification of many new *Actinomyces* species from both human and animal specimens. Presently 46 species and 2 subspecies have been recognized (http://www.bacterio.cict.fr/a/actinomyces.html). Although the syndrome of actinomycosis can be caused by these more recently described agents, most of the infections are not "classic" actinomycosis. Infections due to *Actinomyces neuii* have been increasingly recognized. Nearly all of actinomycotic infections are polymicrobial in nature. *Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans*, *Eikenella corrodens*, *Fusobacterium*, *Bacteroides*, *Capnocytophaga*, *Staphylococcus*, *Streptococcus*, and Enterobacteriaceae are commonly co-isolated ("companion organisms") with the agents of actinomycosis in various combinations depending on the site of the infection.

EPIDEMIOLOGY AND PATHOGENESIS

The etiologic agents of actinomycosis are members of the normal oral flora and are often present in bronchi and the gastrointestinal and female genital tracts. Although males have a higher incidence of infection (perhaps due to more frequent trauma and poorer dental hygiene), actinomycosis occurs in all age groups and geographic locations. Disruption of the mucosal barrier is the critical step for the development of actinomycosis. Subsequently, local infection may ensue and once established, if untreated, spreads contiguously ignoring tissue planes in a slow, progressive manner. Although acute inflammation may initially occur at the site of infection, the hallmark of actinomycosis is the characteristic chronic, indolent phase. This stage is manifested by lesions that usually appear as single or multiple indurations. Central necrosis develops that consists of neutrophils and sulfur granules (a finding virtually diagnostic of this disease). The walls of the mass are fibrotic and characteristically described as "wooden." Over time sinus tracts to the skin, adjacent organs, or bone may develop. Rarely distant hematogenous seeding occurs. Foreign bodies appear to facilitate infection. This occurs most frequently with intrauterine contraceptive devices (IUCDs). Although actinomycosis has been described in the setting of various immunosuppressive therapies or states of host compromise, it remains unclear which arm(s) of host defense prevents/control infection. The contribution of the non-*Actinomyces* co-isolates or companion organisms to the pathogenesis of actinomycosis is also uncertain.

INFECTIOUS SYNDROMES

Clinical presentations are myriad. Once common in the pre-antibiotic era, today the incidence of actinomycosis is diminished and, as a result, so is its timely recognition. It has been called "the most misdiagnosed disease" and stated that "no disease is so often missed by experienced clinicians." Actinomycosis remains a diagnostic challenge. An awareness of the full spectrum of disease will expedite diagnosis and treatment and minimize the unnecessary surgical interventions, morbidity, and mortality that all too often occur with this disease. Three clinical presentations, in particular, warrant consideration of this unique infection. First, the combination of chronicity, progression across tissue boundaries, and masslike features mimics malignancy, with which it is often confused. Second, cure of established actinomycosis

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requires prolonged treatment. Short courses of therapy with active agents usually result in only transient improvement. Therefore, actinomycosis should be thought of with refractory or relapsing infections. Last, development of a sinus tract, which may spontaneously resolve and recur, should prompt consideration of this disease.

Oral–cervicofacial disease

This is the most frequent site for infection. Pain, fever, and leukocytosis are variably present. The usual presentation is a soft-tissue swelling, abscess, or mass lesion that is often mistaken for a neoplasm. The angle of the jaw is the most common location (Figure 123.1), but actinomycosis should be considered with any mass lesion or relapsing infection in the head and neck. Rarely, otitis, sinusitis, and canniculitis can also occur. Isolated masses or ulcerative lesions of the tongue, vallecula, nasal cavity, nasopharynx, soft tissues of the head and neck, salivary glands, patent thyroglossal duct, thyroid, branchial cleft cyst, hypopharynx, or larynx have also been described. Recently, radiation therapy and particularly bisphosphonate therapy have been increasingly recognized for contributing to an increased incidence of actinomycotic infection of the mandible and maxilla. Contiguous spread to the cranium, cervical spine, or the thorax and the attendant complications are potential sequelae.

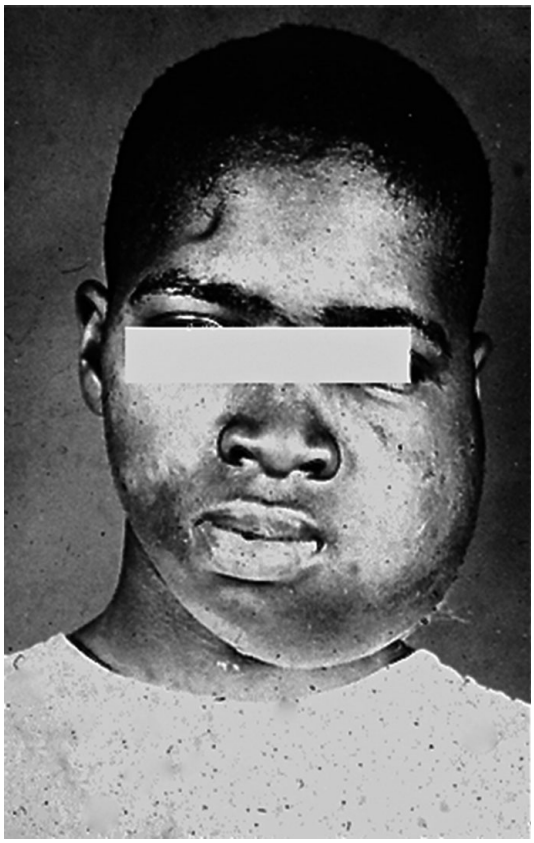

Figure 123.1. Submandibular actinomycotic infection "lumpy jaw." (Courtesy of Dr. Arthur Di Salvo.)

Thoracic disease

The usual presentation is an indolent, progressive course that involves the pulmonary parenchyma and/or the pleural space. Chest pain, fever, and weight loss are common. A cough, when present, is variably productive. The most common radiographic appearance is either a mass lesion or pneumonia. Cavitary disease or hilar adenopathy may develop. Many cases have pleural thickening, effusion, or empyema. Pulmonary disease that crosses fissures or pleura; involves the mediastinum, contiguous bone, or the chest wall; or is associated with a sinus tract should suggest actinomycosis. Mediastinal infection is uncommon. The structures within the mediastinum and the heart, including heart valves, can be involved in various combinations, resulting in a variety of presentations. Isolated disease of the breast occurs rarely.

Abdominal disease

Abdominal actinomycosis is often unrecognized. Months to years usually pass from the inciting event (e.g., appendicitis, diverticulitis, peptic ulcer disease, foreign-body perforation, bowel surgery, or ascension from IUCD-associated pelvic disease) to diagnosis. Because of the flow of peritoneal fluid and/or direct extension of primary disease, virtually any abdominal organ, region, or space can be involved. The usual presentation is either an abscess or a mass lesion that is often fixed to underlying tissue and mistaken for a tumor. Sinus tracts to the abdominal wall or perianal region may develop. Hepatic infection usually presents as single or multiple abscesses or masses. Isolated disease is presumably via hematogenous seeding from cryptic foci. All levels of the urogenital tract can be infected. Bladder involvement, usually due to extension of pelvic disease, may result in obstruction or fistulas to bowel, skin, or uterus. Renal disease usually presents as pyelonephritis and/or renal and perinephric abscess.

Pelvic disease

Actinomycotic involvement of the pelvis is strongly associated with IUCDs. Although the magnitude of risk is unclear, it would appear to be small. Disease rarely occurs when an IUCD has been in place for less than 1 year; however, the risk of infection increases with time and is often seen in the setting of the "forgotten" IUCD. Symptoms are typically indolent with fever, weight loss, abdominal pain, and abnormal vaginal bleeding or discharge being most common. An endometritis, if untreated, may progress to a pelvic mass or a tubo-ovarian abscess. Unfortunately, diagnosis is often delayed, and a "frozen pelvis" mimicking malignancy or endometriosis will develop by the time of recognition.

Central nervous system

Central nervous system (CNS) infection is rare. Single or multiple brain abscesses are most common, usually appearing on computed tomography (CT) as a ring enhancing lesion with a thick wall that may be irregular or nodular. Rarely primary meningitis occurs.

Musculoskeletal infection

Osteomyelitis is usually due to adjacent soft-tissue infection but may be associated with trauma (e.g., fracture of the mandible) or hematogenous spread. The uncommon infection of the extremities is usually a result of trauma. Skin, subcutaneous tissue, muscle, and bone are involved alone or in various combinations. Cutaneous sinus tracts frequently develop. Actinomycotic infections of hip and knee prostheses have also been described.

Disseminated disease

Hematogenous spread of infection from any location may rarely result in multiorgan involvement, with the lungs and liver most commonly affected. The presentation of multiple nodules may mimic disseminated malignancy. *A. meyeri* appears to have the greatest capability of causing this syndrome.

DIAGNOSIS

The diagnosis of actinomycosis is rarely considered. Most often the first mention of actinomycosis is from the pathologist after extensive surgery (Figure 123.2). Because medical therapy alone is often sufficient for cure, the challenge for the clinician is to consider actinomycosis so that this uncommon and unusual infection can be diagnosed in the least invasive fashion and unnecessary surgery can be avoided. CT- or ultrasound-guided aspirations or biopsies are successfully used to obtain clinical material for diagnosis, although surgery may be required. The diagnosis is most commonly made by microscopic identification of sulfur granules (an in vivo matrix of bacteria and host material) in pus or tissues, although occasionally sulfur granules can be grossly identified from draining sinus tracts or pus. Microbiologic identification is less frequent, due to either prior antimicrobial therapy or omission. To optimize yield, the avoidance of even a single dose of antibiotics is mandatory. Because these organisms are normal oral and genital tract flora, their identification in the absence of sulfur granules from sputum, bronchial washings, and cervicovaginal secretions is of little significance. Although not routinely utilized, 16S rRNA gene amplification and sequencing has been successfully used to increase diagnostic sensitivity.

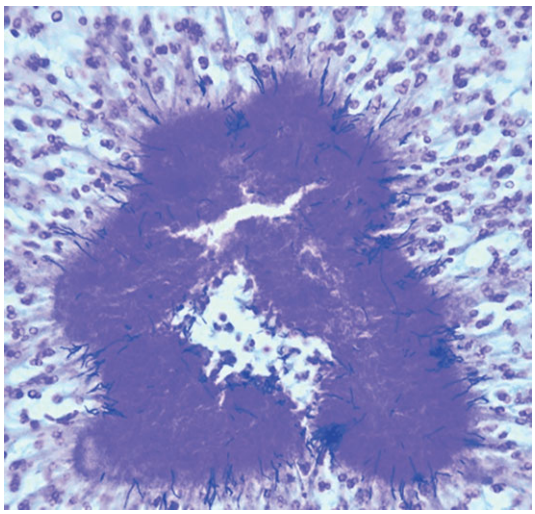

Figure 123.2. Actinomycotic sulfur granule demonstrating the slender, branched gram-positive filaments of *A. israelii*; magnification, ×100. (Courtesy of Dr. A. T. Warfield, Department of Cellular Pathology, University Hospital Birmingham NHS FT, Birmingham, UK.)

TREATMENT

Antimicrobial therapy

Controlled trials either evaluating antimicrobials or designed to define duration of therapy in the treatment of actinomycosis have not been

performed and will never be done. Therefore, treatment decisions are based primarily on the collective clinical experience. Two principles of therapy have evolved. It is necessary to treat this disease both with high doses and for a prolonged period of time. Presumably, this is because of the difficulties of antimicrobials penetrating the thick-walled masses that commonly occur with this infection and/or the sulfur granules themselves.

Although therapy should always be individualized, 18 to 24 million units of penicillin intravenously (IV) for 2 to 6 weeks, followed by oral therapy with penicillin or amoxicillin for 6 to 12 months is a reasonable guideline for serious infections and bulky disease. Cases with less extensive disease, particularly in the head and neck region, may require a shorter course of therapy. If the duration of therapy is extended beyond the resolution of measurable disease, then relapses, one of the clinical hallmarks of this infection, will be minimized. CT and magnetic resonance imaging (MRI) studies are generally the most objective modalities to accomplish this goal. MRI scans are often more sensitive than CT scans for detecting residual infection and should be employed if possible, particularly in areas where the consequences of relapse are particularly significant (e.g., CNS). For penicillin-allergic patients, tetracycline has been used most extensively with success. Erythromycin, doxycycline, and clindamycin are other suitable alternatives (Table 123.1). In the pregnant, penicillin-sensitive patient erythromycin is a safe alternative. Remarkably, little clinical information is available on the newer antimicrobial agents. Anecdotal successes have been reported with imipenem, ceftriaxone, ceftizoxime, and piperacillin–tazobactam (Table 123.1). Available data suggest that oxacillin, dicloxacillin, cephalexin, metronidazole, and aminoglycosides should be avoided.

Table 123.1 Antibiotic therapy for actinomycosis[a]

Group 1: extensive successful clinical experience[b]
Penicillin (18–24 million units/d IV q4h), (1–2 g/d PO q6h)
Erythromycin (2–4 g/d IV q6h), (1–2 g/d PO q6h)
Tetracycline (1–2 g/d PO q6h)
Doxycycline (200 mg/d IV or PO q12–24h)
Minocycline (200 mg/d IV or PO q12h)
Clindamycin (2.7 g/d IV q8h), (1.2–1.8 g/d PO q6–8h)
Group 2: anecdotal successful clinical experience
Ceftriaxone
Ceftizoxime
Imipenam
Piperacillin–tazobactam
Group 3: agents predicted to be efficacious based on in vitro activity
Moxifloxacin
Vancomycin
Linezolid
Quinupristin–dalfopristine
Group 4: agents that should be avoided
Metronidazole
Aminoglycosides
Oxacillin
Dicloxacillin
Cephalexin

Abbreviations: IV = intravenously; PO = orally.
a Additional coverage for concomitant "companion" bacteria may be required.
b Controlled evaluations have not been performed. Dose and duration require individualization depending on the host, site, and extent of infection. As a general rule, a maximum antimicrobial dose for 2–6 weeks of parenteral therapy followed by oral therapy for a total duration (6–12 months) is required for serious infections and bulky disease; whereas a shorter duration may suffice for less extensive disease, particularly in the oral–cervicofacial region.

Home therapy

For home IV therapy, the ease of once-a-day dosing makes ceftriaxone appealing in certain circumstances; however, a greater body of literature supporting its efficacy would be desirable. The availability of portable infusion pumps for home therapy allows for both the appropriate dosing and practical administration of IV penicillin. For infections in critical sites (e.g., CNS) this approach remains the safest until more information is available on other agents. The pharmacokinetic properties, availability of oral and parenteral formulations, and potential efficacy of azithromycin also make this agent appealing. Unfortunately few in vitro and no clinical data exist on its use to treat actinomycosis.

Treatment of co-isolates

It is unclear whether other bacteria frequently co-isolated with the etiologic agents of actinomycosis require treatment; however, many of them are pathogens in their own right. Designing a therapeutic regimen that includes coverage for these organisms during the initial treatment course is reasonable. If microbiology is not available, it is important to consider the site of infection when designing empiric coverage. For example, *Aggregatibacter actinomycetemcomitans, Eikenella*

corrodens, *Fusobacterium*, and *Capnocytophaga* are more likely to be co-isolates in head and neck infection, whereas the Enterobacteriaceae are more commonly co-isolated in abdominal infection.

Surgery or percutaneous drainage

In the pre-antibiotic era, surgical removal of infected tissue was the only beneficial treatment. Despite the availability of effective antimicrobial therapy, combined surgical therapy is still advocated by some authorities. However, an increasing body of literature now supports the approach of initially attempting a cure with medical therapy alone. Successes have been reported in cases of extensive disease, which initially appeared to be incurable using antibiotics alone. CT and MRI should be used to monitor the response to therapy. In most cases either surgery can be avoided or a less extensive procedure will be necessary. This approach is particularly important when the possibility of sparing critical organs is involved, such as the bladder or reproductive organs in women of childbearing age. In a patient with disease in a critical location (e.g., epidural space, selected CNS disease), with significant hemoptysis, or if suitable medical therapy fails, surgical intervention may be appropriate.

In the setting of actinomycosis presenting as a well-defined abscess, percutaneous drainage in combination with medical therapy is a reasonable approach.

Treatment of the immunocompromised host

Actinomycosis has been described in association with human immunodeficiency virus (HIV) infection, steroid use, and lymphoproliferative tumors. Whether these infections were because of disease-associated disruptions of mucosa (e.g., cytomegalovirus infection with HIV infection), host defense abnormalities, immunosuppressive therapy, or some combination of these is unclear. From a treatment perspective it is reasonable to initially use the same approach as that for noncompromised hosts. Aggressive treatment directly against HIV (e.g., highly active antiretroviral therapy) and minimizing immunosuppressive therapy is also desirable if possible. Although prospective controlled data are not available, when actinomyces are identified in the setting of bisphosphonate-related osteonecrosis of the jaw (BRONJ) a prolonged course of antimicrobial therapy is reasonable and appears to be efficacious. The role of surgical debridment for BRONJ is less clear but resection of at least necrotic bone seems prudent.

Refractory disease

Usually actinomycosis responds well to medical therapy. However, refractory or perceived refractory disease has been described in HIV-infected individuals as well as apparently normal hosts. In this setting basic principles of infectious disease apply. Exclude infection elsewhere (e.g., line-related, *Clostridium difficile* colitis) and/or noninfectious causes (e.g., drug fever, unrelated disease) as being responsible. Confirm that high-dose parenteral therapy is being utilized for initial treatment. Identify and drain significant purulent collections associated with the actinomycotic infection. Consider the possibility that untreated co-isolates (companion organisms) may be responsible. Although penicillin-resistant strains or evolution of resistance during therapy have not yet been clearly documented in vivo, this possibility should be considered when other more likely scenarios are excluded. Finally, surgery should be considered when infection is refractory to medical therapy, although as stated above, this usually can be avoided, at least initially.

Actinomyces-like organisms

An unresolved issue is whether screening cervical or endometrial specimens for *Actinomyces*-like organisms (ALOs) or their detection by immunofluorescence (IF) can predict/prevent IUCD-associated disease. Furthermore, a Papanicolaou smear may fail to detect ALOs even in the presence of active actinomycosis. Although the risk appears to be small, the consequences of infection are significant. Therefore, until more quantitative data become available, in the presence of symptoms that cannot be accounted for, regardless of whether ALOs or IF-positive organisms are detected, it would appear prudent to remove the IUCD and, if advanced disease is excluded, empirically treat for 14 days for possible early pelvic actinomycosis. The detection of ALOs or IF-positive organisms in the absence of symptoms warrants patient education and close follow-up, but not removal of the IUCD, unless an equally suitable means of contraception can be agreed upon.

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124. Anaerobic infections

Sydney M. Finegold

Anaerobic infections are common and some are serious, with a high mortality rate. They are easily overlooked because special precautions are needed for specimen collection and transport to do good bacteriologic studies and because some clinical laboratories fail to grow many or most anaerobes (a number of laboratories do not even do anaerobic cultures).

Treatment of anaerobic infections may be difficult. Failure to treat for anaerobes in mixed infections may lead to poor or no response. Many antibacterial agents have poor activity against many or most anaerobes, particularly aminoglycosides, the older quinolones, trimethoprim–sulfamethoxazole, and monobactams. Resistance of anaerobes to antimicrobials is increasing.

The most important anaerobes clinically are various genera of gram-negative rods. *Bacteroides*, especially the *Bacteroides fragilis* group, made up of several species (including *B. fragilis*), is particularly important. The other principal gram-negative genera are *Prevotella, Porphyromonas, Fusobacterium, Bilophila*, and *Sutterella*. Among the gram-positive anaerobes are cocci (formerly in *Peptostreptococcus*, now in several genera) and spore-forming (*Clostridium*) and non-spore-forming bacilli (especially *Actinomyces* and *Propionibacterium*) (Table 124.1).

Table 124.1 Anaerobes most commonly encountered in infection[a]

Bacteroides fragilis group, especially *B. fragilis*
Pigmented and nonpigmented *Prevotella*
Fusobacterium nucleatum
Anaerobic gram-positive cocci
Clostridium perfringens, Clostridium ramosum

[a] These five groups together account for about two-thirds of anaerobes from clinically significant infections involving anaerobes.

Table 124.2 Incidence of various anaerobes as normal flora in the human[a]

	Anaerobic cocci	Anaerobic gram-negative bacilli	Clostridia	NSF-GPR
Mouth	++++[b]	++++	Rare	+ to ++
Intestine	++++	++++	++++	++++
Genitourinary tract[c]	+++	++	+	+ to ++

[a] Skin and upper respiratory tract are less important.

[b] The ranking + to ++++ reflects both consistency of occurrence and density of numbers.

[c] Includes vagina, external genitalia, and urethra.

Abbreviation: NSF-GPR = non-spore-forming gram-negative rods.

SOURCE OF ANAEROBIC INFECTION

Virtually the only source of anaerobes causing infection is the indigenous flora of mucosal surfaces and, to a much lesser extent, the skin (Table 124.2). The major exception is *Clostridium difficile*, the principal cause of antimicrobial agent-associated colitis, which has caused nosocomial infections. Anaerobes outnumber aerobes by 10:1 in the oral and vaginal flora and by 1000:1 in the colon. Factors predisposing to anaerobic infection include disruption of normal mucosal or cutaneous barriers by disease, surgery, or trauma; tissue injury (which reduces oxidation–reduction potential, favoring growth of anaerobes); impaired blood supply; obstruction of a hollow viscus; and foreign body. Other important factors include the numbers of organisms that get into deeper tissues (the inoculum size), various virulence factors (toxins, enzymes, and other substances) produced by anaerobes, and whether the host's defense system is intact.

TYPES OF INFECTION INVOLVING ANAEROBES

In terms of overall frequency, there are four major sites of anaerobic infection: pleuropulmonary, intra-abdominal, female genital tract, and skin

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Table 124.3 Infections commonly involving anaerobic bacteria

Brain abscess
Subdural empyema
Endophthalmitis, panophthalmitis
Periodontal disease
Root canal infection
Odontogenic infections
Chronic sinusitis
Chronic otitis media, mastoiditis
Peritonsillar abscess
Neck space infections
Aspiration pneumonia
Lung abscess
Pleural empyema
Pyogenic liver abscess
Peritonitis
Intra-abdominal abscess
Appendicitis
Wound infection after bowel or female genital tract surgery or trauma
Endometritis
Salpingitis, tubo-ovarian abscess
Pelvic abscess
Human and animal bite infection
Infected decubitus ulcer
Anaerobic cellulitis
Clostridial myonecrosis (gas gangrene)
Synergistic nonclostridial myonecrosis
Anaerobic streptococcal myositis
Necrotizing fasciitis
Chronic osteomyelitis
Actinomycosis
Antimicrobial-induced colitis and pseudomembranous colitis

and soft tissue with or without involvement of underlying bone. Other infections that primarily involve anaerobic bacteria but are seen less commonly include brain abscess and bite-wound infections. Virtually all types of infection occurring in humans may involve anaerobic bacteria, and no organ or tissue of the body is immune to infection with these organisms. Table 124.3 lists infections commonly involving anaerobic bacteria. Abscess formation and tissue destruction are common characteristics of anaerobic infection. Synergy between various anaerobes or between anaerobes and aerobes is often important in mixed anaerobic infections.

Table 124.4 Major clues to anaerobic infection

Foul-smelling discharge
Infection close to mucosal surface
Tissue necrosis, gangrene
Gas in tissues or discharges
Infection associated with malignancy
Infection secondary to human or animal bite
Infection related to the use of aminoglycosides, quinolones, trimethoprim–sulfamethoxazole, monobactams, or other drugs with poor activity against anaerobes
Classic clinical picture such as gas gangrene, actinomycosis
Infections that are classically of anaerobic origin (e.g., brain abscess, lung abscess)
Septic thrombophlebitis
Unique morphology on Gram stain of exudate
No growth on routine culture; sterile pus

Some anaerobic infections are unique (e.g., lung abscess, actinomycosis) and are readily suspected clinically. Major clues to anaerobic infection are listed in Table 124.4. Only the foul or putrid odor of a lesion or its discharge is specific; the other clues nonetheless may be highly suggestive. The Gram stain is useful because many anaerobes are unique morphologically. Information as to the relative numbers of various organisms may be extremely useful in directing empiric therapy.

Relatively recently, a number of serious infections involving various clostridia have been documented. Included are a more serious form of *C. difficile*-associated diarrheal disease or colitis involved in a number of hospital-acquired outbreaks, endometritis and toxic shock syndrome due to *Clostridium sordellii* following abortions, and serious soft-tissue infections (including necrotizing fasciitis and anaerobic myonecrosis) due to *C. sordellii* and *Clostridium novyi* in "skin-popping" drug addicts.

COLLECTION AND TRANSPORT OF SPECIMENS

Proper collection and transport of specimens is crucial for recovery of anaerobes in the laboratory. Because anaerobes are normal flora, the clinician should be certain not to contaminate the specimens with such flora; this may be difficult at times. A good example of the problem

is the patient with suspected aspiration pneumonia. Expectorated sputum is unsuitable because of the large numbers of anaerobes and other organisms present in saliva as indigenous flora; it is necessary to bypass the normal flora. If an empyema is present, thoracentesis provides a good specimen and is indicated therapeutically. In the absence of pleural fluid, bronchoalveolar lavage or use of a plugged double-lumen catheter with a protected bronchial brush, with quantitative culture, should be used.

Proper transport requires placing the specimen under anaerobic conditions in a nonnutritive holding medium (in an oxygen-free glass tube or vial) for the trip to the laboratory.

THERAPY

The two key approaches to treatment are surgery and antimicrobial therapy. Debridement and drainage usually are essential. Failure to carry out prompt and thorough surgical therapy may lead to lack of response to appropriate antimicrobial agents. Some abscesses are amenable to percutaneous drainage under guidance of ultrasound or computed tomography.

Hyperbaric oxygen (HBO) may have value in selected circumstances, such as gas gangrene, to help demarcate the infection; for example, it may indicate where amputation should be done in the case of an extremity infection. There has never been clear-cut clinical evidence of significant benefit from HBO; however, surgical therapy should never be delayed to administer HBO.

Initial antimicrobial therapy is necessarily empiric; it takes some time to get definitive information on the infecting flora because it is usually complex. Rational empiric therapy is based on the clinician's assessment of the nature of the infectious process, knowledge of the usual infecting flora in such infections (Tables 124.5–124.9), and patterns of resistance of anaerobic bacteria to antimicrobial drugs in the particular hospital. Also, the clinician must take into account how the usual flora may have been modified by pathophysiology or disease and by prior antimicrobial therapy. Careful analysis of the Gram stain of the specimen may also suggest the need to modify the empiric approach. In certain situations, the pharmacologic properties of the drugs and whether they are bactericidal or not are important considerations. In central nervous system infections, for example, the drug must cross the blood–brain barrier well. In such infections and in

Table 124.5 Usual flora in anaerobic pleuropulmonary infections[a]

Anaerobes
Anaerobic gram-positive cocci
Pigmented *Prevotella* (*P. denticola, P. melaninogenica, P. intermedia, P. nigrescens, P. loescheii*)
Nonpigmented *Prevotella* (*P. oris, P. buccae, P. oralis*)
Fusobacterium nucleatum
Bacteroides fragilis group
Non-spore-forming gram-positive rods (*Actinomyces*, *Eubacterium*, *Lactobacillus*)
Viridans streptococci

[a] In hospital-acquired infections (e.g., aspiration pneumonia), various nosocomial pathogens, such as *Staphylococcus aureus*, Enterobacteriaceae, and *Pseudomonas*, may be involved in addition to the indigenous flora listed above.

Table 124.6 Usual flora in intra-abdominal infection[a]

Predominant anaerobes
Bacteroides fragilis
Bacteroides thetaiotaomicron
Bilophila wadsworthia
Anaerobic gram-positive cocci
Clostridium
Predominant aerobes and facultatives
Escherichia coli
Streptococcus (viridans group)
Pseudomonas aeruginosa
Enterococcus
Biliary tract infection
Uncomplicated
E. coli, Klebsiella, Enterococcus, and *Clostridium perfringens*
Complicated (e.g., prior surgery, malignancy)
B. fragilis group may also be involved

[a] In hospital-acquired infections, nosocomial pathogens, such as *Staphylococcus aureus* and various Enterobacteriaceae, may also be involved.

Table 124.7 Usual flora in female genital tract infections

Anaerobes
Anaerobic gram-positive cocci
Bacteroides fragilis group
Prevotella (especially *P. bivia, P. disiens*)
Clostridium (especially *C. perfringens*)
Actinomyces, *Eubacterium* (in intrauterine contraceptive device-associated infections)
Aerobes
Streptococcus (groups A, B, others)
Escherichia coli
Klebsiella
Gonococcus (in sexually active patients)
Chlamydia (in sexually active patients)
Mycoplasma hominis (in postpartum patients)

Table 124.8 Usual flora in diabetic foot ulcers

Anaerobes
Anaerobic gram-positive cocci
Bacteroides fragilis group (especially *B. fragilis and B. thetaiotaomicron*)
Other *Bacteroides*
Pigmented *Prevotella*
Aerobes
Enterococcus
Staphylococcus aureus
Streptococci (especially group B)
Proteus mirabilis
Escherichia coli
Other Enterobacteriaceae
Pseudomonas aeruginosa

Table 124.9 Predominant flora of skin and soft-tissue abscess

In intravenous drug abusers
Anaerobes
Fusobacterium nucleatum
Anaerobic gram-positive cocci
Actinomyces odontolyticus
Pigmented *Prevotella*
Aerobes
Staphylococcus aureus
Streptococcus (*S. anginosus* group, viridans group, group A)
In nonintravenous drug abusers
Anaerobes
Anaerobic gram-positive cocci
Pigmented *Prevotella*
Actinomyces
Fusobacterium nucleatum
Aerobes
Staphylococcus aureus
Streptococcus (*S. anginosus* group, group A, viridans group)

Table 124.10 Principal β-lactamase-producing anaerobes

Bacteroides fragilis group
Bacteroides splanchnicus, B. capillosus
Pigmented *Prevotella, Porphyromonas*
Prevotella oralis group
Prevotella: P. oris, P. buccae
Prevotella: P. bivia, P. disiens
Bilophila wadsworthia
Fusobacterium nucleatum
Fusobacterium: F. mortiferum, F. varium
Clostridium ramosum
Clostridium clostridioforme group (*C. clostridioforme, C. bolteae, C. hathewayi*)
Clostridium butyricum

endocarditis, bactericidal activity is important. A good clinician will be in close contact with the microbiology laboratory, particularly in the case of a very sick patient. Ideally, such contact begins before the specimen is submitted and is maintained until full culture results are available. The microbiologist may take advantage of information from the clinician to use special selective or other media in setting up the culture and can often look at cultures more often than is done with routine cultures, using an anaerobic chamber or other device to examine the culture without exposing it to oxygen. Preliminary culture information may dictate modification of the initial empiric antimicrobial regimen. The use of molecular techniques may lead to much more rapid identification than with conventional procedures.

Antimicrobial resistance is an increasing problem with anaerobic bacteria. Various mechanisms for such resistance are known; they are the same as are seen with aerobes. β-lactamase production is one of the most common mechanisms of such resistance; fortunately, this can be overcome to some extent by combinations of β-lactam drugs with β-lactamase inhibitors such as clavulanic acid, sulbactam, or tazobactam. Table 124.10 lists the more common β-lactamase-producing anaerobes. Unfortunately, hyperproduction of β-lactamases and production of metalloenzyme β-lactamases may render some of our better drugs inactive.

Tables 124.11 and 124.12 summarize the activity of various antimicrobials against the major anaerobes encountered clinically, as found in the Wadsworth Anaerobic Bacteriology Laboratory experience. Testing was done by the Wadsworth agar dilution method. Antimicrobials not listed in the table are not approved by the Food and Drug Administration or are generally not recommended for therapy of anaerobic infections. In most cases, clinical data support the use of these agents for management of infection with the organisms indicated. Patterns of susceptibility vary among geographic locations and even among hospitals in the same city, primarily because of the patterns of usage of antimicrobial agents. Four drugs or groups of drugs are active against most clinically significant anaerobic bacteria. These are metronidazole; carbapenems,

Table 124.11 Susceptibility of gram-positive anaerobic bacteria

Percentage susceptible[a,b]	Anaerobic gram-positive cocci (formerly *Peptostreptococcus*	*C. difficile*[c]	*C. ramosum*	*C. perfringens*	Other *Clostridium* species	NSF-GPR[d]
>95	Penicillin G Piperacillin Amoxicillin + clavulanate Ampicillin + sulbactam Piperacillin + tazobactam Ticarcillin + clavulanate Cefoperazone Ceftriaxone Cefoxitin Ceftazidime Ceftizoxime Tigecycline Imipenem Meropenem Ertapenem Chloramphenicol Linezolid Metronidazole Gatifloxacin	Ampicillin Piperacillin Ticarcillin Amoxicillin + clavulanate Ampicillin + sulbactam Piperacillin + tazobactam Ticarcillin + clavulanate Imipenem Meropenem Vancomycin Tigecycline Metronidazole	Amoxicillin + clavulanate Piperacillin + tazobactam Ticarcillin + clavulanate Ceftizoxime Imipenem Ertapenem Metronidazole Vancomycin	Ampicillin Piperacillin Ticarcillin Ampicillin + sulbactam Amoxicillin + clavulanate Piperacillin + tazobactam Ticarcillin + clavulanate Ceftizoxime Imipenem Ertapenem Chloramphenicol Ciprofloxacin Gatifloxacin Tigecycline Linezolid Vancomycin Metronidazole Azithromycin Clarithromycin Erythromycin	Amoxicillin Ampicillin Carbenicillin Piperacillin Ticarcillin Ampicillin + sulbactam Amoxicillin + clavulanate Imipenem Ertapenem Chloramphenicol Metronidazole	Piperacillin Amoxicillin + clavulanate Ampicillin + sulbactam Piperacillin + tazobactam Ticarcillin + clavulanate Cefotaxime Ceftizoxime Imipenem Meropenem Ertapenem Chloramphenicol Clindamycin Tigecycline Levofloxacin
85–95	Levofloxacin Clindamycin Vancomycin	Ceftriaxone Chloramphenicol	Ampicillin Piperacillin Ampicillin + sulbactam Chloramphenicol Clindamycin	Clindamycin	Moxalactam Penicillin G	Cefoxitin Ceftriaxone Penicillin G Gatifloxacin Azithromycin Clarithromycin Erythromycin Cefoperazone
70–84	Ciprofloxacin Moxifloxacin Azithromycin Clarithromycin Erythromycin	Ertapenem Linezolid	Cefoxitin Clindamycin		Levofloxacin Vancomycin Linezolid Clindamycin Tetracycline	Moxalactam Moxifloxacin Linezolid Tetracycline Vancomycin
50–69	Tetracycline	Clindamycin Tetracycline Azithromycin Clarithromycin Erythromycin	Tetracycline	Tetracycline	Cefoperazone Cefotaxime Cefoxitin Ceftizoxime Ceftriaxone Ciprofloxacin Azithromycin Clarithromycin Erythromycin	Ciprofloxacin Metronidazole
<50		Cefoxitin Ceftizoxime Ciprofloxacin[c]	Ciprofloxacin Moxifloxacin Azithromycin Clarithromycin Erythromycin Linezolid		Ceftazidime	

[a] The order of listing of drugs within percent susceptible categories is not significant.
[b] According to the NCCLS-approved breakpoints (M11-A3), using the intermediate category as susceptible.
[c] Breakpoint is used only as a reference point. *Clostridium difficile* is primarily of interest in relation to antimicrobial-induced pseudomembranous colitis. These data must be interpreted in the context of level of drug achieved in the colon and impact of agent on indigenous colonic flora. Fluoroquinolones may be an important factor in hospital outbreaks of *C. difficile*-associated disease.
[d] Non-spore-forming, gram-positive rods.

Table 124.12 Susceptibility of gram-negative anaerobic bacteria

Percentage susceptible[a,b]	*B. fragilis*	Other *B. fragilis* group[c]	Other *Bacteroides*	*C. gracilis*	*Prevotella*	*Porphyromonas*	*Sutterella wadsworthensis*	*F. nucleatum*	*F. mortiferum* and *F. varium*	Other *Fusobacterium*	*B. wadsworthia*
>95	Piperacillin Amoxicillin + clavulanate Piperacillin + tazobactam Ticarcillin + clavulanate Ampicillin + sulbactam Cefoxitin Meropenem Ertapenem Imipenem Chloramphenicol Levofloxacin Metronidazole	Ampicillin + sulbactam Piperacillin + tazobactam Ticarcillin + clavulanate Ertapenem Imipenem Meropenem Chloramphenicol Gatifloxacin Metronidazole	Cefoperazone Piperacillin Amoxicillin + clavulanate Ampicillin + sulbactam Ticarcillin + clavulanate Cefoxitin Ceftizoxime Cefotaxime Imipenem Chloramphenicol Levofloxacin Metronidazole Clindamycin	Piperacillin Ticarcillin + clavulanate Amoxicillin + clavulanate Piperacillin + tazobactam Cefoxitin Ceftizoxime Ceftriaxone Imipenem Meropenem Ertapenem Chloramphenicol Ciprofloxacin Metronidazole Azithromycin Clindamycin Erythromycin Tetracycline	Ticarcillin + clavulanate Cefoxitin Piperacillin Ceftizoxime Amoxicillin + clavulanate Ampicillin + sulbactam Piperacillin + tazobactam Imipenem Meropenem Ertapenem Tigecycline Chloramphenicol Metronidazole Clindamycin Gatifloxacin	Ceftriaxone Piperacillin Amoxicillin + clavulanate Cefoxitin Ceftizoxime Ertapenem Imipenem Meropenem Chloramphenicol Tigecycline Linezolid Metronidazole Azithromycin Moxifloxacin	Amoxicillin +clavulanate Ticarcillin + clavulanate Cefoxitin Ceftriaxone Ciprofloxacin Imipenem Meropenem Ertapenem	Piperacillin Amoxicillin + clavulanate Piperacillin + tazobactam Ticarcillin + clavulanate Cefoxitin Ceftizoxime Ceftriaxone Imipenem Meropenem Ertapenem Chloramphenicol Tigecycline Linezolid Levofloxacin Gatifloxacin Moxifloxacin Metronidazole Clindamycin Tetracycline	Piperacillin Piperacillin + tazobactam Ticarcillin + clavulanate Cefoxitin Imipenem Meropenem Chloramphenicol Linezolid Metronidazole	Ampicillin + sulbactam Piperacillin + tazobactam Cefoxitin Imipenem Meropenem Chloramphenicol Linezolid Metronidazole Clindamycin Tetracycline	Ampicillin + sulbactam Cefoxitin Ceftizoxime Piperacillin Ticarcillin Amoxicillin + clavulanate Ampicillin + sulbactam Cefoxitin Ceftizoxime Imipenem Chloramphenicol Ciprofloxacin Metronidazole Tetracycline
85–95	Ceftizoxime Clindamycin Moxifloxacin Gatifloxacin	Amoxicillin + clavulanate Piperacillin Cefoxitin Ceftizoxime	Ceftazidime Ceftriaxone Clarithromycin Erythromycin Linezolid	Gatifloxacin Moxifloxacin	Ceftriaxone Azithromycin Clarithromycin Erythromycin Linezolid	Ciprofloxacin Clarithromycin Clindamycin Erythromycin	Piperacillin Piperacillin + tazobactam Ceftizoxime	Azithromycin	Amoxicillin + clavulanate Ceftizoxime Ceftriaxone Moxifloxacin	Piperacillin Amoxicillin + clavulanate Ticarcillin + clavulanate Cefotaxime Ceftizoxime Ceftriaxone	Clindamycin

Percentage susceptible[a,b]	*B. fragilis*	Other *B. fragilis* group[c]	Other *Bacteroides*	*C. gracilis*	*Prevotella*	*Porphyromonas*	*Sutterella wadsworthensis*	*F. nucleatum*	*F. mortiferum* and *F. varium*	Other *Fusobacterium*	*B. wadsworthia*
70–84	Moxalactam Ceftriaxone Clarithromycin Tigecycline Linezolid	Levofloxacin Moxifloxacin Clarithromycin Clindamycin Tigecycline Linezolid	Moxalactam Ofloxacin Azithromycin		Ciprofloxacin Oflaxacin Moxifloxacin		Metronidazole	Ciprofloxacin	Clindamycin Tetracycline	Ceftazidime Moxalactam Ciprofloxacin Azithromycin	Linezolid
50–69	Cefoperazone Cefotaxime Ceftazidime	Cefoperazone Moxalactam Ofloxacin	Ciprofloxacin Tetracycline Tigecycline		Tetracycline	Tetracycline	Clindamycin		Ciprofloxacin		Ertapenem
<50	Vancomycin Ciprofloxacin Azithromycin Erythromycin Tetracycline	Vancomycin Cefotaxime Ceftazidime Ceftriaxone Ciprofloxacin Azithromycin Erythromycin					Linezolid Vancomycin	Clarithromycin Erythromycin	Vancomycin Azithromycin Clarithromycin Erythromycin	Clarithromycin Erythromycin	Amoxicillin Ampicillin Vancomycin

[a] The order of listing of drugs within percentage susceptible categories is not significant.

[b] According to the NCCLS-approved breakpoints (M11-A3), using the intermediate category as susceptible.

[c] Excluding *B. fragilis*.

such as imipenem; chloramphenicol; and combinations of β-lactam drugs with a β-lactamase inhibitor. Non-spore-forming anaerobic gram-positive bacilli (e.g., *Actinomyces* and *Propionibacterium*) are commonly resistant to metronidazole. There are disturbing reports of resistance in small numbers of strains of the *B. fragilis* group to all of the above agents. Three other drugs or groups of drugs have good activity but are less active than the four groups just mentioned. These are cefoxitin, clindamycin, and broad-spectrum penicillins such as ticarcillin and piperacillin. Some 15% to 25% of strains of the *B. fragilis* group are resistant to these latter compounds in many hospitals in the United States and elsewhere. Cefoxitin and clindamycin are relatively weak in activity against clostridia other than *Clostridium perfringens* (20% to 35% of such strains are resistant), and some anaerobic cocci are resistant to clindamycin.

Some cephalosporins, such as ceftizoxime and ceftriaxone, have sufficient antianaerobic activity to be useful in treating certain anaerobic infections and are comparable with cefoxitin and clindamycin plus gentamicin in double-blind comparative studies. These cephalosporins have been shown clearly to be effective in three types of infections: appendicitis with no more than localized complications, female genital tract infections such as pelvic inflammatory disease and endometritis, and infected foot ulcers or similar soft-tissue infection with or without underlying bone infection. One may save on drug costs with these cephalosporins; this also saves the more potent drugs for serious infections. However, they should not be prescribed for severely ill patients.

Because most anaerobic infections are mixed, involving aerobic or facultative bacteria in addition to anaerobes, antimicrobial therapy must cover the key pathogens of all types. Some of the drugs discussed earlier have significant activity against certain aerobes as well, but it may be necessary to add another agent to cover the other flora.

In general, for therapy of serious anaerobic infections, antimicrobials should be given parenterally in the maximum approved dosages, taking into account the weight and renal and hepatic function of the patient. This is because penetration of drugs into abscesses, necrotic tissue, and poorly perfused tissue, all common in serious anaerobic infections, is less than optimal.

Relatively prolonged therapy is also an important consideration in anaerobic infections to avoid relapse; for example, lung abscess usually requires therapy for several weeks, empyema for 2 to 3 months, and actinomycosis for 6 to 12 months or longer. Duration of therapy must be individualized, taking into account the site, type, extent, and severity of the infection, the nature of the infecting organisms, whether or not the host is immunocompromised or in poor condition because of associated or underlying illness, the speed of response to treatment, and other such factors.

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125. Anthrax and other *Bacillus* species

Tirdad T. Zangeneh, Marc Traeger, and Stephen A. Klotz

INTRODUCTION

Anthrax is a disease caused by the gram-positive, aerobic bacterium *Bacillus anthracis* and was recognized in antiquity. The disease figures prominently in the history of modern medicine because it was the first bacterial illness for which successful vaccines were prepared, almost simultaneously by William Smith Greenfield in London and Louis Pasteur in Paris. Anthrax is a zoonosis of herbivores which is encountered worldwide and human cases continue to be seen not infrequently in Turkey, Iran, Afghanistan, Thailand, and countries of sub-Saharan Africa. Grazing wild animals and cattle are very susceptible and human disease in animal husbandmen and herders is closely tied to exposure to infected beasts. Propagating the bacteria in the spore form is used in bioterrorism, a novel and more recent form of human exposure to anthrax, utilizing delivery systems such as the postal service.

To understand anthrax one must keep in mind the natural cycle of disease in animals: spores survive prolonged periods in alkaline soils, rainwater concentrates spores in low-lying depressions and susceptible herbivores gather in these locales during dry periods and inhale aerosolized spores or swallow spores loosely attached to forage. These geographic and climatic factors are usually present prior to animal outbreaks and may culminate in humans being infected accidentally. Spores arise from bacilli exposed to ambient air when blood from dying animals reaches the soil or carcasses are torn apart by scavengers. When the bacilli are exposed to air, spores form in the central and subterminal part of the bacillus. Spores may survive for prolonged periods (~90 years) in soil rich with organic material, a pH greater than 6.1 (alkaline soils) with high concentrations of Ca^{++}. This characterizes a wide geographic swathe in the middle United States from Texas to North Dakota. It is also true for soils in the steppes of Asia and in sub-Saharan Africa where anthrax remains common in wildlife. Although anthrax is considered an obligate pathogen, it is likely that in some circumstances a vegetative bacillus-spore cycle occurs independent of infection in the soil alone.

Currently, human anthrax infections in the resource-rich countries occur as a result of animal infection occurring thousands of miles away from the victim. Due to the worldwide trade in hides and wool, occasional occupational/recreational anthrax infections occur. There have even been recent reports of anthrax among intravenous drug users in Great Britain, their heroin contaminated at the source in Afghanistan. The widespread use of animal vaccines has reduced the number of livestock infections and, secondarily, human infections, but epizootics continue to occur in wildlife particularly in South Africa and even in the United States and Canada.

EPIDEMIOLOGY OF ANTHRAX

Human anthrax infections related to the pursuit of agriculture typically take the form of cutaneous anthrax. This has been the pattern in Turkey and Zimbabwe where the disease is endemic. Occasionally gastrointestinal anthrax occurs and is almost always secondary to consumption of an animal dead from anthrax and usually in rural areas. Inhalational anthrax and meningitis are rare in the agricultural setting. Other persons at risk apart from the animal husbandmen/herders are veterinarians, slaughterhouse workers, and individuals handling bone meal.

Although anthrax occurs among wild animals in many resource-rich countries, human disease is almost always due to importation of contaminated animal products from resource-poor, rural areas of the world endemic for anthrax. Currently, the hyperendemic areas with ongoing animal disease according to the World Health Organization (WHO) are Afghanistan, Turkey, Thailand, and a number of sub-Saharan nations including Zimbabwe. The United States, Canada,

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Table 125.1. Clinical clues that one may be dealing with anthrax

Think anthrax
Employment history: herdsman, veterinarian, textile worker, hide/wool worker
Chest x-ray findings: widened mediastinum; pleural effusion (hemorrhagic)
Cutaneous lesions: necrotizing ulcer with bullae; eschar (bacteria present beneath lesion)
Hemorrhagic meningitis: gram-positive bacteria present in CSF

Table 125.2 Differential diagnosis of cutaneous lesion of anthrax

Zoonotic disease	Differentiating points
Tularemia (*Francisella tularensis*)	Prominent lymphadenopathy
Orf	Painless bullae
Cat scratch	Fleeting eschar
Tick-borne *Rickettsia*: *R. africae*, STARI, RMSF	Small eschar, often with body rash
Plague	Lymphadenopathy; Four Corners area of the United States

Abbreviations: STARI = Southern tick-associated rash illness; RMSF = Rocky Mountain spotted fever.

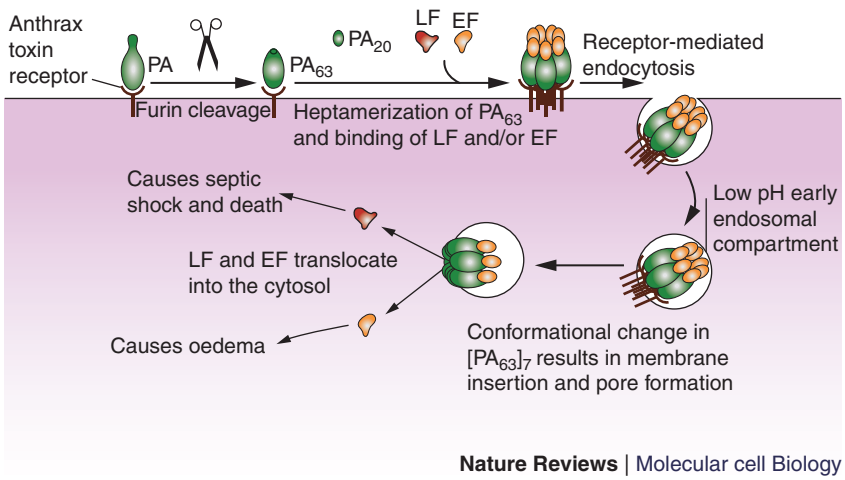

Figure 125.1 Protective antigen (PA) is secreted by *Bacillus anthracis* bacilli and binds to cellular anthrax toxin receptor. A 20-kDa fragment of PA is cleaved by furin, the resulting PA63 fuses with six other PA63 fragments forming a pore for the entry of EF and LF. The structure is brought into the cytosol in an endosome where EF and LF then translocate from the endosome into the cytosol causing edema and cell death, respectively.

and Europe are considered countries with only sporadic disease.

Industrial anthrax is related to the use of animal products such as hair, wool, bone meal, and hides that are contaminated with spores of *B. anthracis*. This form of disease may occur years after the animals are slaughtered. Individuals at risk include tannery and textile workers and anyone using imported wool or yarn, hair, and hides from endemic areas. Disease is usually cutaneous (Table 125.1).

PATHOGENESIS OF ANTHRAX

Animal studies demonstrate that spores introduced through the skin rapidly germinate and within hours the subcutaneous lesions swell and numerous encapsulated gram-positive rods, often "box-car" in shape, are present. The capsule is composed of poly-D-glutamic acid and probably protects the bacterium from host recognition and attack by neutrophils (it is thought to be antiphagocytic). It is a bona fide virulence factor carried on a plasmid, pX02, and loss of the plasmid renders the bacterium less virulent (Table 125.2). The successful animal vaccine developed by Max Sterne uses a strain cured of pX02. Wildtype *B. anthracis* possesses a second plasmid, pX01, that controls toxin production. The toxin consists of three proteins, protective antigen (PA), edema factor (EF), and lethal factor (LF), typical binary toxins with an enzymatic site and binding site. After proteolysis of a small fragment from PA, the protein binds to six other PA fragments forming a heptameric channel to which LF and EF competitively bind and are then endocytosed. EF leads to increased levels of cyclic AMP and swelling whereas LF leads to cell death (Figure 125.1).

Spores inhaled into the lung reach the alveoli where they are phagocytosed by macrophages. Macrophages then transit through the lymphatic

system. Germination of the spores may occur up to 60 days following inhalation as shown in monkeys. In gastrointestinal anthrax hemorrhage and edema are located in the intestinal wall. In some animals the M cell in Peyer's patches may be the site of entry of the microorganism.

CLINICAL MANIFESTATIONS OF ANTHRAX

The clinical presentation of anthrax is variable and dependent on the route of exposure. Presentations include cutaneous, inhalational, and enteric (gastrointestinal and oropharyngeal) forms, which may result in disseminated disease involving the central nervous system (meningitis) and secondary bacteremia leading to sepsis. The majority of infections are due to cutaneous disease and these infections have the lowest mortality. Cutaneous lesions referred to as eschars develop as single or multiple lesions after exposure to *B. anthracis* spores. Spores enter breaks in the skin and following an incubation period ranging from several hours to 3 weeks the inoculum site develops into a papule followed by a ring of vesicles, accompanied by edema, regional lymphadenopathy, and necrosis. The lesion then forms the typical dark eschar, which is accompanied by profound edema usually from 5 to 7 days. Resolution occurs over a period of several weeks. Although the eschar is usually not painful most patients may experience constitutional symptoms or may present with sepsis especially with lesions involving the face, neck, and upper chest. Infection involving the gastrointestinal tract occurs after ingestion of meat from animals dying of anthrax. The disease has an incubation period of 1 to 6 days and the presentation may initially include mild symptoms such as fever, nausea, vomiting, and mild diarrhea but then progresses to more severe symptoms of bloody diarrhea, acute abdominal pain, hematemesis, and ascites. Complications include obstruction, perforation, sepsis, and death. Pathologic evaluation demonstrates ulcerating, necrotizing lesions accompanied by regional lymphadenopathy. Inhalation anthrax is a rare but dangerous form of the disease, which has public health implications due to its association with bioterrorism. Infection involves lymph nodes rather than lung parenchyma, which makes the term "pulmonary" a misnomer since complications result from germinating spores transported to the lymphatic system by macrophages. The disease has a biphasic presentation with nonspecific initial symptoms of fever, headache, chills, malaise, nonproductive cough followed by a more rapid progressive form when patients experience dyspnea, cyanosis, respiratory failure, sepsis, and death. The incubation period ranges from 4 to 11 days. The chest x-ray findings most consistent with inhalation anthrax include mediastinal widening, pleural effusions, and the presentation of hyperdense necrotic-appearing lymph nodes involving the mediastinum on computerized tomography. Infection of the central nervous system is a life-threatening complication of any of the major forms of anthrax and carries a poor prognosis. In contrast to common causes of bacterial meningitis, the cerebral spinal fluid contains large numbers of red blood cells, indicating a hemorrhagic component (Table 125.3).

Table 125.3 Virulence factors possessed by *Bacillus anthracis*

Virulence factor	Contribution to disease
Plasmid X02	Encodes for poly-D-glutamic acid capsule which may mask bacterium from host defenses
Plasmid X01	Encodes for tripartite toxin complex: protective antigen, lethal factor and edema factor
Spore	Survival of infectious propagule for up to ~90 years in conducive soils; exosporium allows for delay of germination within alveolar macrophages

TREATMENT OF ANTHRAX

Treatment for inhalational anthrax includes ciprofloxacin or doxycycline plus consideration of one or two other antimicrobials, such as rifampin, vancomycin, imipenem, chloramphenicol, penicillin or ampicillin, clindamycin, and clarithromycin. Doxycycline may be less optimal for cases with meningitis because of poor central nervous system penetration. For cutaneous anthrax, ciprofloxacin or doxycycline are recommended for initial therapy. Duration of combined intravenous and oral therapy should continue for 60 days for all anthrax cases because of the potential persistence of spores after an aerosol exposure. For additional details of antimicrobial regimens, see Chapter 122, Bioterrorism, Table 122.4. A new modality of therapy is the use of a monoclonal antibody (raxibacumab) that inhibits PA binding to anthrax toxin receptors.

Novel therapeutics

Nonantimicrobial therapeutics targeting various stages of anthrax infection are the subject of intense investigation since the disease carries a high mortality. Medications that have been

approved for other conditions have been under investigation. These include but are not limited to amiodarone, verapamil, nifedipine, statins, celecoxib, dantrolene, *N*-acetyl-*L*-cysteine, cisplatin, and chloroquine to name a few. Through in vitro studies, these medications have demonstrated activity against some of the components of anthrax toxin. Another area of novel therapeutics includes the use of naturally occurring human physiologic molecules such as inter-alpha inhibitor proteins which are under investigation for their protease inhibitor activity during inflammatory states such as sepsis. Dominant-negative mutants of PA are also being investigated for their role in disruption of pore formation and prevention of toxin delivery at the intracellular level by coassembling with wild-type proteins. Other areas of nonantimicrobial therapeutics include the use of lytic enzymes from bacteriophages, inhibition of quorum-sensing, anthrax toxin receptor blockade, anti-spore germination through the use of several chemotherapeutic agents, and interleukin-1 receptor antagonist.

BIOTERRORISM AND ANTHRAX

The Working Group on Civilian Biodefense has identified *B. anthracis* as one of the most serious biologic weapon threats to cities or regions. Presentation of bioterrorism-related anthrax will typically result in inhalational and cutaneous cases. The sudden appearance of several cases of severe acute febrile illness with fulminant courses should prompt the clinician to consider anthrax, and therefore bioterrorism, as the etiology and delivery mechanism of the disease.

A cluster of cutaneous anthrax cases should also alert the clinician to the possibility of bioterrorism-associated anthrax. (See Chapter 122, Bioterrorism.)

PROPHYLAXIS OF ANTHRAX

Pre-exposure vaccination

An acellular vaccine against *B. anthracis* has been approved for human vaccination in the United States (anthrax vaccine absorbed or AVA). Pre-exposure vaccination is recommended by the Advisory Committee on Immunization Practices for persons with specific occupational and laboratory exposures to *B. anthracis*. Work that involves producing quantities of *B. anthracis* or occupations with high potential for aerosol production where standards are insufficient to prevent exposure to anthrax spores are occupational indications to receive routine vaccination with AVA. Laboratorians using standard Biosafety Level 2 practices in the routine processing of clinical samples are not at increased risk for exposure to *B. anthracis* spores. Routine vaccination of veterinarians in the United States is not recommended unless the veterinarians will be handling potentially infected animals with a high incidence of anthrax. Pre-exposure AVA vaccination may be indicated for military and other select populations or groups for which a calculable risk of exposure can be assessed. The recommended vaccination schedule includes subcutaneous injections at 0, 2, and 4 weeks, then 6 months, 12 months, and 18 months. An annual booster injection is recommended to maintain immunity.

Postexposure prophylaxis

Those at risk for anthrax following a *B. anthracis* spore exposure are identified by public health officials depending on epidemiologic circumstances. Prophylaxis is indicated for those exposed to an airspace contaminated with aerosolized *B. anthracis*. Ciprofloxacin, doxycycline, and penicillin G procaine have been approved by the US Food and Drug Administration (FDA) for prophylaxis of inhalational *B. anthracis* infection. Although the optimal duration of prophylaxis is uncertain, antibiotics were recommended for 60 days for those exposed in the US anthrax attacks of 2001, based on animal studies of anthrax deaths and spore clearance after exposure. The Working Group on Civilian Biodefense recommends monotherapy with ciprofloxacin for adults, children, and pregnant women, recognizing that fluoroquinolones are not generally recommended for children or pregnant women because of risks of arthropathy in children. However, the working group determined that the risk of anthrax and its consequences outweighs the risks of fluoroquinolone use in these groups. Doxycycline is recommended as an alternative in all groups, with cautions and recommendations for its use in pregnant women and children similarly acknowledged. Amoxicillin was listed as a prophylaxis or treatment option by the Centers for Disease Control and Prevention (CDC) following the US anthrax attacks of 2001 only after 14 to 21 days of fluoroquinolone or doxycycline administration because of concern of a β-lactamase-producing *B. anthracis*. However, it was not recommended as a first-line prophylaxis

agent because of lack of FDA approval, data regarding efficacy, and uncertainty about the drug's ability to achieve adequate therapeutic levels at standard doses.

Postexposure vaccination

Postexposure vaccination of exposed persons is recommended in conjunction with the 60-day prophylactic antibiotic course by the Working Group on Civilian Biodefense, and a three-dose series of the vaccine was offered to persons at high risk for exposure following the US anthrax attacks of 2001. The vaccine is stored in the National Strategic Stockpile (SNS) to be used for postexposure prophylaxis in the event of a terrorist attack. Animal studies using monkeys support the use of vaccine in conjunction with antibiotics following exposure to aerosolized *B. anthracis* spores. Although 5 of 29 animals died after completing a 30-day course of antibiotics following *B. anthracis* spore exposure, none of 9 receiving doxycycline for 30 days plus vaccine at baseline and at day 14 following exposure died. However, 8 of 10 animals treated with vaccine only subsequent to aerosolized spore exposure died.

To date, no anthrax infections have been reported among persons exposed following the US anthrax attacks of 2001 who took antibiotics, including those who did not complete the 60-day course of therapy.

LABORATORY DIAGNOSIS OF ANTHRAX

The most useful diagnostic laboratory test for anthrax is the blood culture. If drawn before antibiotics are started in those with inhalational anthrax, the standard blood culture may show growth of large gram-positive bacilli with preliminary identification of *Bacillus* species. During the US anthrax attacks, eight of eight case patients with inhalational anthrax who had blood cultures obtained prior to initiation of antibiotics had positive blood cultures for *B. anthracis*. *Bacillus* species are routinely identified in blood cultures within 24 hours following inoculation, but some laboratories do not further identify *Bacillus* species unless specifically requested because of the frequency of *Bacillus cereus* contaminants. If *B. anthracis* cannot be specifically excluded from cultures in a clinical laboratory, isolates can be transferred to a Laboratory Response Network (LRN) laboratory to identify or rule out *B. anthracis*. In specialized and LRN laboratories, other definitive diagnostic tests can be performed, such as immunohistochemical (IHC) staining or polymerase chain reaction (PCR) assays of biopsied tissue or body fluids. Cerebrospinal fluid (CSF) cultures may be useful for diagnosis.

For cutaneous anthrax, a Gram stain and culture of vesicular fluid should be obtained and if negative or if antibiotics were initiated prior to the sampling, a punch biopsy should be performed for IHC staining or PCR.

Nasal swabs are not used for diagnosis of inhalational anthrax, since they may be negative in those with infection. However, they were useful as epidemiologic tools to identify the source and route of exposure and mechanism of release in the US anthrax attacks. A positive nasal swab indicates exposure to *B. anthracis* and is an indication for clinical or prophylactic treatment.

Sputum samples for Gram stain and culture are generally not helpful to diagnose inhalational anthrax due to the frequent lack of a pneumonic process. Antibody testing to the PA of *B. anthracis* has not been established as a diagnostic tool.

NON-ANTHRAX *BACILLUS* SPECIES AND THE DISEASES THEY CAUSE

Bacillus cereus and other non-anthrax-related species are recognized contaminants, but also clearly pathogenic. These bacteria are ubiquitous in the environment, one of the most common microbes on the Earth's crust, present in wide diverse ecologic niches, and found in animal and plant food sources. Members of the genus are spore-forming, aerobic or facultative anaerobic, gram-positive or gram-variable with close phenotypic and genetic similarities to one another and are easily grown on most culture media. Optimum temperature for growth is between 28 and 35°C. The *B. cereus* group includes *B. cereus*, *B. anthracis*, *B. thuringiensis*, *B. mycoides*, *B. pseudomycoides*, and *B. weihenstephanesis*. The use of 16S rRNA for the comparison of the nucleotide sequences has highlighted the close relationship of *B. cereus*, *B. anthracis*, and *B. thuringiensis*. Other species, *B. subtilis*, *B. licheniformis*, *B. megaterium*, *B. pumilus*, and *B. sphaericus*, bear a more distant relationship and are clinically not as important in human infections. *B. cereus* has served as the model on several taxonomic studies and is the main focus of discussion in this section. *B. thuringiensis* is utilized as a biopesticide. *B. cereus* toxin is important in cases of foodborne illness. Additionally, intestinal and non-intestinal tissue destructive toxin production may occur

secondary to hemolysins, phospholipases, emesis-inducing toxin, and pore-forming enterotoxins.

EPIDEMIOLOGY OF NON-ANTHRAX *BACILLUS* SPECIES

Nosocomial infections include bacteremia and hospital-acquired pneumonias. These are usually due to microorganisms present in decaying organic matter, soil, fomites, water, and food sources. Foodborne outbreaks are due to the microorganism's presence in food sources and human intestinal flora. *B. cereus* species are often regarded as contaminants when recovered in blood cultures and have been implicated in cases of pseudo-outbreaks since the microorganism may survive usual disinfectants and inadequate sterilization techniques, and has the capability to adhere to intravascular catheters. Populations at risk for disease include injection drug users, immunocompromised hosts, neonates, and long-term hospitalized critically ill patients with nosocomial infections.

CLINICAL MANIFESTATIONS OF NON-ANTHRAX *BACILLUS* INFECTIONS

The clinical presentation of non-anthrax *Bacillus* infections is variable and includes wound and burn-related infections; endophthalmitis; bacteremia; central nervous system infections; intravascular infections including endocarditis; respiratory tract infections; complicated bone, skin and soft-tissue infections; and toxin-mediated foodborne illnesses. Most infections are due to *B. cereus*, but other species including *B. circulans, B. licheniformis, B. megaterium, B. pumilus, B. sphaericus*, and *B. subtilis* have been reported. While occupational exposure to *B. cereus* resulting in bacteremia and pneumonia has been reported, nosocomial infections such as ventilator-associated pneumonias, catheter-related bloodstream infections, and meningitis, through exposure to fomites, are increasingly being reported among immunocompromised hospitalized patients. Exotoxin-mediated tissue destructive ocular infections such as endophthalmitis resulting from exogenous (trauma) and endogenous (hematogenous) sources lead to rapid vision loss. These infections are typically more aggressive and rapid in nature in comparison to infections by other bacteria. Central nervous system infections have been reported in immunocompromised patients who acquired the infections from hematogenous, intrathecal procedures, and possible gastrointestinal sources. Complicated skin and soft-tissue infections due to penetrating trauma, surgery, injection drug use, or burns are associated with a high mortality and in some cases have mimicked the eschars of *B. anthracis*. Cutaneous infections with necrotizing fasciitis and myonecrosis may resemble *Clostridium perfringens* gas gangrene infections. Intravascular infections including native valve and prosthetic valve endocarditis, and device-related infections such as with pacemakers, have been described.

Gastrointestinal disease caused by *B. cereus* is due to the ability of the microorganism to survive heat and changes in environment and infiltrate human food sources. Its ability to cross-contaminate various food sources by spore formation indicates its ubiquitous presence in the food chain and opportunity for foodborne diseases. The most commonly reported clinical manifestations of foodborne illness with *B. cereus* are emetic and diarrheal syndromes, mediated by various toxins. The presentations range from asymptomatic to mild, to fatal cases. In emetic disease the incubation period ranges from 0.5 to 6 hours after ingestion of starchy foods such as rice contaminated by spores with an infective dose of 10^5 to 10^8 colony-forming units (CFU). Preformed toxins including cyclic peptide and cereulide mediate the disease process. The patients experience nausea, vomiting, and malaise with symptoms lasting from 6 to 24 hours. In diarrheal disease the incubation period ranges from 8 to 16 hours after ingestion of foods with high protein contents such as meat and milk products, mediated by hemolysin BL, nonhemolytic enterotoxin, and cytotoxin K enterotoxins in the small intestine. Patients often present with nausea, abdominal pain, and non-bloody diarrhea that lasts from 12 to 24 hours.

TREATMENT OF NON-ANTHRAX *BACILLUS* INFECTIONS

Through its production of β-lactamases *B. cereus* is resistant to most β-lactam antibiotics including penicillins and cephalosporins. Reports of resistance to erythromycin, tetracycline, and carbapenems have created a problem for the clinician in choosing an initial treatment regimen. Some experts consider vancomycin the drug of choice and there are multiple reports indicating that ciprofloxacin has been found to be effective in the treatment of skin and soft-tissue infections. Newer studies utilizing several antibiotic susceptibility

methods, including E-test, have indicated uniform sensitivity to levofloxacin, moxifloxacin, rifampin, daptomycin, and linezolid. As is the case in most intravascular infections, removal of the source is key to achieving control of infection. Unfortunately, the reputation of *Bacillus* species as contaminants often leads to under recognition, disregarding crucial information, leading to delay in treatment of severe, life-threatening infections. Treatment of gastrointestinal disease is supportive.

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126. *Bartonella bacilliformis*

Nuria Sanchez Clemente

INTRODUCTION

Bartonella bacilliformis is a gram-negative, facultative intracellular, aerobic coccobacillus which is a member of the alpha-proteobacteria group along with *Rickettsia* and *Brucella*.

It is responsible for a spectrum of disease which, despite its limited distribution, has been given a multitude of names including bartonellosis, Carrion's disease, Oroya fever, and verruga peruana.

The disease is restricted to the Andean cordillera in Peru, Ecuador, and Colombia with sporadic cases being reported in Bolivia, Chile, and Guatemala. Classically, endemic areas are said to be confined to inter-Andean valleys at altitudes between 500 and 3200 m above sea level (Figure 126.1). This focality is mainly due to the characteristics of its putative principal sandfly vector, *Lutzomyia verrucarum*, which has a weak, hopping flight and is intolerant of extreme temperatures.

Young children under 10 are the most affected age group in endemic communities, partly because of a predominantly younger population but also due to the presumed protective immunity that develops with repeated infection.

CLINICAL FEATURES

There are two well-described phases of the illness.

The initial acute phase, known as Oroya fever, occurs typically around 2 to 6 weeks after inoculation of the microorganism by the bite of an infected sandfly. It is characterized by fever, pallor, malaise, joint pain, headache, and anorexia. In severe cases, with high parasitemia, this progresses to severe hemolytic anemia.

High mortality rates of 44% to 88% have been reported in untreated individuals in endemic

Figure 126.1 Laguna Paron is the largest lake in the Cordillera Blanca of the Peruvian Andes. It is 30 km from Caraz, in the Ancash region: one of the most endemic areas for *Bartonella bacilliformis*. Author: Nuria Sanchez Clemente.

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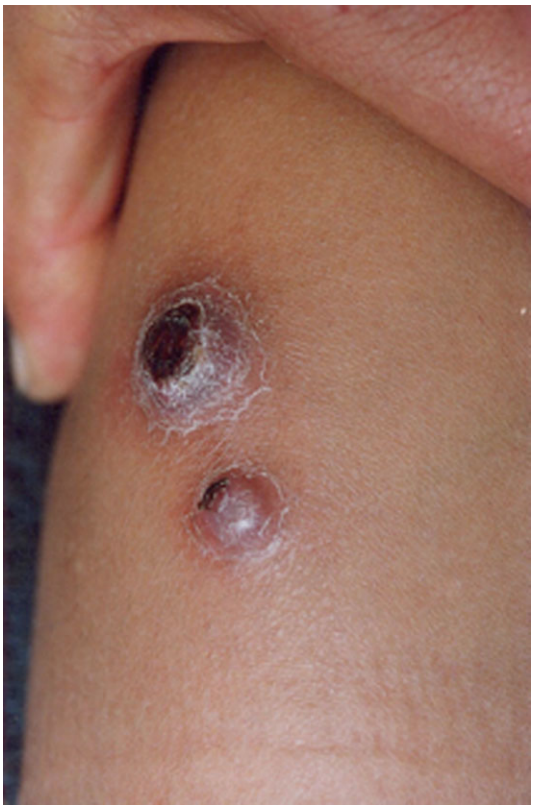

Figure 126.2. Mular (above) and miliary (below) lesions in verruga peruana. Author: Ciro Maguiña.

areas. Most deaths are associated with secondary bacterial infection, most commonly with *Salmonella* species but also with *Toxoplasma*, *Histoplasma*, mycobacteria and fungi. Other complications include pericardial effusion, acute respiratory distress syndrome, hepatitis, convulsions, and coma. In pregnancy, infection can lead to miscarriage, premature labor, and maternal death.

The subsequent chronic eruptive phase, which may occur weeks to months after the acute illness, is characterized by the eruption of crops of miliary, mular, or nodular verrugas or warts, containing sero-sanguinous fluid. These occur mainly over the extremities but can also affect the face and trunk. Miliary lesions (Figure 126.2, lower lesion) are the most common; occurring in the upper dermal layers they can crop in large numbers and can be pruritic. There may also be mucosal involvement. Mular lesions (Figure 126.2, upper lesion) are >5 mm in diameter and have an eroded center. Nodules are larger diffuse subdermal swellings. The latter two can be painful especially if occurring over joints. Secondary bacterial infection is a recognized complication.

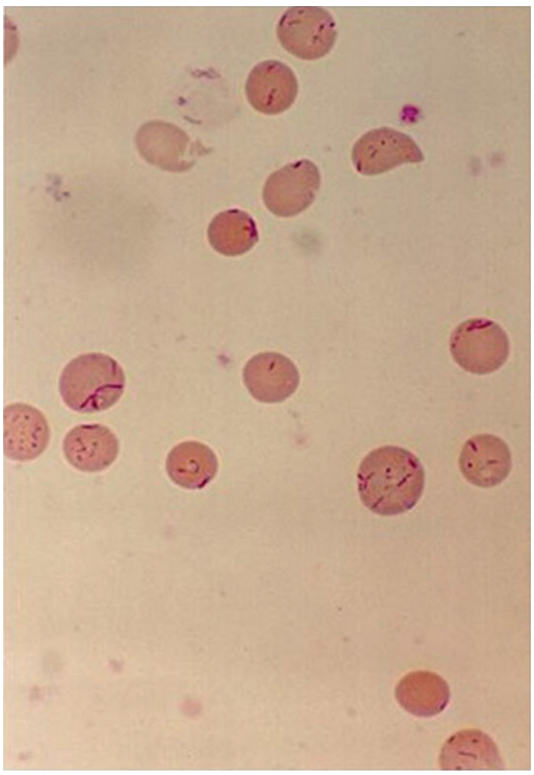

Figure 126.3 Thin blood film showing intraerythrocytic *Bartonella bacilliformis*. Author: Nelson Solórzano

The eponym Carrion's disease recognizes the contribution of Daniel Alcides Carrion, a Peruvian medical student who in 1885 asked a fellow student to inoculate him with blood from a cutaneous lesion from a diseased patient, in order to test his hypothesis that the two clinical entities were actually manifestations of the same disease. His hypothesis was proven to be tragically correct as he developed, and soon after succumbed to, the acute febrile form of the illness hitherto known as Carrion's disease, becoming a martyr of Peruvian medicine.

DIAGNOSIS

In endemic areas, cases are treated empirically during outbreaks. However, the most frequently used diagnostic test is peripheral blood smear (Figure 126.3). When stained with Giemsa, the blue intra- and extra-erythrocytic coccobacilli of *B. bacilliformis* can be seen microscopically. Few studies have looked at the sensitivity and specificity of this easy and affordable test. One study which used PCR as a reference standard found a sensitivity of 36%, and a specificity of 96% in patients with the acute form of the disease. In the

Table 126.1 Antibiotic management of acute and chronic bartonellosis according to severity

Type of disease, severity	Antibiotic
Acute, mild to moderate	**Chloramphenicol** 50 mg/kg/d for first 3 d then 30 mg/kg to complete 14 d **Ciprofloxacin** 5 mg/kg BID for 14 d **Amoxicillin–clavulanate** 20 mg/kg BID for 14 d **Trimethoprim–sulfamethoxazole** 5 mg/kg BID for 14 d
Acute, severe	First line: **ciprofloxacin** 10–15 mg/kg BID for 14 d and **ceftriaxone** 70 mg/kg IV for 7–10 d Second line: **ciprofloxacin** (as above) and **ceftazidime** 30 mg/kg TID IV for 7–10 d or **amikacin** 7.5 mg/kg BID IV for 7–10 d
Chronic, all	**Azithromycin** 10 mg/kg/d for 7 d **Rifampin** 10 mg/kg/d for 21–28 d **Erythromycin** 12.5 mg/kg QID for 14 d **Ciprofloxacin** 5 mg/kg BID for 14 d

chronic eruptive phase, the sensitivity of PCR is even lower and therefore not usually carried out.

Blood cultures are rarely used as a diagnostic method as they require prolonged incubation for several weeks in blood-rich medium.

Histopathologic samples of the verrugas are rarely taken in the chronic eruptive phase, if the diagnosis is unclear. Biopsy of the lesion classically shows angioblastic proliferation with copious macrophages and lymphocytes. Giemsa staining demonstrates *B. bacilliformis* in the endothelial cells and extracellular matrix.

Serologic methods such as indirect fluorescence antibody test (IFA) and enzyme-linked immunosorbent assay (ELISA) have been developed for use in both phases of the illness but are only available in tertiary centers away from endemic areas. Sensitivity using IgM is superior to IgG ELISA (85% vs. 70%); specificity has been quoted as 100% for both. IFA has a reported sensitivity of 85% and a specificity of 92%.

Similarly, PCR tests also exist and recent studies have evaluated blood spots for PCR detection with encouraging results.

MANAGEMENT

There are no published controlled clinical trials of therapy for acute or chronic Carrion's disease. Treatment guidelines are based on observational studies (Table 126.1).

Severe cases are those in which there are any of the following features: hemodynamic instability, metabolic acidosis, signs of cardiac failure, respiratory compromise, neurologic involvement, severe anemia, hepatitis, gastrointestinal involvement, renal failure, raised inflammatory markers.

Prevention of the disease is mostly centered on vector control with the use of intra- and extradomiciliary DDT and pyrethroid sprays. Bed nets can also be efficacious but should be impregnated with insecticide as sandflies may penetrate the mesh due to their small size.

Due to its focal geographic nature and the fact that it affects small, isolated, rural communities, Carrion's disease has been truly neglected. Diagnostic and treatment guidelines are supported only by very low evidence studies and expert opinion. Further research is needed to improve the understanding of this fascinating disease.

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127. Cat scratch disease and other *Bartonella* infections

William A. Schwartzman

INTRODUCTION

Cat scratch disease (CSD) was first described in 1950 by Rene Debré as "La Maladie de Griff de Chat." Its cause remained a mystery until the late twentieth century, when amplification and sequencing of 16S rRNA genes was introduced as a method of identifying organisms that had not been successfully cultured. In 1992, David Relman and co-workers used this technique to identify the agent of CSD, and bacillary angiomatosis and parenchymal bacillary peliosis (BAP). He found that the causative organism was a small gram-negative coccobacillus closely related to the agents causing trench fever, brucellosis, and crown gall disease in plants (*Agrobacterium tumefaciens*).

The organism was first named *Rochalimaea henselae*, and was subsequently grouped within the family Bartonellaceae, along with a number of other organisms, including the agents of trench fever, *Bartonella quintana* (formerly *Rochalimaea quintana*). *Bartonella bacilliformis*, the agent of acute and chronic Carrión's disease is a related ancestor of modern members of the family Bartonellaceae. Recent reports suggest that similar clinical syndromes in the Andean highlands may also be caused by *Bartonella rochalimae* and possibly *Candidatus* Bartonella ancashi 20.0. These organisms, and probably others of the genus, share the ability to invade vascular endothelial cells, bone marrow erythroblasts, and mature erythrocytes. They also share the ability to induce macrophage-mediated secretion of proinflammatory cytokines (notably interleukin-10 [IL-10]) andvascular endothelial cell growth factor (VEGF) and the ability to suppress vascular endothelial cell apoptosis. These virulence factors give them the ability to disseminate within the host, causing proliferative vascular lesions and prolonged bacteremia in humans and mammalian reservoirs.

Since the identification of *Bartonella henselae*, there has been an explosion of knowledge about the manifestations of CSD and those of the expanding roster of *Bartonella* species that populate their mammalian reservoirs; from small rodents to horses, cows, kangaroos, and, in one report, porpoises (Table 127.1).

The clinical spectrum of CSD in the immunocompetent host includes classic CSD as well as ophthalmologic, neurological, cardiovascular, parenchymal, musculoskeletal, and immune complex–mediated syndromes such as glomerulonephritis; as well as prolonged fever without adenopathy or focal lesions. Parenchymal masses associated with CSD have been mistaken for malignancies such as breast cancer or lymphoma.

In hosts with compromised cell-mediated immunity, including patients with acquired immunodeficiency syndrome (AIDS), solid organ transplant recipients, and patients with hematologic malignancies, *B. henselae* and *B. quintana* cause vascular tumors called bacillary angiomas (BA) and blood-filled cavities of liver and spleen, termed bacillary peliosis hepatis; these lesions are referred to collectively as "BAP."

CLASSIC CAT SCRATCH DISEASE

CSD is the most common cause of regional lymphadenitis in children and young adults. Approximately 24 000 cases occur each year with a prevalence of roughly 9.3/10 000 ambulatory patients per year and a seroprevalence ranging from 3% to 6%. CSD tends to occur in late summer or fall and to vary in frequency with the geographic distribution of the cat flea, *Ctenocephalides felis*.

The first clinical manifestations of CSD appear 5 to 7 days after the scratch or bite from an infected cat, kitten, or cat flea, with the appearance of a small erythematous nodule at the site of bacterial entry. Although this inoculation papule may go unnoticed, it is said to be present in 70% of CSD cases. This nodule represents the initial

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Table 127.1 *Bartonella* species currently reported to have caused zoonotic infections

Species	Reservoir	Vector	Human disease
B. henselae	Cat, dog, raccoon	Cat flea *(Ctenocephalides felis)*, other?	CSD, retinitis, IE, myocarditis, encephalopathy, aseptic meningitis, myelitis, neuropathy, osteomyelitis, BAP, glomerulonephritis, purpura, pseudomalignancy, prolonged asymptomatic bacteremia
B. quintana	Rat, human?	Louse	CSD, IE, trench fever, encephalopathy, BAP, osteomyelitis, prolonged asymptomatic bacteremia
B. vinsonii subsp. *berkhoffii*	Coyote, dog	Unknown	IE
B. vinsonii subsp. *arupensis*	White-footed mouse	Unknown	IE, neurologic disorders
B. koehlerae	Cat, raccoon	Flea, *C. felis*	IE
B. elizabethae	Rat	Oriental rat flea *Xenopsylla cheopsis*	IE
B. washoensis	California ground squirrel *(Spermophilus beecheyi)*	Unknown	Fever, myocarditis
B. alsatica	Rabbit	Unknown	IE
B. grahamii	Wild mice	Unknown	Neuroretinitis
B. clarridgeiae	Cat, raccoon	Flea, *C. felis*	Possible CSD

Abbreviations: CSD = cat scratch disease; IE = infective endocarditis; BAP = bacillary angiomatosis and parenchymal bacillary peliosis.

host response to bartonella and is characterized by palisading macrophages, acute and chronic inflammatory cell infiltration, as well as activation and invasion of vascular endothelial cells. Painful swelling of the proximal lymph nodes follows the appearance of the inoculation papule by 7 to 14 days and may be accompanied by constitutional symptoms and fever. The histopathology of the lymph node is highly characteristic of CSD, involving both acute and chronic inflammatory cells and the presence of microabscesses that are described as "stellate." Aggregates of small coccobacilli may be identified in these abscesses using either silver impregnation stains such as Warthin–Starry and Steiner stains or by immunofluorescent staining with commercially available monoclonal antibodies specific for *B. henselae* or *B. quintana*. The clinical diagnosis of classic CSD can also be confirmed by PCR of tissue or the demonstration of elevated immunoglobulin G (IgG) and IgM antibodies to *B. henselae* or *B. quintana*. Classic CSD usually resolves over several weeks to months without treatment. Although one prospective randomized controlled trial indicated that a 5-day course of azithromycin might hasten the resolution of lymph node swelling, most experts do not recommend antimicrobial therapy for mild to moderately severe CSD. Where lymph nodes become fluctuant and painful, needle aspiration may be all that is required to relieve discomfort and hasten resolution. The syndrome of classic CSD in immunocompetent

Table 127.2 Treatment recommendations for *Bartonella* infections

Clinical presentation	Adult treatment recommendations
Mild to moderate classic CSD	No antimicrobials recommended
Severe CSD with large painful lymphadenopathy	Azithromycin, 500 mg PO, d 1, 250 mg d 2–5, aspiration if fluctuant
Retinitis	Doxycycline[a], 100 mg PO BID for 4–6 wk, + rifampin, 300 mg PO BID for 4–6 wk; consider topical corticosteroids
Encephalopathy	Doxycycline[a], 100 mg PO or IV for 6 wk, + rifampin, 300 mg PO BID for 4–6 wk; duration is not a matter of consensus at this time
Suspected *Bartonella* BCNE	Gentamicin, 3 mg/kg/d × 14 d, + ceftriaxone, 2 g/d IV or IM × 6 wk
Confirmed *Bartonella* BCNE	Gentamicin, 3 mg/kg/d IV × 14 d, + doxycycline[a], 100 mg BID × 6 wk
Trench fever, prolonged *B. quintana* bacteremia	Gentamicin, 3 mg/kg/d IV × 14 d, + doxycycline[a], 200 mg/d PO × 4 wk
BA	Erythromycin, 500 mg PO QID × 3 mo, or doxycycline, PO QID 100 mg BID × 3 mo
PH	Erythromycin, 500 mg PO QID × 4 mo, or doxycycline[a], PO QID 100 mg BID × 4 mo

[a] Substitution of minocycline for doxycycline has not been addressed in published reports.

Abbreviations: CSD = cat scratch disease; BCNE = culture-negative infectious endocarditis; BA = bacillary angioma; PH = peliosis hepatitis.

Adapted from Rolain JM, Brouqui P, Koehler JE, Maguina C, Dolan MJ, Raoult D. Recommendations for treatment of human infections caused by Bartonella species. *Antimicrob Agents Chemother*. 2004;48:1921–1933.

hosts is thought to be due to an exuberant host response to relatively few organisms, which is one possible explanation for the relatively minor impact of antimicrobials in this setting (Table 127.2).

OPHTHALMOLOGIC CSD

Approximately 3% of CSD patients develop ocular pathology. These manifestations may be unilateral or bilateral and include conjunctivitis, retinitis, choroiditis, iridocyclitis, endophthalmitis, or orbital abscess with osteomyelitis.

Most frequently patients present with retinitis and vision loss in the context of classic CSD; however, this may also appear without adenopathy. CSD retinitis may be indicated by the presence of characteristic exudates radiating from the macula, the so-called "macular star" or stellate retinitis.

The diagnosis may be confirmed by demonstrating elevated IgG or IgM antibodies to *B. henselae* or PCR of tissue biopsy specimens.

Parinaud's oculoglandular syndrome (POGS) is a nodular, or "cobblestone," conjunctivitis accompanied by reactive preauricular lymphadenopathy. This is thought to represent the ocular equivalent of classic CSD, secondary to conjunctival inoculation of *B. henselae*.

Resolution of ocular CSD may be spontaneous; however, treatment with 4 to 6 weeks of doxycycline, with rifampin, with or without topical corticosteroids is recommended.

NEUROLOGIC CSD

Neurologic manifestations of CSD are relatively rare, accounting for 0.17% to 2% of cases. These include encephalopathy involving cortex, internal capsule, or midbrain; myelopathy; granulomatous cerebral angiitis; vertebral osteomyelitis; and peripheral neuropathy.

This encephalopathy may present with agitation, delirium, or new onset of seizures, including status epilepticus, coma, cerebellar ataxia, and disruptions of basal ganglia or midbrain. Anecdotal reports of successful treatment have included supportive measures with antiepileptic medication, usually accompanied by intravenous antibiotics with or without high-dose corticosteroids. A combination of intravenous or oral doxycycline with rifampin for at least 14 days is recommended; however, the most appropriate choice of antimicrobials, optimum duration of therapy, and the role of corticosteroids in these cases have not been resolved.

A number of mechanisms have been proposed for CSD encephalopathy, including direct bacterial involvement of neurons, host inflammatory response, autoimmune disease, and toxin production.

In immunocompromised patients, an acute psychiatric syndrome similar to acute mania may occur, which improves rapidly with antimicrobial therapy directed against *B. henselae*. An association has been reported between intrathecal synthesis of *B. henselae* antibodies and human immunodeficiency virus (HIV)-associated encephalopathy; although there is no evidence that this improves with treatment for bartonella.

CARDIOVASCULAR INFECTIONS

Bartonella quintana and *B. henselae* are significant causes of blood culture-negative infectious endocarditis (BCNE). Estimates of the relative contributions of *Bartonella* species to these infections are based on several large case series from reference centers equipped to diagnose these relatively fastidious organisms, including the agent of Q fever, *Coxiella burnettii, Legionella pneumophila, Brucella* species, *Chlamydia psittaci, Tropheryma whipplei, Mycoplasma hominis*, nutritionally deficient streptococci, and the fungal causes of BCNE.

In a series of 349 cases of BCNE reported by Houpikian and Raoult in 2005, *Bartonella* species accounted for 29% of all cases. *Bartonella quintana* represented 75% of these and *B. henselae* 25%. As reported in previous series, *B. quintana* endocarditis was associated with body louse infestation, immunodeficiency, and chronic alcoholism, whereas *B. henselae* endocarditis was associated with cat contact and pre-existing valvular disease. The overall mortality was 7% with no difference between the two species. The aortic valve was the predominant site for both species, and valve replacement was performed in 75% of cases. Several cases of renal failure secondary to necrotizing crescentic glomerulonephritis have been reported in the context of both *B. henselae* and *B. quintana* endocarditis.

To date, four additional *Bartonella* species have been reported to cause infective endocarditis (IE) in humans: *Bartonella vinsonii, Bartonella vinsonii* subsp. *berkhoffii, Bartonella elizabethae, Bartonella koehlerae*, and *Bartonella alsatica*. The diagnosis of *Bartonella* endocarditis was made by culture in roughly 30% of cases, whereas PCR of valvular tissue yielded 67%. Serologic demonstration of

anti-*Bartonella* antibody titers ≤1:800 by direct fluorescent antibody (DFA) provided an acceptable noninvasive method of diagnosis in this series.

Suspected *Bartonella* BCNE should be treated with gentamicin for 2 weeks, combined with 6 weeks of intravenous or intramuscular ceftriaxone, to cover other possible causes of BCNE, with or without oral or intravenous doxycycline for 6 weeks. For proven *Bartonella* endocarditis, a combination of gentamicin for 2 weeks plus intravenous or oral doxycycline for 6 weeks is recommended.

Although rare, myocarditis has been associated with *Bartonella* infections. *Bartonella washoensis*-associated myocarditis was reported in a 70-year-old immunocompetent man, presumably associated with the presence of a large reservoir of the organism in the California ground squirrels (*Spermophilus beecheyi*) in recreational areas near Reno, Nevada. *Bartonella henselae* has been associated with a case of chronic active myocarditis in a 43-year-old immunocompetent man with classic CSD. An autoimmune reaction triggered by the *B. henselae* infection was postulated.

PROLONGED BACTEREMIA WITHOUT ENDOCARDITIS

Prolonged symptomatic or asymptomatic bacteremia is more frequently caused by *B. quintana* but may also be caused by *B. henselae* as well as other less common members of the genus. When accompanied by fever and constitutional symptoms, prolonged, relapsing *B. quintana* bacteremia was called trench fever in World War I and was at first thought to be a variant of endemic typhus, until Dr. Henrique da Rocha Lima determined it to be a distinct louse-borne infection. Following World War II, trench fever was considered to be an historical relic, until its resurrection in the late twentieth century as a significant cause of illness among the world's growing population of urban homeless, so-called urban trench fever.

Although the relation of prolonged bacteremia to infectious endocarditis has not been established, it is assumed that antimicrobial treatment of *B. henselae* and *B. quintana* bacteremia may have a role in preventing endocarditis. The currently recommended therapy for *B. henselae* and *B. quintana* bacteremia is intravenous gentamicin for 14 days with oral or intravenous doxycycline for 28 days. A thorough search for evidence of endocarditis should accompany the treatment of *Bartonella* bacteremia.

PARENCHYMAL CSD

CSD with or without regional lymphadenopathy may be accompanied by hepatic or splenic foci of infection. The clinical presentation of hepatosplenic bartonellosis includes chronic or subacute course characterized by fever and abdominal pain that may be accompanied by nausea and vomiting. Hepatic transaminases may be elevated and may demonstrate disproportionate elevations of hepatic alkaline phosphatase over aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Abdominal ultrasound or computerized axial tomography may demonstrate radiolucencies in liver and spleen. Histopathology of these lesions frequently demonstrates either necrotizing granulomas or stellate microabscesses similar to those described in the lymph nodes of classic CSD. Anecdotal reports suggest that doxycycline plus rifampin for periods of from 7 to 14 days may be effective in these cases, but spontaneous resolution has also been documented and there is currently no consensus favoring antimicrobial treatment.

MUSCULOSKELETAL

Bartonella henselae is a rare cause of osteomyelitis. *Bartonella quintana* has been linked to most bartonella-related cases, especially in children. Small case series describe typical presentations, including fever and bone pain in children or young adults with cat or kitten exposure, with or without associated lymphadenopathy. These may involve single or multiple foci of infection and frequently involve the axial skeleton or pelvic bones. The etiologic diagnosis in these cases was made by serology, histopathology, or PCR of bone biopsy specimens. There is no evidence beyond anecdotal reports that antimicrobial therapy is effective.

BARTONELLA IN IMMUNOCOMPROMISED PATIENTS

Infections in immunocompetent hosts are characterized by an exuberant inflammatory response to relatively few organisms and a poor response to antimicrobial agents. However, in those with compromised cell-mediated immunity, such as

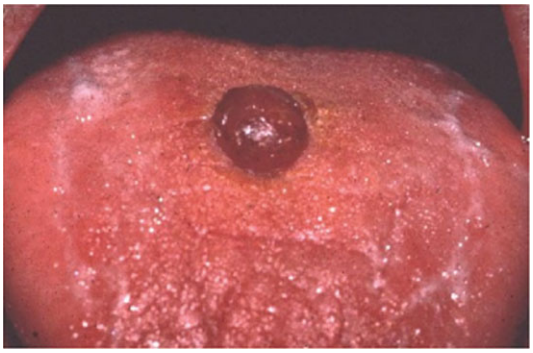

Figure 127.1 Lingual bacillary angiomatosis in acquired immunodeficiency syndrome.

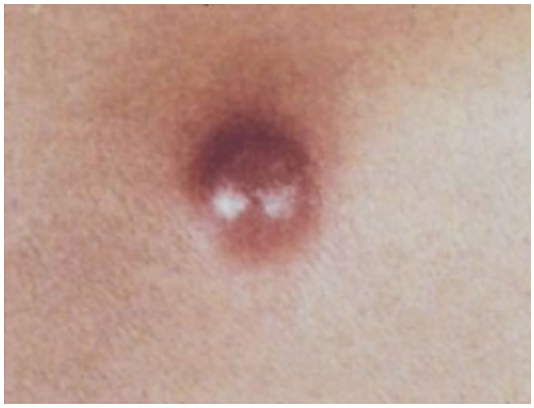

Figure 127.2 Cutaneous bacillary angiomatosis in acquired immunodeficiency syndrome.

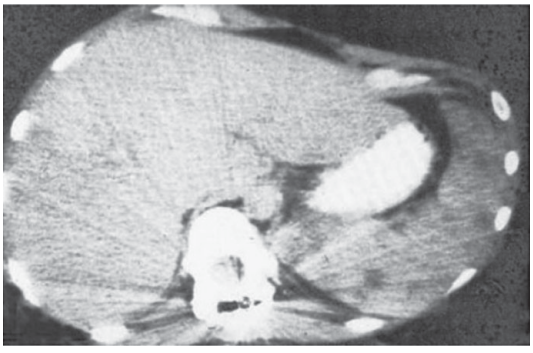

Figure 127.3 Computed tomography scan of splenic bacillary angiomatosis and peliosis.

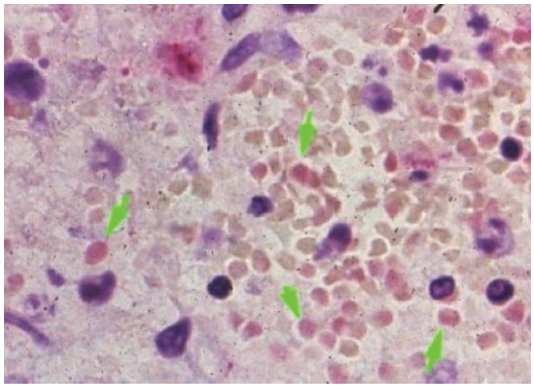

Figure 127.4 *Bartonella henselae* peliosis hepatitis in acquired immunodeficiency syndrome, immunohistochemical stain with rabbit anti-*B. henselae* GroEL. Erythrocytes with dark red stain (e.g., those indicated with green arrows) are infected with *B. henselae*.

individuals with AIDS or hematologic malignancies, organ transplant recipients, and those receiving immunomodulating agents for treatment of hepatitis C or rheumatologic diseases, the same organisms commonly cause systemic infections characterized by BAP lesions, which teem with organisms and respond dramatically to antimicrobial therapy.

BAP may develop in practically any anatomical site or organ, including skin, mucosa of the nasopharynx, gastrointestinal tract, central nervous system, bone, or lymph nodes. Cutaneous BA usually forms a 1-cm to 2-cm erythematous nodule with a surrounding collar of scaling skin (Figures 127.1 and 127.2). These are friable, bleed easily, and may itch.

The microscopic appearance of BA is of disorganized vascular channels, with prominent, rounded endothelial cells, projecting into irregular vascular lumens. These lesions are easily distinguished from the more organized spindle cells of Kaposi's sarcoma. When stained with hematoxylin and eosin, azurophilic granular material can be seen, representing clumps of bacteria. Although they may also be seen with Brown–Brenn tissue Gram stain or silver impregnation stains such as Steiner or Warthin–Starry, they are more easily visualized by immunofluorescent staining.

The second type of vascular lesion, bacillary parenchymal peliosis or peliosis hepatitis (PH), may involve liver or spleen. Computed tomography (CT) or magnetic resonance imaging may demonstrate hypodense lesions (Figure 127.3). Histologically, PH lesions are blood-filled cavities that appear to arise where normal sinusoidal endothelial cells have become disrupted by bartonella infection. The endothelial cells, erythrocytes, and macrophages of

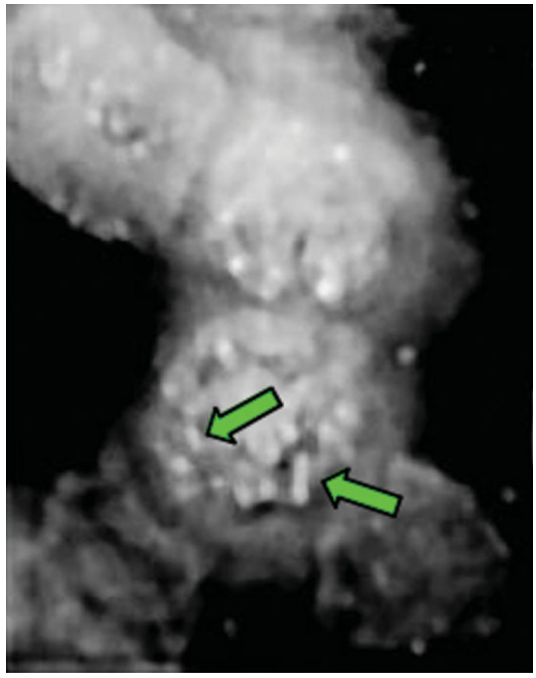

Figure 127.5 Immunofluorescent image (100×) of erythrocytes in Figure 127.4, optical section at the mid-erythrocyte level, image deconvolved to eliminate haze. Numerous small bacilli are seen within the erythrocytes (green arrows).

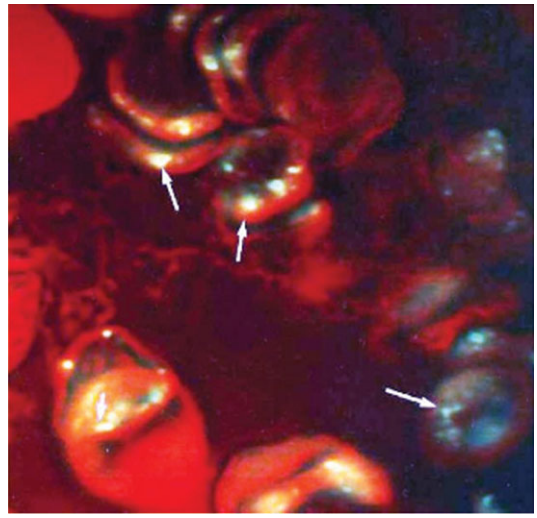

Figure 127.6 Confocal laser image of same specimen as in Figure 127.5 with superimposed phase contrast image of erythrocytes (red pseudo color, fluorescent bacteria are indicated by white arrows).

these lesions contain intracellular bacteria (Figures 127.4–127.6).

Treatment of patients with BAP usually results in a rapid clinical improvement. Treatment should continue for at least 3 months to avoid relapses. Although erythromycin is recommended, doxycycline appears to be as effective, with fewer gastrointestinal side effects.

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128. *Bordetella*

Sarah S. Long

Bordetellae are fastidious, non-carbohydrate-fermenting, tiny, gram-negative coccobacilli that grow aerobically on starch blood agar or synthetic medium supplemented with nicotinamide and amino acids for growth and charcoal or cyclodextrin resin for protection from fatty acids and other inhibitory substances. Bordetellae have multiple attachment proteins, including a 69-kDa outer membrane protein (pertactin), filamentous hemagglutinin, and fimbriae. *Bordetella pertussis* is the only species that expresses the major virulence protein, pertussis toxin. *Bordetella pertussis* and *Bordetella parapertussis* are exclusive human pathogens. *B. pertussis* is the cause of epidemic pertussis and the usual cause of sporadic pertussis. *B. parapertussis* is an infrequent cause of pertussis in the United States and is genetically more closely aligned with *Bordetella bronchiseptica*, a common veterinary pathogen causing upper respiratory tract illnesses in animals. *Bordetella holmesii*, first described as a cause of bronchitis, endocarditis, and septicemia in immunocompromised patients, recently has been documented to cause pertussis-like illnesses. Occasional case reports of *B. bronchiseptica* in humans include upper and lower respiratory tract illnesses, endocarditis, septicemia, post-traumatic meningitis, and peritonitis. *Bordetella hinzii* has caused bloodstream infection in a handful of cases, associated usually with pulmonary symptoms. Asplenia or immunosuppression has been present in many adults infected with *Bordetella* non-*pertussis* and non-*parapertussis* species. Exposure to pets also is a factor.

EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS

Pertussis is the only vaccine-preventable disease for which universal immunization is given and the incidence of which continues to rise. The >42 000 cases reported in the United States in 2012 were the highest number reported for any year in the last half century. The actual number of cases is likely to be exponentially greater than that reported, because pertussis is undersuspected, underdiagnosed, and underreported. It was estimated during a prospective vaccine trial in adults that there likely are >600 000 cough illnesses due to *B. pertussis* in the United States annually. Age-related incidence of pertussis is highest in infants ≤2 months of age (~150 per 100 000), but the greatest number of cases and the reservoirs for *B. pertussis* are in school-aged children, adolescents, and adults who have waning vaccine immunity and lack the frequent natural subclinical reinfections that boosted immunity in a previous era. Additional factors in resurgence are speculated to include increased awareness, improved diagnostics, use of acellular vaccines for all doses, and pathogen adaptation.

Classic pertussis illness occurs almost exclusively in unimmunized older infants and children. It includes 2-week stages: an afebrile, upper respiratory tract illness with escalating cough (catarrhal stage) followed by paroxysms of machine-gun bursts of coughing, frequently with whoops and posttussive vomiting (paroxysmal stage), fading into fewer and less severe paroxysms (convalescent stage). Young infants have rapid onset of "fits" of gagging, gasping, and cyanotic or apneic episodes, with paroxysmal cough and whoop occurring only later, sometimes during convalescence. Adults do not have distinct stages, and at least one-third have only a prolonged nonspecific cough illness. Clues to pertussis in adolescents and adults are (1) pure or predominant cough illness that is escalating after 1 week, (2) cough illness in which there are sudden paroxysms (repeated bursts of cough on one breath, bulging watery eyes, red face), or (3) cough illness associated with posttussive emesis. Several studies suggest that 13% to 32% of patients with this symptom complex have pertussis. Patients are afebrile, have few upper or lower respiratory tract signs or symptoms, do

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not have myalgia or malaise, and are well between paroxysms. Adults with pertussis describe a typical paroxysm as beginning with an aura of anxiety and fear to take a breath, followed by strangulating cough, feeling of suffocation, and posttussive exhaustion. Whoop is uncommon.

DIAGNOSIS

Differential diagnosis predominantly includes other infectious agents such as *Mycoplasma pneumoniae, Chlamydia pneumoniae*, adenovirus, influenza, and parainfluenza. History of illness onset is most helpful. These other infections typically begin abruptly and include fever, systemic symptoms, multiple mucous membrane involvement, or rash – none of which is part of pertussis. Simple laboratory tests generally are not helpful in differentiating causes, as only unimmunized persons with pertussis have remarkable lymphocytosis.

Current methods for confirmation of infection due to *B. pertussis* (i.e., culture, polymerase chain reaction [PCR], and serology) have limitations in sensitivity, specificity, or practicality; relative value depends on setting (sporadic vs. outbreak), phase of disease, and purpose of use (diagnostic vs. epidemiologic). Culture requires (1) collection of a posterior nasopharyngeal specimen obtained either by aspiration or with Dacron or calcium alginate swab, (2) use of Regan–Lowe transport medium, and (3) inoculation of specialized agar medium and incubation for up to 10 days. PCR has sensitivity similar to that of culture, averts difficulties of isolation, and has rapid result, but standardized validated primers should be used. Use of insertion sequence (IS) *481* increases sensitivity of PCR but does not distinguish between *B. pertussis*, *B. parapertussis* and *B. holmesii*. The PCR test requires similar collection of a posterior nasopharyngeal specimen using a Dacron swab (not a calcium alginate) or nasal wash technique. Serologic testing for increase/seroconversion of immunoglobulin G (IgG) antibody to pertussis toxin (PT-IgG) in acute and convalescent serum in a previously unimmunized individual, or a single level in the second to third week of cough illness that is >2 standard deviations above the expected resting level in distantly immunized individuals is diagnostic. Generally, PT-IgG level >2 years after immunization of >90 EU/mL is highly suggestive, and levels >50 EU/mL are suggestive of symptomatic *B. pertussis* infection.

In unimmunized individuals, pertussis usually is confirmed easily by positive PCR and culture. However, these tests are positive in <20% of cough illnesses due to *B. pertussis* in adolescents and adults. A single elevated serum PT-IgG antibody level is the best diagnostic test in adolescents and adults.

TREATMENT

An antimicrobial agent is given when pertussis is suspected or confirmed, for potential clinical benefit and to limit the spread of infection to others (Table 128.1). In vitro, *B. pertussis* is

Table 128.1 Recommended antimicrobial agents for treatment and postexposure prophylaxis of pertussis[a]

	Age group			
AGENTS	≤1 MONTH	1–5 MONTHS	≥6 MONTHS AND CHILDREN	ADULTS
Primary agents				
Azithromycin	Recommended agent 10 mg/kg/d, once daily ×5 d	10 mg/kg once daily ×5 d	10 mg/kg (max 500 mg) once on d 1; then 5 mg/kg (max 250 mg) once on d 2–5	500 mg once on d 1; then 250 mg once on d 2–5
Clarithromycin	Not recommended	15 mg/kg/d divided BID ×7 d	15 mg/kg/d (max 1 g/d) divided BID ×7 d	1 g/d divided BID ×7 d
Erythromycin	Not preferred	40–50 mg/kg/d divided QID ×14 d	40–50 mg/kg/d (max 2 g/d) divided QID × 14 d	2 g/d divided QID × 14 d
Alternate agent				
TMP–SMX	Contraindicated	Contraindicated at age <2 mo. At ≥2 mo, TMP 8 mg/kg/d–SMX 40 mg/kg/d divided BID ×14 d	TMP 8 mg/kg/d–SMX 40 mg/kg/d (max TMP 320 mg/d) divided BID ×14 d	TMP 320 mg-SMX 1600 mg/d divided BID ×14 d

Abbreviations: TMP–SMX = trimethoprim–sulfamethoxazole; BID = twice a day; QID = four times a day.

[a] Recommendations of the Centers for Disease Control and Prevention and the American Academy of Pediatrics. *Morbid Mortal Weekly Rep.* 2005:54(RR-14):1–16.

susceptible to erythromycin, newer macrolides, quinolones, and third-generation cephalosporins. Ampicillin, rifampin, and trimethoprim–sulfamethoxazole have modest activity, but first- and second-generation cephalosporin do not. In clinical studies, erythromycin is superior to amoxicillin for eradication of *B. pertussis*. Rare isolates resistant to erythromycin have been reported. Azithromycin is the drug of choice for all age groups. Rare cases of idiopathic hypertrophic pyloric stenosis (IHPS) have been reported in neonates given azithromycin (which risk is less than following erythromycin). The US Food and Drug Administration (FDA) also warns of risk of fatal heart rhythms with use of azithromycin in patients already at risk for cardiovascular events, especially prolongation of the QT interval. *B. parapertussis* is less susceptible in vitro to all agents except macrolides. *Bordetella bronchiseptica* is susceptible in vitro to antipseudomonal penicillins, aminoglycosides, and quinolones but generally is not susceptible to cephalosporins; clinical failure has occurred with agents effective in vitro. *Bordetella holmesii* has in vitro susceptibilities similar to *B. bronchiseptica*, but isolates have been susceptible to third-generation cephalosporins.

Secondary sinusitis, otitis media, bronchitis, or pneumonia can complicate *B. pertussis* infection, which denudes ciliated epithelium and inhibits local phagocytic function. Pathogens of secondary infections are *Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae*, and *Moraxella catarrhalis*. Convalescence from uncomplicated pertussis is protracted, with exacerbations of paroxysmal cough during subsequent respiratory illnesses; these are not caused by reinfection or reactivation of *B. pertussis*.

Control and prevention

Postexposure prophylaxis (PEP) using the same agents, doses, and duration as for treatment (Table 128.1) should be given promptly to all household contacts and other close contacts regardless of their age or history of immunization. Benefits of PEP using azithromycin for infants far outweighs risk of IHPS. PEP of contacts has little effect if instituted ≥2 weeks after exposure to the index case. Healthcare personnel (HCP) not wearing a mask who were exposed at close range to an individual with pertussis before the fifth day of treatment should be given PEP promptly, especially if they have contact with young infants, regardless of receipt of Tdap (tetanus toxoid, reduced content diphtheria toxoid, and reduced content acellular pertussis antigens). Cases and contacts with any respiratory tract illness should be excluded from high-risk settings (e.g., school, healthcare facilities) until the fifth day of treatment.

Five doses of DTaP vaccine should be given on the recommended schedule before 7 years of age. Since 2006, Tdap was recommended for universal immunization at 11 to 12 years of age (with catch-up of older adolescents), and for certain adults. By 2012, the Centers for Disease Control and Prevention (CDC) recommended a single dose of Tdap for *all* people 11 years of age and older (i.e., including those ≥65 years of age) regardless of time since Td and regardless of perceived risks of acquisition or transmission or the ages of likely contacts. Although Boostrix is the only licensed Tdap for use in those ≥65 years of age and is preferred, either Boostrix or Adacel can be used. In 2012, the CDC also recommended Tdap for pregnant women in the third trimester of *every* pregnancy (optimally between 26 and 37 weeks of gestation) to prevent infant deaths and severe morbidity by creating a passage antibody bridge until the infant can receive DTaP. When preparing for arrival of all newborns, and when pertussis is suspected or confirmed, immunization status of contacts should be sought and evaluated, and DTaP (for children ≤7 years) or Tdap (for people who have not previously received Tdap) should be given promptly if indicated. There is no recommendation for Tdap revaccination for any age or risk group outside of pregnancy.

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129. *Branhamella–Moraxella*

Lisa S. Hodges and Joseph A. Bocchini, Jr.

Moraxella catarrhalis is an important etiologic agent of otitis media in children, sinusitis in children and adults, and bronchopulmonary infection in adults with chronic obstructive pulmonary disease (COPD) or impaired host defenses.

Moraxella catarrhalis is a gram-negative unencapsulated diplococcus similar in morphology to the *Neisseria*. The bacterium was first described by Ghon and Pfeiffer as *Micrococcus catarrhalis* in 1902 and has since undergone several reclassifications. In 1970 it was placed into the genus *Branhamella* based on fatty acid content and DNA homology. *Moraxella (Branhamella) catarrhalis* is the most widely accepted nomenclature at this time.

EPIDEMIOLOGY

Moraxella catarrhalis is a normal inhabitant of the upper respiratory tract, but can be a pathogen in susceptible hosts. Colonization is seasonal, with an increase in prevalence during winter and spring months. Age and comorbidity are the major determinants of colonization. The mode of transmission is assumed to be direct contact with respiratory secretions or droplet spread. Approximately two-thirds of children become colonized during the first year of life. One prevalence study demonstrated that colonization with *M. catarrhalis* in infants occurs earlier than with *Streptococcus pneumoniae* or *Haemophilus influenzae*, and persists longer. Infants who become colonized with *M. catarrhalis* before 3 months of age are more likely to develop an episode of acute otitis media (AOM) or otitis media with effusion (OME) by the time they are 6 months old. Carriage rates in healthy adults are only 3% to 5%. In contrast, *M. catarrhalis* has been recovered in 5% to 32% of adults with COPD. Approximately half of adults with COPD who are newly colonized will develop an acute exacerbation of COPD.

The pneumococcal conjugate vaccine has altered patterns of nasopharyngeal colonization, permitting replacement with nonvaccine pneumococcal serotypes, nontypeable *H. influenzae*, and *M. catarrhalis*.

PATHOGENESIS

The pathogenesis of infection is complex with both host and bacterial factors determining the evolution from colonization to clinical disease. *Moraxella catarrhalis* expresses adhesion factors and several outer membrane proteins that facilitate preferential binding to mucosal surfaces of the upper and lower respiratory tract and to middle ear epithelial cells. Biofilm formation in sequestered sites such as the middle ear suggest its potential role in the development of AOM with effusion.

Prior colonization of the nasopharynx by *M. catarrhalis* appears to enhance the adherence and invasion of human epithelial cells by *Streptococcus pyogenes*.

Following infection, the organism has the ability to act through Toll-like receptors to induce proinflammatory cytokines in the bronchial epithelium that, in addition to causing acute exacerbations of COPD, may also be responsible for its pathogenesis. *Moraxella catarrhalis* also has the ability to inhibit this proinflammatory process and evade the host immune response, allowing for persistent mucosal colonization.

CLINICAL SYNDROMES

Moraxella catarrhalis is the third most common etiologic cause of AOM and sinusitis in infants and children after *S. pneumoniae* and *H. influenzae*. Cultures of middle ear fluid and of sinus aspirates reveal that 15% to 20% of these infections are caused by *M. catarrhalis*. Most are mixed infections that resolve spontaneously. Suppurative

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complications are uncommon. *Moraxella catarrhalis* has also been recovered from children with OME.

Acute exacerbations of chronic bronchitis in adults with COPD and other chronic lung diseases is the most common lower respiratory tract infection caused by this organism. *Moraxella catarrhalis* is responsible for 30% of acute exacerbations of COPD, second only to *H. influenzae*. Exacerbations are characterized by cough, purulent sputum production, shortness of breath, low-grade fever, and a lack of leukocytosis. It is usually mild to moderate in severity with either patchy or lobar alveolar infiltrates on chest radiograph. CT findings include ground-glass opacities, bronchial wall thickening, and centrilobular nodules. Bacteremia is rare, and pleural effusion and empyema are uncommon.

Less common clinical syndromes associated with *M. catarrhalis* include conjunctivitis in infants that mimics the opthalmia neonatorum of *Neisseria gonorrhoeae*. Bacteremia in children may present like occult pneumococcal bacteremia but has also been reported in association with focal infections such as preseptal cellulitis, septic arthritis, osteomyelitis, and prosthetic vascular graft infection, and a purpuric rash similar to that seen in meningococcemia has been reported. Bacteremia in adults has been reported as a consequence of pneumonia and sepsis has been reported in patients with leukemia, AIDS, and agammaglobulinemia. Pancreatitis, peritonitis, and ventriculitis have also been described. Meningitis, especially in children, has occurred as a result of hematogenous spread from the nasopharynx, or as a consequence of ventriculoperitoneal shunt placement or surgery.

Nosocomial outbreaks with a single strain of *M. catarrhalis* have been reported, in respiratory units and healthcare facilities.

DIAGNOSIS

A presumptive diagnosis can be made from a sputum smear that demonstrates many polymorphonuclear leukocytes with intracellular and extracellular gram-negative diplococci. Because *M. catarrhalis* is somewhat resistant to decolorization, this step in the Gram-stain procedure requires special attention. *M. catarrhalis* can be isolated on blood or chocolate agar media with the addition of CO_2.

THERAPY

In many cases of otitis media and mild to moderate exacerbations of COPD, spontaneous resolution of *M. catarrhalis* infection occurs with the development of strain-specific immunity, an important consideration in determining the need for antimicrobial therapy in an individual patient.

Virtually all strains of *M. catarrhalis* now produce β-lactamase and are resistant to penicillin, amoxicillin, and ampicillin. The addition of a β-lactamase inhibitor (clavulanate, sulbactam, or tazobactam) to a penicillin restores its bactericidal activity against *M. catarrhalis*.

In addition, *M. catarrhalis* is susceptible to amoxicillin–clavulanate, ampicillin–sulbactam, piperacillin–tazobactam, second- and third-generation cephalosporins (including the oral agents), aminoglycosides, aztreonam, and carbapenems. It is also sensitive to macrolides, tetracyclines, trimethoprim–sulfamethoxazole (TMP–SMX), and fluoroquinolones.

Most infections caused by *M. catarrhalis* can be treated with oral antibiotics. For AOM or sinusitis (documented by tympanocentesis or sinus aspiration), amoxicillin–clavulanate administered for 10 days (otitis media) or 2 weeks (sinusitis) is the drug of choice. In patients with known penicillin allergy, macrolides, TMP–SMX, or fluoroquinolones may be used where appropriate.

Acute exacerbations of chronic bronchitis caused by *M. catarrhalis* can also be treated with a variety of oral antibiotics, including amoxicillin–clavulanate, second- or third-generation cephalosporins, TMP–SMX, macrolides, doxycycline, or fluoroquinolones.

Parenteral antibiotics are preferred for more invasive disease. The drug of choice for *M. catarrhalis* pneumonia is ampicillin–sulbactam; however, ceftriaxone could also be used. In patients with known penicillin allergy, a macrolide or a fluoroquinolone is an acceptable alternative.

In most patients with otitis, sinusitis, or an acute exacerbation of chronic bronchitis, the etiologic agent will not be known. The decision to treat and the choice of empiric therapy should consider *M. catarrhalis* but include all common pathogens associated with the specific infection syndrome.

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130. Brucellosis

Carlos Carrillo and Eduardo Gotuzzo

Brucellosis is a zoonotic disease found in Latin America, Mediterranean countries (Spain, Italy, Greece), and Arabian countries (Iraq, Kuwait). According to the Centers for Disease Control and Prevention (CDC), the number of cases dropped from 6147 in 1947 to 104 in 1991 with modern bovine brucellosis eradication, mainly by pasteurization of milk or dairy products.

Most cases of brucellosis in the United States are related to occupational exposure to *Brucella abortus*. The affected are mainly men and occasionally laboratory and technical personnel. However, in Texas and Florida, the ingestion of unpasteurized dairy products is the common mechanism, and the pathogen responsible is *Brucella melitensis*, attacking men and women in equal proportion and sometimes children. *B. melitensis* produces a more severe clinical pattern and can even produce a chronic form. The attack rate is higher, especially in family outbreaks, with rare subclinical infections. *B. abortus* produces a mild disease with low attack rates (<10%) and more subclinical cases.

CLINICAL MANIFESTATIONS

Brucellosis is one of the most protean diseases because any system can be involved. We prefer to divide it into three forms.

Acute brucellosis

Usually, there is high fever, mainly in the evening, with malaise, headache, perspiration, arthralgias, and myalgias. In most cases, constipation, back pain, and loss of weight (as much as 20 pounds in 2 months) are found. Generally, granulomatous hepatitis, hematologic disorders, and articular compromise (especially, peripheral arthritis and sacroiliitis) are seen.

In this form of the disease, any of the routine agglutination assays produce an appropriate diagnosis (immunofluorescence [IF], enzyme-linked immunosorbent assay [ELISA], counterimmunoelectrophoresis [CIE], and Bengal rose test) with high specificity and sensitivity. Rarely, false-positive results may be caused by *Francisella tularensis* and *Yersinia enterocolitica*. With the epidemic of cholera in Latin America, the cross-reaction between *Vibrio cholerae* and *Brucella* is significant, producing false-positive serology to *Brucella* in patients with cholera. Even vaccines against cholera produce false-positive reactions transiently.

The medium Ruiz-Castañeda with Carrillo's modification (addition of 0.025% sodium phosphate sulfonate [SPS] and 0.05% of cysteine) increased the yield of *Brucella*. In the acute form, two blood cultures are as efficient as one bone marrow culture.

Subacute brucellosis (Figure 130.1)

Subacute form (undulant fever or Malta fever) is the typical and classic form described in endemic areas. There is intermittent low fever, often with articular compromise (peripheral arthritis, sacroiliitis, and/or spondylitis), hematologic changes (e.g., pancytopenia, thrombocytopenia, hemolytic anemia), or hepatic damage (granulomatous hepatitis). Patients with incomplete treatment are also included in this form of brucellosis.

In this form of the disease, the 2-mercaptoethanol test detects IgG, and titer above 1:80 defines active infection. *Brucella* are isolated in 40% to 70% of serial blood cultures; the bone marrow culture (0.5 to 1 mL of aspirate from the iliac crest) permits isolation in 90% of these patients.

Chronic brucellosis (Figure 130.2)

In the chronic form with more than 1 year of illness, there usually is an afebrile pattern with myalgia, fatigue, depression, arthralgias, and so on. The most important differential diagnosis is chronic fatigue syndrome.

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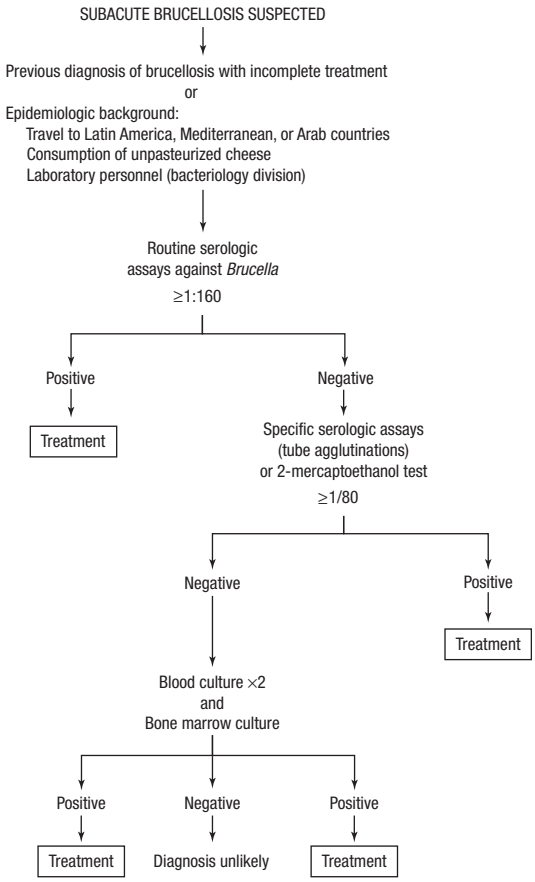

Figure 130.1 Algorithm for the evaluation and treatment of subacute brucellosis.

Other localized forms are granulomatous or recurrent uveitis and spondylitis. Peripheral arthritis and sacroiliitis are rare.

This form of disease is produced mainly by *B. melitensis*. It is found mainly in adults older than 30 years of age, especially older than 50 years old, and is rare in children.

The routine serologic tests and blood cultures give a diagnosis only 10% to 20% of the time. We recommend Coombs test specific for *Brucella* or blocking antibodies. The bone marrow in our experience produces a positive culture in 50% to 75% of patients.

THERAPY

The intracellular character of *Brucella* results in an important therapeutic challenge, especially in subacute and chronic forms. Antibiotics should have in vitro activity, but the intracellular concentration must be adequate.

Tetracyclines have shown excellent in vitro activity throughout the world. The MIC90 (minimum inhibitory concentration required to inhibit growth of 90% of the organisms) was 2 µg/mL for tetracycline and 0.125 µg/mL for doxycycline in our surveillance in Peru. During the past 25 years, the antibiotic activity pattern of tetracycline against *B. melitensis* has not changed, which is remarkable because these are still our drugs of choice.

In addition, for oxytetracycline and doxycycline the minimal bactericidal concentration (MBC) was equal to MIC. All these features in conjunction with worldwide experience point to tetracyclines as the keystone of treatment.

The differences among tetracyclines are tolerance, dosage, and safety profile; however, the new ones have better tolerance and fewer side effects and can be used with meals without reducing efficacy. We prefer to use doxycycline or minocycline.

The other important aspect is the need to combine antibiotics to reduce the rate of relapse. Most antibiotics can reduce the fever, but recurrence is high.

Rifampin has been introduced as a preferential agent because of its excellent in vitro activity and intracellular concentration. The possibility of rapid resistance was shown in our strains when 5 of 10 strains exposed in vitro to rifampin developed resistance by the seventh day.

The third effective group of drugs against *Brucella* is the aminoglycosides, with good in vitro activity and good clinical response. The largest study was done with streptomycin; however, gentamicin, netilmicin, and amikacin showed the same and even better results in open trials.

Comparative studies have been done of doxycycline plus rifampin versus doxycycline plus streptomycin (D-S). Both schedules had a high cure rate (more than 95%); however, D-S had a lower relapse rate.

The doxycycline levels in the plasma of patients treated with rifampin were significantly lower than those of patients treated with D-S. Patients who were rapid acetylators had lower levels because they had higher clearance rates. In addition, the half-life and the area under the curve were significantly lower in these patients. All these new data suggest that relapses may result from this interaction.

Adults

Our standard treatment for adult patients is oral doxycycline, 100 mg twice a day for 45 days, plus streptomycin, 1 g intramuscularly per day for

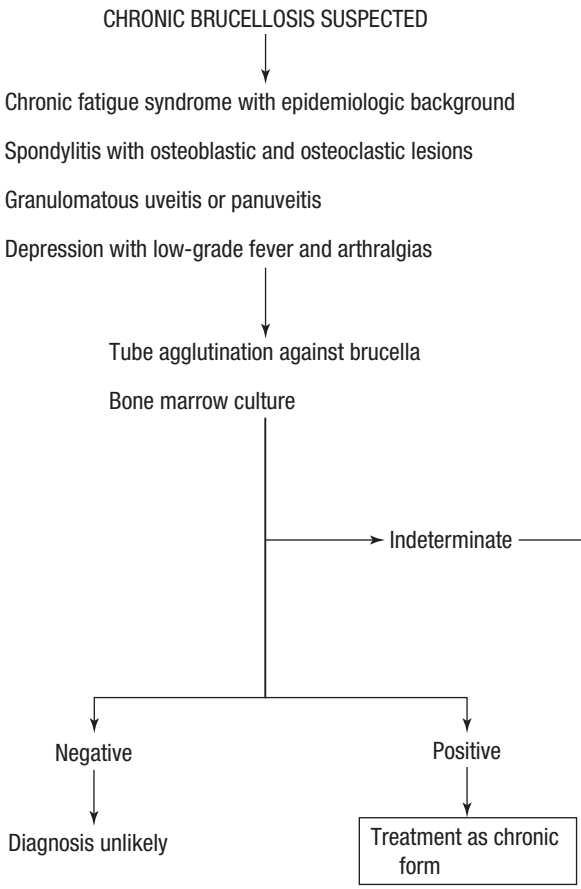

Figure 130.2 Algorithm for the evaluation and treatment of chronic brucellosis. 2-ME = 2-mercaptoethanol.

2 weeks (prolonging treatment with streptomycin for more than 2 weeks has not proved to be more effective); or doxycycline, 100 mg twice a day, plus rifampin, 600 mg once a day, both for 45 days. Only in a case of spondylitis, endocarditis, or brain abscess do we prolong treatment for 3 months.

In chronic brucellosis we prefer to use standard treatment for 45 days and then 3 months of doxycycline only. Some experts recommend adding levamisole for this special form during 3 months.

Children

In children younger than 8 years of age, tetracyclines cannot be used. The combination of rifampin, 15 to 20 mg/kg once a day for 4 weeks, and aminoglycosides at standard dose for 5 to 10 days is highly effective in children.

The use of trimethoprim–sulfamethoxazole (TMP–SMX) has also been recommended in children. TMP–SMX may be used at 240 mg for 4 weeks plus rifampin 20 mg/kg once a day for 4 weeks. This schedule has a high level of tolerance and few adverse effects; however, the efficacy is not as acceptable as with other schedules. Some report excellent results of TMP–SMX for 4 weeks plus gentamicin for 5 to 10 days.

Pregnancy and brucellosis

Brucellosis during pregnancy is a special problem because the best drug should be avoided and the clinical course and fetal prognosis are poor.

In our experience with more than 70% of women with brucellosis, early and adequate treatment showed excellent evolution of pregnancy, and the babies were normal. However, when antibiotic treatment is begun late, the prognosis is worse.

The best schedule is TMP–SMX plus rifampin for 6 weeks. Folic acid supplements should be given.

Another option is aminoglycoside for 10 days plus rifampin or TMP–SMX for 6 weeks.

Other antibiotics

Some drugs, such as chloramphenicol, erythromycin, ampicillin, and cephalosporins, showed moderate in vitro activity, but the clinical experience is not as good as with the other drugs.

Recently, the fluoroquinolones showed better in vitro activity, and they have good intracellular penetration. However, some trials showed that norfloxacin and ciprofloxacin had less clinical efficacy. Only ofloxacin in one trial showed good efficacy.

Steroids

We recommend corticosteroids only for 3 to 6 weeks for uveitis and for 2 to 10 weeks for severe thrombocytopenic purpura. If there is no response, we maintain steroids for 2 to 4 months. After this time if the thrombocytopenia is still evident, we recommend splenectomy.

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131. *Campylobacter*

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Campylobacter (Greek *campylo*, curved; *bacter*, rod) are motile, non-spore-forming gram-negative rods. Today they are recognized as a very common cause of gastrointestinal (GI) infection in humans in many parts of the world. *Campylobacter* organisms were first isolated in the early 1900s from aborted sheep fetuses. However, it was not until the 1970s that *Campylobacter* were isolated from stool.

While there are many members of the genus *Campylobacter*, the major enteric pathogen for humans is *Campylobacter jejuni*, although *Campylobacter coli*, *Campylobacter fetus*, *Campylobacter upsaliensis*, and *Campylobacter lari* are also pathogenic to humans. *C. jejuni* is most frequently associated with GI disease, and *C. fetus* usually causes systemic infection, often in debilitated patients. *Campylobacter* are microaerophilic, and although all will grow at 37°C (98.6°F), *C. jejuni* grows best at 42°C (107.6°F). A number of selective media are in use for the detection of *Campylobacter* spp. and the organisms grow optimally in a gas mixture of 5% to 10% oxygen, 1% to 10% carbon dioxide, and some hydrogen. Growth may be present following overnight incubation, but 2 days are needed before a negative report can be issued.

Although several serotypes of *C. jejuni* have been reported, there are few data regarding the relative virulence of these different types, although some appear to be more closely associated with the development of Guillain–Barré syndrome (GBS) than others.

EPIDEMIOLOGY

Campylobacter is one of the most commonly diagnosed enteric bacterial infections in many parts of the United States and Europe. It is estimated that there are more than 2 million cases per year in the United States. It is especially common in children younger than 1 year of age and in young adults, and it occurs most often in the summer. *Campylobacter* species are found in fowl and many wild and domestic animals, and most human infections probably result from contamination of milk and other animal food sources, especially poultry. The recent increase in consumption of raw milk has led to illness associated with *Campylobacter*. The organisms can also be transmitted by direct contact with infected animals and contaminated water, and cross-contamination between infected poultry and other foods is probably one of the most frequent modes of transmission. Small numbers of organisms may cause disease; as few as 800 have been shown to cause infection in volunteer studies, but the infecting dose is usually about 10^4. Although asymptomatic carriage of *Campylobacter* is thought to be uncommon in developed countries, in less developed nations carriage rates as high as 37% have been reported among children.

CLINICAL FEATURES

The incubation period for *C. jejuni* infection varies and is typically between 1 and 7 days, with most cases occurring 2 to 4 days after exposure. Very short incubation periods of fewer than 12 hours have been reported. *Campylobacter jejuni* illness typically presents with a prodrome of fever, headache, myalgia, and malaise for up to 24 hours before intestinal symptoms develop. The fever may be as high as 40°C (104°F), and the diarrhea varies from a few loose stools to copious watery discharge. Blood is often present in the stool but varies in amount. The illness usually lasts less than a week, but patients untreated with antibiotics often continue to excrete the organisms for several weeks. Documented bacteremia is thought to occur in the early stages of infection in up to 1% of cases. Routine surveillance of infection in England and Wales detected 394 cases of *Campylobacter* bacteremia in 11 years that increased with age, with a range of 0.3/1000 in children aged 1 to 4 years to 5.9/1000 in patients aged 65 years or more. Overall 89% of the

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identified isolates were *C. jejuni* or *C. coli*. This may explain why focal infections such as endocarditis, meningitis, septic abortion, acute cholecystitis, pancreatitis, and cystitis have all been documented. Postinfectious reactive arthritis may also occur, especially in human leukocyte antigen (HLA)-B27-positive individuals. One of the most serious consequences of infection with *C. jejuni* is the development of GBS. This is an autoimmune disorder of the peripheral nervous system resulting in an ascending flaccid paralysis that carries a mortality rate of up to 5%. GBS is thought to be caused by molecular mimicry between polysaccharides on the outer surface of *C. jejuni* and gangliosides in the myelin sheaths of peripheral nerves.

In contrast to *C. jejuni, C. fetus* commonly produces systemic disease, often in vascular sites: endocarditis, pericarditis, and mycotic aneurysms of the abdominal aorta. Central nervous system infections such as meningoencephalitis also occur with *C. fetus*, as do other localized infections, including septic arthritis, spontaneous bacterial peritonitis, salpingitis, lung abscess, empyema, cellulitis, urinary tract infection, vertebral osteomyelitis, and cholecystitis. In patients with acquired immunodeficiency syndrome (AIDS), *Campylobacter* species other than *C. fetus* and *C. jejuni* may also cause bacteremia.

DIAGNOSIS

Campylobacter have a characteristic darting motility, and a presumptive diagnosis of *Campylobacter* infection may be made by examination of stool passed within 2 hours using direct dark-field or phase-contrast microscopy. Leukocytes and red cells are also often seen in stool samples, with 75% of patients having polymorphonuclear leukocytes in their stool. Confirmation of the diagnosis of *C. jejuni* infection is based on a positive stool or blood culture as noted above, although *Campylobacter* is fastidious and may die during transport to the laboratory. DNA probes, polymerase chain reaction, and serologic testing all have been used to confirm diagnosis but are not routinely available. Direct detection of *Campylobacter* antigens in stool using enzyme immunoassays is a relatively new approach that is now commercially available. This method has the attraction of not requiring live organisms but has the detraction of not producing an isolate that will be available for antimicrobial sensitivity testing. *Campylobacter fetus* may be isolated from blood held in culture up to 14 days. The fastidious nature of the organisms means that failure to culture *Campylobacter* does not rule them out as the cause of significant clinical disease.

THERAPY

As with all diarrheal diseases, fluid replacement and attention to electrolyte balance is the most important therapy in *Campylobacter* diarrhea. Oral rehydration is usually adequate, but patients with severe dehydration should be given volume replacement with intravenous solutions of electrolytes and water.

Most *Campylobacter* infections are mild and self-limited and do not result in a visit to a physician. These mild infections do not usually require antimicrobial therapy. Antimicrobial therapy should be reserved for patients who are severely ill, elderly, pregnant, or immunocompromised but may on occasion also be indicated in patients with bloody stools, high fever, extraintestinal infection, worsening symptoms or relapses, and those with symptoms lasting longer than 1 week. Treating patients later in the course of the disease (after several days of symptoms) will remove *Campylobacter* from the stool, but it is not likely to have a dramatic effect on the duration of symptoms. Person-to-person spread generally is not considered a major concern with *Campylobacter*, so treating to prevent this is not generally recommended (except in the case of food handlers). However, there may be exceptions to this, for example, the reduction of spread in day-care settings. Antibiotic therapy can have a dramatic positive effect on symptoms of *C. jejuni* infection, justifying a trial of therapy in severe or persistent illness.

Campylobacter jejuni is usually susceptible to many antimicrobial agents in vitro, including macrolides, tetracyclines, aminoglycosides, chloramphenicol, quinolones, and nitrofurans. The clinically important antibiotics include the macrolides, fluoroquinolones, aminoglycosides, and carbapenems. They are inherently resistant to trimethoprim and most cephalosporins except cefotaxime, ceftazidime, and cefpirone.

Erythromycin was, for years, the first-line drug to treat *Campylobacter*. However today the first-line agents for *Campylobacter* gastroenteritis include fluoroquinolones (if sensitive) or azithromycin. In patients with uncomplicated *Campylobacter* infection a first-line treatment would be levofloxacin or azithromycin 500 mg PO daily for 3 days or until signs and symptoms of disease have improved. For those with

complications or underlying immunosuppression, a longer course (7 to 14 days) may be warranted. If a patient is not able to tolerate oral treatment or if they are severely ill other options include the use of an aminoglycoside or a carbapenem but it is recommended that susceptibility testing should be performed prior to their use.

Campylobacter resistance has not become a huge issue but is certainly more of a concern than it used to be. Generally the rate of macrolide-resistance among *Campylobacter* has remained stable at <5% in most parts of the world – but has been reported to be higher in Thailand and in Ireland. The prevalence of fluoroquinolone-resistant *Campylobacter* is rising. Resistance rates of greater than 50% have been reported in Spain, Hungary, and several developing countries. The rate of fluoroquinolone resistance is also increasing in Southeast Asia and in the United States; in the United States, resistance increased from 0% to 19% between 1989 and 2001. This growing level of resistance to fluoroquinolones is important in the context of treating infections that may have been acquired in areas of high resistance or if treatment is appearing to fail.

PROGNOSIS AND PREVENTION

Most patients recover totally following infection with *C. jejuni*. Complications such as reactive arthritis and GBS are unusual. Systemic *C. fetus* infections have a significant mortality, especially in patients with underlying disease such as diabetes mellitus or cirrhosis or who are immunocompromised. Transmission of *Campylobacter* infection can be reduced by careful food handling, with special attention to cross-contamination from poultry products. Proper cooking of food, pasteurization of milk, and protection of water supplies are all critical in preventing infection with *Campylobacter*.

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132. *Clostridium*

Derek Forster

INTRODUCTION

The genus *Clostridium* contains many species of bacteria that cause human diseases. These bacteria produce some of the most deadly toxins ever discovered. Distinctive infections include botulism, tetanus, gas gangrene, and food poisoning from *Clostridium perfringens*. With few exceptions, clostridia are obligate, anaerobic, spore-forming bacilli that are ubiquitous in the environment, in soil and marine sediment. Although a member of the *Clostridium* genus, *Clostridium difficile* is discussed separately (Chapter 51, Antibiotic-associated diarrhea).

BOTULISM

Botulism is a rare but potentially fatal disease caused by *Clostridium botulinum* bacteria, which produce botulinum toxin, one of the most potent bacterial toxins ever described. It can be classified into four categories which reflect the mode of acquisition: foodborne botulism, infant and adult enteric botulism, wound botulism, and inhalational botulism. A recent category, iatrogenic botulism, has also been described in patients who have received botulinum toxin injections. All modes of acquisition can lead to the clinical syndrome of botulism, which manifests as symmetric flaccid paralysis of the voluntary musculature.

The word botulism is derived from the latin word *botulus*, which means sausage, and is a reference to an early investigation of "sausage poisoning" in a southern German town in which affected patients developed gastrointestinal and neuromuscular symptoms. This investigation is believed to be the first described outbreak of foodborne botulism.

There are eight strains of *C. botulinum* that are classified according to the type of toxin they produce. Of the eight toxin types, only types A, B, E, and occasionally F cause human disease. The spores are heat-resistant and able to survive at 100°C for several hours. In contrast to the spores, the toxins are heat-labile and are readily denatured by heating to temperatures above 80°C.

Epidemiology

FOODBORNE BOTULISM

Foodborne botulism is caused by the ingestion of contaminated improperly cooked or raw foods containing preformed toxin. The toxin is absorbed in the small intestine whereby it enters the bloodstream and causes disease as it reaches the peripheral nervous system. The ingestion of spores alone does not cause botulism because the competitive environment of the gastrointestinal tract does not allow the spores to vegetate and produce toxin. The exceptions to this are infantile botulism and adult enteric botulism, which are discussed later.

Foodborne botulism represents the greatest public health concern related to botulism and is most frequently recognized in small outbreaks involving home-canned fruits and vegetables but has also been associated with commercial products and restaurants. In the USA, 263 cases from 160 foodborne botulism events occurred between 1990 and 2000. Toxin type A was the most common, causing 51% of all cases. The highest percentage of cases occurred in Alaska where 103 (39% of cases) were due to ingestion of non-commercial fish and marine mammal products. Another study evaluated the epidemiology of endemic foodborne botulism among Alaskan natives from 1947 to 2007 and concluded that the incidence was decreasing but still remained >800 times the overall US rate.

WOUND BOTULISM

Wound botulism is caused by contamination of a wound with *C. botulinum* spores that germinate and produce toxin. Reported cases have increased dramatically over the last 20 years and are now

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mainly attributed to injection drug use. These cases have been associated with the use of "black tar" heroin administered subcutaneously or intramuscularly, a technique known as "skin popping." Wound botulism has also been described following open fractures and surgery.

INFANT AND ADULT ENTERIC BOTULISM

Infant botulism occurs when spores (not toxins) are ingested and then vegetate in the intestinal tract due to a lack of competing bacteria, producing toxin. It is the most common form of botulism in the United States with 2419 cases identified from 1976 to 2006. The main reservoir leading to infection is thought to be environmental dust containing spores. This correlates with the fact that states with high soil botulinum spore counts have the highest incidence of cases. California accounts for nearly 50% of all US cases. Honey remains the only identified food and the only avoidable source of infant botulism. Educational efforts have increased public awareness and ingestion of honey by infants has decreased markedly; however, significant decreases in cases have not been seen.

Adult enteric botulism, like infant botulism, occurs from infection of the intestinal tract with vegetative bacteria that leads to toxin production. It is considered rare in the adult but those at risk include patients with a disruption of their bowel flora due to anatomic abnormalities, functional disorders, or antibiotic use. Protracted symptoms and relapse due to persistent production of toxin may be seen.

INHALATIONAL BOTULISM

Inhalational botulism is not a naturally occurring disease. It has been described among users of intranasal cocaine, leading to a local wound infection in the sinuses where the bacteria ultimately germinate and produce toxin. This form also represents a potential route for bioterrorism attacks. A deliberate release of aerosolized toxin could produce an outbreak of botulism with considerable mortality.

IATROGENIC BOTULISM

Iatrogenic botulism is a recently described entity that is caused by the direct injection of botulinum toxin for cosmetic purposes. In 2004, four cases of botulism were linked to the use of a highly concentrated, unlicensed botulinum toxin. These patients may have received doses nearly 3000 times the estimated human lethal dose by injection and had pretreatment serum toxin levels up to 43 times the estimated lethal human dose. All four patients survived but suffered a long hospital course.

Pathogenesis

Regardless of the mode of acquisition, once toxin has entered the bloodstream it reaches the peripheral cholinergic synapse where it eventually prevents the release of acetylcholine. It binds to a specific receptor called synaptotagmin on the presynaptic cleft of the synapse. Once bound, the toxin enters the cell via receptor-mediated endocytosis where it irreversibly disrupts the release of acetycholine. The exact mechanism of this action varies and depends on the type of toxin present. Return of function requires the formation of a new presynaptic terminal with a new synapse which generally takes 6 months or longer to occur. For this reason, clinical recovery is prolonged.

Clinical

The classic description of botulism is the acute onset of symmetric cranial nerve palsies with subsequent symmetrical descending flaccid paralysis that may progress to respiratory arrest. Fever is typically not present unless it is a component of a wound infection as with wound botulism. Sensory deficits are absent. Although botulinum toxin may be transported in a retrograde fashion via the nerves, central nervous system (CNS) involvement is rare and the patient almost always remains responsive.

As the disease progresses, descending paralysis of the neck, shoulders, upper extremities, and lower extremities can occur. Respiratory arrest can occur when the diaphragm and accessory breathing muscles become involved. Constipation is invariably present at later stages. The severity of disease ranges from mild involvement of the cranial nerves to full paralysis requiring mechanical ventilation and reflects the amount of toxin in the bloodstream.

Other symptoms depend on the mode of acquisition. With foodborne botulism, patients may have a prodrome of nausea, vomiting, abdominal pain, and dry mouth. In wound botulism, local wound infection with fever may be present. The incubation period is difficult to ascertain given the frequency of injection drug use but is generally longer than other forms of botulism (7 to 14 days) because of the time required for spores to vegetate, produce local

infection, and generate toxin. At the time of evaluation, the local wound infection may have resolved, making history the key to diagnosis. The presentation of infantile botulism varies but may involve constipation, weakness, feeding difficulties, hypotonia, drooling, irritability, and a weak cry.

The major differential diagnoses are myasthenia gravis, Lambert–Eaton myasthenia syndrome, tick paralysis, Guillain–Barré syndrome and poliomyelitis. The edrophonium test may be positive in botulism and thus may not distinguish botulism from myasthenia gravis. Guillain–Barré syndrome frequently begins with sensory complaints and rarely as cranial nerve dysfunction. Fever is usually present in poliomyelitis but not in botulism. Cerebrospinal fluid (CSF) analysis is normal in botulism.

Diagnosis

The clinical syndrome of botulism is distinctive and thus a careful history and physical examination are essential to considering and making the diagnosis. Confirmation involves detection of the toxin in the patient's serum, gastric secretions, stool, or a food sample. This is done via mouse bioassay, which is performed in a limited number of public health laboratories.

Other diagnostic tools include anaerobic cultures of serum, stool, and implicated food if available; however, the strict anaerobic conditions needed for growth make isolation of *C. botulinum* difficult. Enzyme-linked immunosorbent assays and polymerase chain reaction have been used for detection in contaminated food samples but are not available for widespread use.

Treatment

The mainstay of therapy is supportive care with intubation and mechanical ventilation if necessary. The only specific therapy is botulinum antitoxin, which exists as two forms: equine serum heptavalent botulism antitoxin and human-derived botulism immune globulin. The equine antitoxin is used to treat adults and children $>$ 1 year of age. Rates of hypersensitivity (including anaphylaxis) have been reported to be between 9% and 20% and thus a test dose is often given prior to administration. Human botulinum immune globulin (BabyBIG) is the recommended antitoxin for use in infantile botulism (children $<$ 1 year of age). Antitoxin administration should not be delayed while awaiting the results of diagnostic testing. The antitoxin is available through the Centers for Disease Control and Prevention (CDC). A pentavalent antitoxin is only available through the department of defense.

Antibiotic therapy is often used for wound botulism. Penicillin G provides effective coverage of clostridial species with metronidazole a good alternative for penicillin-allergic patients. Wound debridement should be performed even if the wound appears unimpressive. A polymicrobial infection may be present, and thus broader coverage can be considered, but the use of aminoglycosides and clindamycin is contraindicated as they may induce neuromuscular blockade and thus worsen the effects of the toxin. Antibiotics are not recommended for infant botulism or adults with suspected enteric botulism as this may increase the toxin available for absorption. In the setting of foodborne botulism, laxatives, enemas, or other cathartics may be given if no significant ileus is present.

Prevention

A pentavalent botulinum toxoid vaccine was available for occupational exposure to botulinum toxins but was discontinued in 2011.

TETANUS

Tetanus is a neurologic disorder characterized by muscle spasms; it is caused by *Clostridium tetani*, an obligately anaerobic gram-positive bacillus found worldwide in soil. It has a characteristic "tennis racket" or "drumstick" appearance on Gram stain (Figure 132.1). Because of vaccination, the annual incidence of cases in the United States has decreased markedly from 1947 to 2008 (Figure 132.2). In the United States, there were

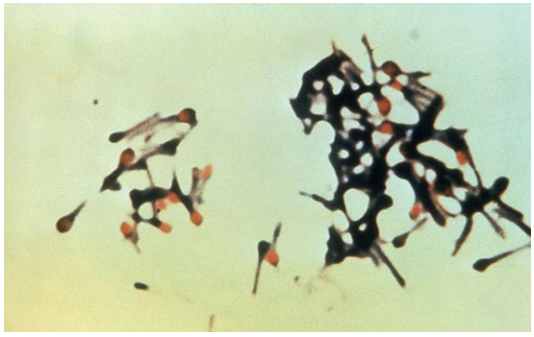
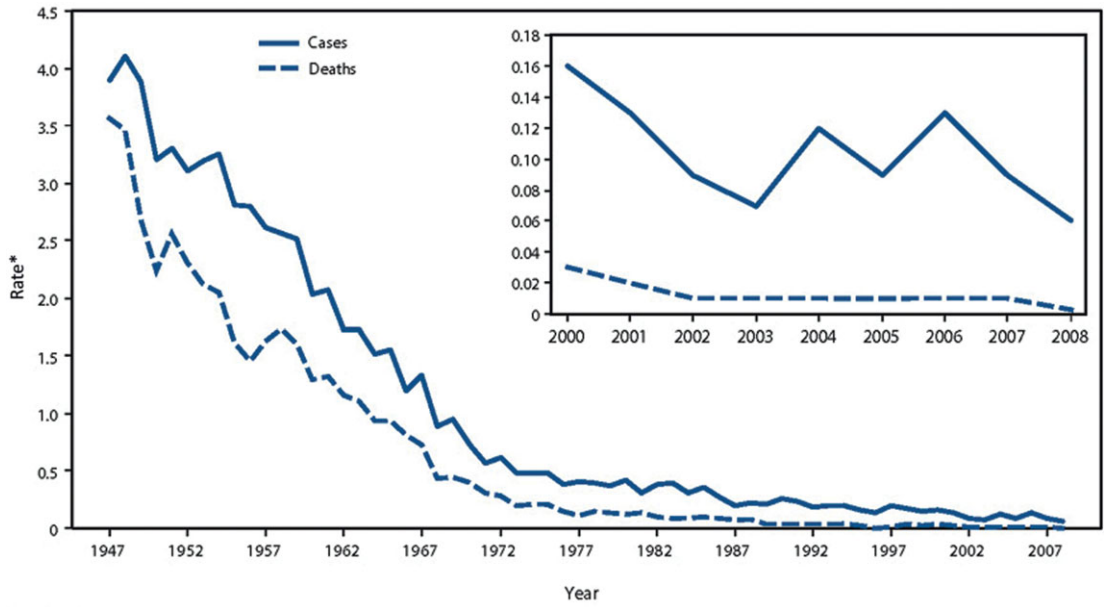


Figure 132.1 "Tennis racket" or "drumstick" appearance of *Clostridium tetani*. (http://www.cdc.gov/tetanus/about/photos.html)



*Per 1 million population.

Figure 132.2 Annual rate of tetanus cases and tetanus deaths in the United States during 1947–2008, according to the National Notifiable Disease Surveillance System. From 1947–2008. (Centers for Disease Control and Prevention (CDC). Tetanus surveillance – United States, 2001–2008. *MMWR Morb Mortal Wkly Rep*. 2011;60 (12):365–369 available from: PM:21451446)

233 cases from 2001 to 2008. Most of the cases were in individuals over 65, reflecting waning immunity. In developing countries tetanus remains endemic with an estimated one million cases occurring worldwide annually with 300 000 to 500 000 deaths. Prevention of neonatal tetanus has been a target of the World Health Organization which has resulted in a decrease in the number of cases and deaths.

Pathogenesis

A wound infection with *C. tetani* is the first step of the disease process. Once the bacterium vegetates it produces tetanospasmin (tetanus toxin) and tetanolysin. Tetanospasmin enters the nervous system through presynaptic terminals and interrupts neuromuscular transmission whereby it can initially cause local paralysis. Once it enters the nervous system, retrograde transport facilitates its movement to the CNS where it prevents the release of inhibitory neurotransmitters, which results in an unopposed excitatory signal. This effect is also seen in the autonomic nervous system, causing a hypersympathetic state. Tetanospasmin binding is irreversible, and thus the effects last the lifetime of the neuron. The other toxin produced is tetanolysin, which causes tissue necrosis and thus a more favorable environment for growth of the bacterium.

Clinical

Tetanus exists in four clinical forms: generalized, local, cephalic, and neonatal. These forms reflect the location of initial involvement as well as the extent of disease. The incubation period is variable and can be as short as 1 day or as long as several months. The distance from the site of inoculation of the organism to the CNS is a major determinant of the incubation period, with longer distances resulting in a longer incubation period.

Generalized tetanus is the most commonly recognized form which often presents with trismus but later manifests as tonic contraction of skeletal muscles with intermittent muscular spasms. Decorticate posturing with flexion of the arms and extension of the legs is classically described with generalized spasms. There is no impairment in consciousness and thus the spasms are intensely painful. Symptoms of autonomic hyperactivity including irritability, restlessness, sweating, and tachycardia may be seen early in the course with progression to cardiac

arrhythmias, labile blood pressures, and fevers in the later stages. This autonomic instability is the leading cause of death with a fatality rate of 11% to 28%.

Localized tetanus involves the muscles at the site of inoculation, presenting as tonic and spastic contractions. It may be mild and may persist for weeks to months. Although it may resolve spontaneously without long-term sequelae, it is often a prodrome of generalized tetanus. The reported incidence of localized tetanus is 13%.

Cephalic tetanus is a form of localized tetanus that involves the head or neck. Although it initially involves only the cranial nerves, it can be a prodrome of generalized tetanus. It can also spontaneously resolve without complications. The incubation period for progression to generalized tetanus is short due to its proximity to the CNS.

Neonatal tetanus typically occurs in the first 28 days of life. It develops in infants of unvaccinated mothers when infection of the umbilical stump with *C. tetani* occurs due to poor aseptic technique at delivery or contamination with dirt, straw, or other materials. Cultural practices involving the application of clarified butter, juices, and cow dung to the umbilical stump have also been implicated in the development of disease. It may manifest initially as general weakness and a failure to nurse but progresses to rigidity, spasms, trismus, and seizures. Sepsis, related to bacterial infection of the umbilical stump, occurs in about half of the patients and accounts for significant mortality which can exceed 90%.

Diagnosis

The diagnosis of tetanus is primarily based on the typical findings mentioned above. There is no definitive testing to confirm or exclude the diagnosis. Antitetanus antibodies are often undetectable in clinical disease. Culture for *C. tetani* is of little value because of poor sensitivity and specificity as positive cultures may be present without disease and represent colonization rather than true infection. Inadequate immunization and inadequate wound prophylaxis are important risk factors for the development of tetanus and thus, knowing a patient's prior vaccination status can be helpful when entertaining the diagnosis. Patients should also be questioned regarding prior tetanus prone injuries and physical exam should include evaluating for any possible inoculation sites.

There are several considerations in the differential diagnosis including drug-induced dystonia, trismus due to dental infections, strychnine poisoning, and neuroleptic malignant syndrome. Drug-induced dystonia, in contrast to tetanus, produces deviation of the eyes and an absence of tonic muscular contractions between spasms. Also, administration of anticholinergics will reverse the spasms in drug-induced dystonia but not in tetanus. Trismus due to dental infections is seen in the presence of an obvious dental abscess. Strychnine poisoning can cause a syndrome similar to tetanus. Testing of blood, urine, and tissue samples for strychnine can be done in settings when accidental or intentional poisoning is considered. Neuroleptic malignant syndrome can present with muscular rigidity and autonomic instability as well as fever and altered mental status, both of which are not seen in tetanus.

Treatment

The initial treatment of tetanus should include early and aggressive airway management. If endotracheal intubation is required, benzodiazepine sedation and neuromuscular blockade should be used because passage of the endotracheal tube can trigger spasms. Subsequent control of spasms requires the use of benzodiazepines at doses higher than typically required for sedation. Neuromuscular blockade may be required if adequate control is not achieved with benzodiazepines. Magnesium sulfate may be helpful as an adjunct to treatment. It blocks catecholamine release from nerves and reduces receptor responsiveness to catecholamines. It has been shown to reduce the use of other drugs for control of spasms and aid in the control of autonomic dysfunction but has not been shown to reduce mortality or the need for mechanical ventilation. Patients should be placed in darkened, quiet areas in the ICU to avoid triggering muscular spasms. This becomes more important in resource-limited settings where access to some medications and mechanical ventilation may not be available.

Passive immunization with human tetanus immune globulin (HTIG) to bind free toxin should be given as soon as the diagnosis of tetanus is considered. The dose for treating active tetanus is 3000 IU given intramuscularly. This shortens the course of tetanus and reduces the severity. Intrathecal administration may provide benefit when given in combination with

intramuscular HTIG. Because infection does not confer immunity, active immunization with tetanus toxoid should also be initiated.

Antibiotics are generally recommended but their benefit is unclear. Antimicrobial susceptibilities demonstrate reliable sensitivity to penicillin and metronidazole as well as cephalosporins, imipenem, macrolides, and tetracycline. Favorable results with metronidazole compared to penicillin were described in one study with reduction in mortality and shorter hospitalization; however, subsequent studies have failed to show a difference. A possible explanation of poorer response to pencillin would be γ-aminobutyric acid (GABA) antagonism which is known to occur and results in CNS excitability. This effect is also seen with later-generation cephalosporins. Local wound management should be undertaken but surgical intervention, if necessary, should be performed after spasms are controlled.

Prevention

Tetanus is considered a preventable disease with vaccination. Current recommendations from the Advisory Committee on Immunization Practices (ACIP) include a combination vaccine containing diphtheria, tetanus, and pertussis (DTaP) as primary vaccination given at ages 2, 4, and 6 months, followed by a dose at age 15 to 18 months and again at age 4 to 6 years. A Tdap should be given for children ages 11 to 12. Adults should receive tetanus booster every 10 years with one booster being given as a Tdap to also provide boosted immunity for pertussis. Patients that sustain an unclean wound that is not considered minor should also receive a booster if more than 5 years has passed from their last immunization.

CLOSTRIDIAL MYONECROSIS (GAS GANGRENE)

Clostridial myonecrosis is a deep space infection that results in destruction of healthy muscle tissue and causes systemic toxicity. It can result from trauma with direct inoculation or contamination and subsequent infection of a wound from *C. perfringens*. These account for about 70% of cases. It can also arise spontaneously from hematogenous seeding with *Clostridium septicum*. As with other species of clostridia, they are found commonly in soil. *Clostridium perfringens* is also found commonly in the intestines of humans and animals and requires a microaerophilic environment to thrive, which is in contrast to *C. septicum* which can grow in oxygen-rich environments. It is a life-threatening infection with mortality reported in 19% of traumatic cases and up to 81% of spontaneous cases. Other less common species that can cause disease include *C. sordelli*, *C. novyi*, *C. bifermentans*, and *C. histolyticum*.

Pathogenesis

Traumatic injury can result in vascular compromise to previously healthy tissue and provide an anaerobic environment which is ideal for the growth of *C. perfringens* as well as some other species listed above. Once the spores germinate, they produce alpha and theta toxin that cause tissue destruction, hemolysis, vasodilatation, and alterations in the extravascular migration of neutrophils. It is this alteration of neutrophil migration that accounts for the characteristic absence of purulence in the necrotic tissues. Alpha toxin can contribute to shock by suppressing myocardial contractility, which further compromises cardiac output in the setting of endothelial dysfunction and systemic vasodilatation.

Spontaneous clostridial myonecrosis is typically the result of hematogenous seeding from bacteria (usually *C. septicum*) that gain access to the bloodstream through the gastrointestinal tract. In stark contrast to *C. perfringens*, these bacteria do not require an anaerobic environment and thus can affect previously normal and healthy tissue. *C. septicum* also produces several toxins; however, their contribution to pathogenesis is less clearly known. As with *C. perfringens*, neutrophils are notably absent in the necrotic tissues. There are some predisposing factors which include colonic or hematologic malignancy, inflammatory bowel disease, recent gastrointestinal surgery, neutropenia, and acquired immunodeficiency syndrome.

Clinical

Severe pain is one of the hallmark findings in early disease and is present in both traumatic and spontaneous cases. In traumatic cases, erythema of the inoculation site may be seen. The classic skin findings include the rapid development of a bronze appearance, followed by purple or red discoloration with formation of fluid-filled blisters. As stated above, purulence is uncommon. The extremities become tense from

progressive edema of the deeper structures and gas may be appreciated on palpation. Anemia may result from the hemolytic effect of alpha toxin. Progression to sepsis and multiorgan failure may occur rapidly and can be seen within hours of the initial presentation.

Diagnosis and treatment

Early consideration of gas gangrene is critical to treatment success. The clinical signs mentioned above should point to the diagnosis. Gas in the tissues can be demonstrated by radiography, ultrasound, CT scan, or MRI; the latter two modalities also show deep structures in detail to determine if the infection is localized or if it is involving adjacent structures. Gram stain of involved tissue or fluid may demonstrate gram-positive or gram-variable rods with culture providing a definitive diagnosis.

The most essential component of therapy is early surgical debridement of the involved tissues. Antibiotics comprise another key component of therapy and reduce mortality when combined with early surgery. Penicillin remains one of the most widely used antibiotics to treat clostridial myonecrosis. The addition of clindamycin provides a highly active regimen and through its inhibition of protein synthesis may also decrease toxin production. Other antibiotics with activity include tetracyclines, metronidazole, erythromycin, and carbapenems. Hyperbaric oxygen has been used as an adjunct to therapy with reported improved survival rates; however, its use remains controversial. *Clostridium septicum* can survive and grow in an oxygen-rich environment and thus spontaneous cases caused by this organism would be unlikely to benefit from the use of hyperbaric oxygen.

FOOD POISONING CAUSED BY *CLOSTRIDIUM PERFRINGENS*

C. perfringens is the second most common bacterial cause of foodborne illness in the United States, with one million cases each year. It results from the ingestion of a large inoculum of vegetative bacteria. Once ingested, the bacteria release an enterotoxin that causes watery diarrhea, abdominal cramping, vomiting, and fever. The incubation period is short, generally between 7 and 15 hours with spontaneous resolution of symptoms occurring at 24 to 48 hours. Meats are the most common contaminated foods with most cases occurring as a common source outbreak. Diagnosis requires the detection of bacterial toxin in stool or by detection of at least 10^6 *C. perfringens* spores per gram of stool in symptomatic patients. Therapy is supportive with hydration playing a major role. Of the five strains of *C. perfringens* (A through E) type A accounts for the majority of cases.

OTHER CLOSTRIDIAL INFECTIONS

Other clostridial infections may occur as part of a disease process described above or as part of a separate entity. For example, clostridial bacteremia may occur in the setting of clostridial myonecrosis, with *C. perfringens* and *C. septicum* accounting for the majority of cases. The association with *C. septicum* bacteremia and the presence of an underlying hematologic or colonic malignancy should be noted. Clostridia can also cause infections of the gallbladder with *C. perfringens* again accounting for the majority of cases. In this setting, gas may be demonstrated in the biliary tract and would be an indication for surgical intervention. Clostridia may be present as a component of polymicrobial abdominal infections that result from contamination of the peritoneum from intestinal contents. Although rare, they have also been described in anaerobic pulmonary infections.

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133. Corynebacteria

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CORYNEBACTERIUM DIPHTHERIAE (DIPHTHERIA)

Diphtheria is an acute, infectious, preventable, and sometimes fatal disease caused by *Corynebacterium diphtheriae*. The infection is usually localized to the upper part of the respiratory tract and/or the skin; from here it gives rise to local and systemic signs or it can be an asymptomatic carrier state. These signs are the result of a toxin produced by the microorganisms multiplying at the site of infection. The systemic complications particularly affect the heart (22%), the peripheral nerves (5%), and/or the kidneys (renal failure in severe cases).

Cause

Diphtheria is distributed worldwide, there are four biotypes: gravis, intermedius, mitis, and belfanti. All are associated with epidemic and endemic diphtheria. The highest incidence occurs in temperate climates. It occurs predominantly under poor socioeconomic conditions, where crowding is common and where many persons are either not immunized or inadequately immunized. In the United States 20% to 60% of adults are susceptible to diphtheria since the immunity wanes and it is not customary to receive boosters. In the 1990s there were reports of diphtheria outbreaks in the newly independent states of the former Soviet Union. Outbreaks were also experienced in other European countries and were characterized by a high fatality rate, and a large number of complications and adult cases. Diphtheria is seen in developed countries in people that travel to and return from endemic areas as well as in immigrants from endemic areas.

The only significant reservoir of *C. diphtheriae* is the human host. The organism is transmitted directly from one person to another, and intimate contact is required. Transmission is usually by way of infected droplets of nasopharyngeal secretions. Infective skin exudate has been involved in human-to-human transmission. Transmission may also occur via animals, fomites, or milk. The infectious period is usually 2 weeks from onset of symptoms, as long as 6 weeks, and, if treated with antibiotics, to less than 4 days.

Immunity depends on antitoxin in the host's blood. Antitoxin is formed by immunization or by clinical or subclinical infection, including skin infections. Immunity does not prevent carriage. Since immunity varies the Centers for Disease Control and Prevention (CDC) recommends that adults receive a diphtheria-toxoid-containing vaccine (Tdap) every 10 years after completing a primary childhood vaccination series. Despite incomplete immunity the rate of clinical disease is low, US incidence of ~0.001 cases/100 000 population.

Clinical features

Diphtheria may be symptomless or rapidly fatal. The incubation period varies from 1 to 7 days but is most commonly 2 to 4 days.

RESPIRATORY DIPHTHERIA

Diphtheria infection of the respiratory tract is usually caused by toxin-producing strains of *C. diphtheriae*, rarely by toxigenic strains of *Corynebacterium ulcerans*, *Corynebacterium pseudotuberculosis* or *Corynebacterium hemolyticum*.

ANTERIOR NARES DIPHTHERIA

The infection is localized to the anterior nasal area and is manifested by unilateral or bilateral serous or serosanguineous discharge that erodes the adjacent skin, resulting in small crusted lesions. The membrane may be seen in the nose.

TONSILLAR (FAUCIAL) DIPHTHERIA

Tonsillar diphtheria is the most common presentation and the most toxic form. The onset is usually sudden, with fever rarely exceeding 38°C (100.4°F), malaise, and mild sore throat. The

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pharynx is moderately infected, and a thick, whitish-gray tonsillar exudate is often seen. The tonsillar and cervical lymph nodes are enlarged. The exudate may extend to other areas and result in nasopharyngeal diphtheria and massive cervical lymphadenopathy (bull neck appearance also called malignant diphtheria). The most common complaints are sore throat (85%), pain on swallowing (23%), nausea and vomiting (25%), and headache (18%).

PHARYNGEAL DIPHTHERIA

Pharyngeal diphtheria is diagnosed when the membrane extends from the tonsillar area to the pharynx.

LARYNGEAL AND BRONCHIAL DIPHTHERIA

Laryngeal and bronchial diphtheria involves the larynx. The voice becomes hoarse and inspiratory and expiratory stridor may appear; dyspnea and cyanosis occur, and the accessory muscles of respiration are used. Tracheostomy or intubation is needed.

CUTANEOUS DIPHTHERIA

Classically described as diphtheria in tropical areas, cutaneous diphtheria now is seen in nontropical areas as well. It takes the form of a chronic nonhealing ulcer, sometimes covered with a grayish membranous exudate. Another form is secondary infection of a pre-existing wound. Finally, superinfection with *C. diphtheriae* may occur in a variety of primary skin lesions, such as impetigo, insect bites, ecthyma, and eczema.

Complications of diphtheria

MYOCARDITIS

Although electrocardiographic (ECG) changes have been described in up to 66% of cases, overt clinical myocarditis is less common (10%–22%). The onset is insidious, occurring in the second or third week of the infection. The patient exhibits a weak, rising pulse; distant heart sounds; and profound weakness and lethargy. Overt signs of heart failure can occur. The most common ECG changes are flattening or inversion of T waves, bundle branch block or intraventricular block, and disorders of rhythm. Serial determination of cardiac enzyme concentrations identifies most patients with myocarditis. The prognosis is poor, especially when heart block supervenes.

PERIPHERAL NEURITIS

Neurologic toxicity has been described in about 5% of patients with diphtheria, but in severe diphtheria up to 75% of patients develop neurologic complications. The most common form of cranial nerve palsy is paralysis of the soft palate. There may be nasal regurgitation and/or nasal speech. This condition is usually mild, and recovery occurs within 2 weeks. Ciliary paralysis and oculomotor paralysis are the next most common forms. Peripheral neuritis affecting the limbs may appear during the fourth to eighth week. It is usually manifested by weakness of the dorsiflexors and decreased or absent deep-tendon reflexes. Diphtheritic polyneuritis has been described after cutaneous diphtheria.

Diagnosis

Diagnosis is made on clinical grounds and can be confirmed by laboratory tests (Figure 133.1). The clinical features of a fully developed diphtheritic membrane, especially in the pharynx, are sufficiently characteristic to suggest diphtheria and for treatment to be started immediately.

Specific diagnosis of diphtheria depends completely on demonstration of the organism in stained smears and its recovery by culture. In experienced hands, methylene blue-stained preparations are positive in 75% to 85% of cases. The bacilli can be recovered by culture in Loeffler's or Tindale's medium within 8 to 12 hours if patients have not been receiving antimicrobial agents. *Corynebacterium diphtheriae* can be seen as gram-positive bacilli in a "Chinese letter" distribution pattern on Gram or methylene blue stain (Figure 133.2); one can find metachromatic granules on Loeffler's stain and black colonies with halos with growth on Tindale's medium. The presence of β-hemolytic streptococci does not rule out diphtheria because such streptococci are recovered in up to 20% to 30% of patients with diphtheria.

Toxin detection should be performed to differentiate toxigenic from nontoxigenic strains, but is not the reason not to administer antitoxin. Toxin production can be demonstrated by the ELEK test and or rapid enzyme immunoassay (ELISA).

The differential diagnosis of tonsillar-pharyngeal diphtheria should include streptococcal pharyngitis, adenoviral exudative pharyngitis, infectious mononucleosis, and Vincent's angina, among others (Table 133.1).

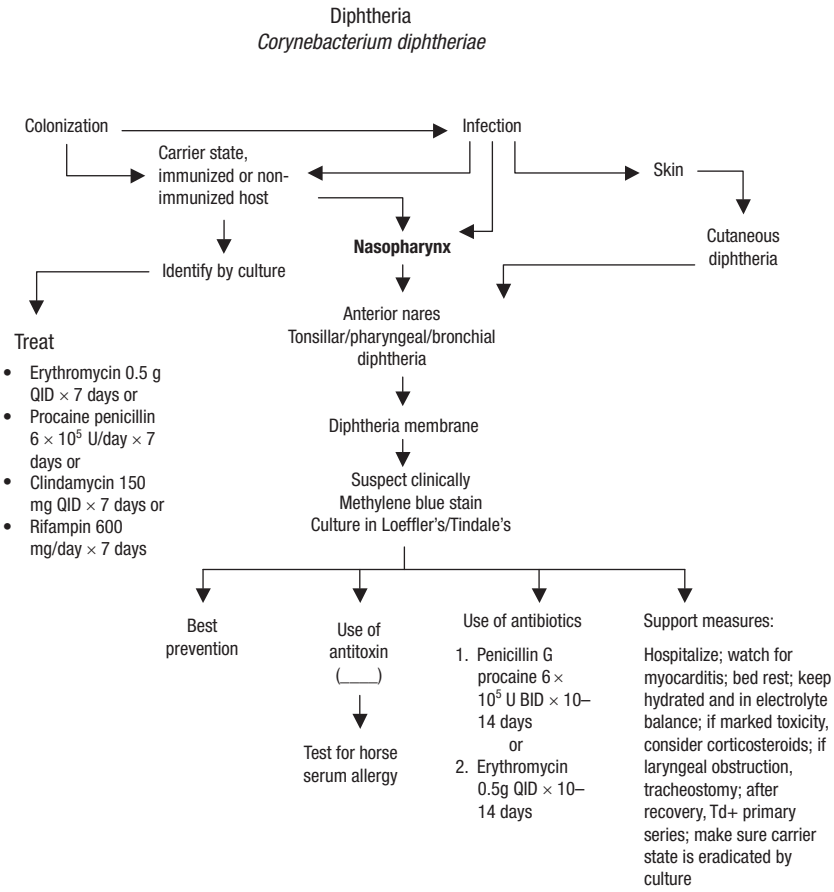

Figure 133.1 Diagnostic and treatment approach to diphtheria.

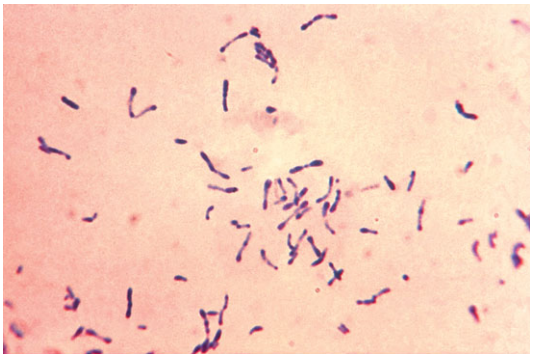

Figure 133.2 Gram-positive bacilli in a "Chinese letter" distribution pattern on Gram stain.

Therapy

The best and most effective treatment of diphtheria is prevention by immunization with diphtheria toxoid. The most important aspect of treatment is to administer the antitoxin and antibiotics as soon as diphtheria is clinically suspected, without awaiting laboratory confirmation. The patient should be hospitalized, isolated, and kept in bed for 10 to 14 days (see Figures 133.1 and 131.3).

USE OF ANTITOXIN

The antitoxin is equine, and the minimal effective dose remains undefined; therefore, dosage is based on empiric judgment. It is usually accepted that for patients with mild or moderate cases, including those with tonsillar and pharyngeal membrane, 20 000 to 40 000 units for pharyngeal disease of <48 hours duration, 40 000 to 60 000 units for nasopharyngeal disease, and 80 000 to 100 000 units for >3 days of illness or "bull neck" is appropriate. Doses should be given intravenously over 60 minutes as recommended by the American Academy of Pediatrics.

Table 133.1 Differential diagnosis of diphtheria

Affected area	Other conditions
Nose	Sinusitis, foreign body, snuffles of congenital syphilis, rhinitis
Fauces and pharynx	Streptococcal or adenoviral exudative pharyngitis, ulcerative pharyngitis (herpetic, Coxsackie-viral), infectious mononucleosis, oral thrush, peritonsillar abscess, retropharyngeal abscess, Vincent's angina, lesions associated with agranulocytosis or leukemia
Larynx	Laryngotracheobronchitis, epiglottitis
Skin	Impetigo, pyogenic ulcers, herpes simplex infection

Before administration of the antitoxin, any history of allergy or reactions to horse serum or horse dander must be determined. All patients must be tested for antitoxin sensitivity with dilute horse antitoxin in saline 1:10 and an eye test. This is followed by a scratch test with a 1:100 dilution; if negative in half an hour, the scratch test is followed by an intradermal test, 1:100 dilution. If all tests are negative, antitoxin can be given. The intravenous route is recommended. A slow intravenous infusion of 0.5 mL antitoxin in 10 mL saline is followed in half an hour by the balance of the dose in a dilution of 1:20 with saline, infused at a rate not to exceed 1 mL/min. Others give the antitoxin dose intramuscularly in mild to moderate cases only.

If the patient is sensitive to horse serum, desensitization should be carried out with care, preferably in an intensive care unit. Epinephrine, intubation equipment, and respiratory assistance should be available. The following doses of horse serum antitoxin should be injected at 15-minute intervals if no reaction occurs:

1. 0.05 mL of 1:20 dilution subcutaneously
2. 0.10 mL of 1:10 dilution subcutaneously
3. 0.3 mL of 1:10 dilution subcutaneously
4. 0.1 mL of undiluted antitoxin subcutaneously
5. 0.2 mL of undiluted antitoxin subcutaneously
6. 0.5 mL of undiluted antitoxin subcutaneously
7. Remaining estimated therapeutic dose intramuscularly.

During all tests and on injection of antitoxin, a syringe containing epinephrine 1:1000 dilution in saline should be at hand to be used immediately in a dose of 0.01 mL/kg subcutaneously or intramuscularly at any sign of anaphylaxis. A good precaution is to have open venous access with normal saline prior to the test. If needed, a similar amount of epinephrine diluted to a final concentration of 1:10 000 in saline may be given slowly intravenously and repeated in 5 to 15 minutes. Other information and instructions in the package insert accompanying the antitoxin should be observed.

ANTIBIOTICS

Corynebacterium diphtheriae is susceptible to several antimicrobial agents. After cultures have been performed, antibiotics should be administered to prevent multiplication of the microorganism at the site of infection and to eliminate the carrier state. The antibiotics of choice are erythromycin (500 mg four times a day for 14 days) or penicillin G 25 000 to 50 000 units to a maximum of 1.2 million units IV every 12 hours until the patient can take oral penicillin V (250 mg QID) for a total of 14 days. Erythromycin has been favored since reports show greater efficacy than penicillin.

SUPPORTIVE MEASURES

Complications such as dehydration, malnutrition, and congestive heart failure should be diagnosed promptly and properly treated. In cases of severe laryngeal involvement, marked toxicity, or shock, corticosteroids (prednisone 3 to 5 mg/kg/day) have been advocated, but there are no hard data on their effectiveness. For laryngeal obstruction with respiratory stridor, a tracheotomy must be performed promptly.

Before the patient is discharged, specimens from throat and nose or suspected lesions should be cultured. At least two and preferably three consecutive negative cultures should be obtained.

After recovery, toxoid administration against tetanus and diphtheria (Td) should be administered to complete a primary immunization series if the patient has not been immunized.

Carriers

The chronic carrier state may occur despite immunity derived either from clinical disease or from immunization. The carrier state occasionally persists in the absence of antecedent disease. Erythromycin, 0.5 g orally four times a day for 7 days in adults, is the treatment of choice for the carrier state. Alternative antibiotics are procaine penicillin G, 600 000 U intramuscularly daily for 14 days, clindamycin, 150 mg orally four times a day for 7 days, or rifampin, 600 mg/day orally for 7 days.

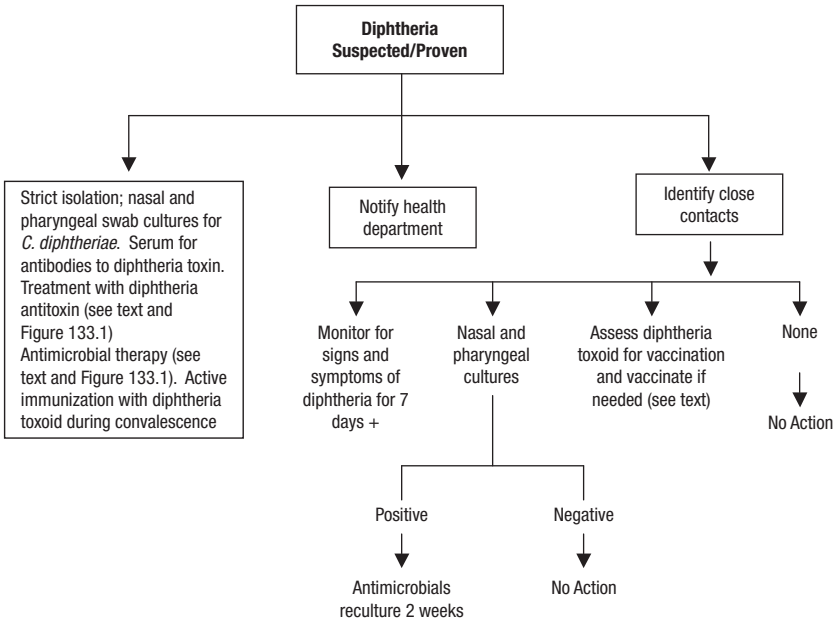

Figure 133.3 Public health management of diphtheria.

Epidemics

The approach to epidemic disease is as follows:

1. Identify all primary cases, hospitalize, and treat.
2. Use toxoid in all the population at risk.
3. Culture all contacts for diphtheria, and treat all persons with *C. diphtheriae* in throat, nose, or skin lesions with erythromycin for 7 days to eliminate carrier state (Figure 133.3).
4. Watch primary contacts closely during the first week of exposure and treat at first signs or symptoms. Alternatively, all susceptible primary contacts can be given 1500 to 3000 U of diphtheria antitoxin, administered as previously described, in addition to toxoid. This low-level dose will boost them while they are forming their antibody.

Prevention

Children who have had a complete course of primary immunization with diphtheria–tetanus–pertussis (DTaP) vaccine may be given a booster injection on exposure to diphtheria. This is done in case of outbreaks but is not routine. Antibiotic prophylaxis is highly effective.

Household and other close contacts of a patient with diphtheria should be observed attentively for 7 days. They should receive either an intramuscular injection of 600 000 to 1.2 million units of benzathine penicillin or a 7- to 10-day course of erythromycin taken orally. Cultures should be performed before and after treatment. An injection of toxoid appropriate for age and immunization status can also be given. Susceptible close contacts who have had no (or only one) prior injections of toxoid should promptly be given 3000 to 10 000 units (depending on body size) of antitoxin, with the usual precautions being followed. When indicated, active immunization with toxoid should be continued to completion. Routine immunization for diphtheria is discussed in Chapter 115, Immunizations.

NONDIPHTHERIC CORYNEBACTERIA

Nondiphtheric corynebacteria were once considered commensals. They are present in the skin and often are recovered from blood cultures. The presence of the microorganism in the blood has been considered contaminant, but there are many instances in which nondiphtheric corynebacteria are associated with bacteremias, sepsis, pneumonias, endocarditis, central nervous system infections, and intraocular infections, especially in immunocompromised patients and patients with vascular and central nervous system catheters and prosthetic devices. A common predisposing factor is neutropenia.

Table 133.2 Epidemiology and clinical features of selected nondiphtheric corynebacteria

Corynebacterium	Epidemiology	Clinical features
C. jeikeium	Skin, systemic	Soft-tissue, pneumonias, shunt infections; skin rash; endocarditis
C. minutissimum	Skin	Erythrasma, reddish-brown macular lesions, fluoresce under Wood's lamp
C. ulcerans	Skin, systemic	Cardiac and central nervous system involvement; diseases in horses and cattle
C. pseudotuberculosis	Skin exposure, farm animals, raw milk	Dermonecrotic toxin, suppurative granulomas, lymphadenitis, disease in farm animals
C. bovis	Shunts, skin	Meningitis, spinal epidural; abscess; ventriculoperitoneal or jugular shunts
C. pseudodiphtheriticum	Systemic	Pneumonia endocarditis, tracheitis, urinary tract
C. striatum	Immunosuppressed	Pneumonias, meningitis, abscesses, bacteremias

The diagnosis of infections with nondiphtheric corynebacteria usually involves their recovery from blood or other sterile body fluid. Corynebacteria can be identified by conventional methods; since 2000, a new system, the Rapid CORYNE System, was found to be excellent and an alternative to conventional methods.

Clinically, there are no specific findings that suggest nondiphtheric corynebacteria, but their association with central lines, skin, and subcutaneous infections in immunocompromised patients leads the clinician to associate a given infection with a gram-positive rod. Table 133.2 lists the epidemiology and clinical features of selected nondiphtheric corynebacteria.

Corynebacterium jeikeium

Corynebacterium jeikeium is a gram-positive coccobacillus or coccus resembling the streptococcus. Characteristically, it shows high-grade antibiotic resistance, being susceptible only to vancomycin in vitro and in vivo.

CLINICAL FEATURES

Diseases associated with *Corynebacterium jeikeium* include soft-tissue infections, pneumonitis with or without cavitation, continuous ambulatory peritoneal dialysis-related peritonitis, neurosurgical shunt infections, skin rash, catheter-related epicardial abscess, and endocarditis. It should always be considered a possible cause of sepsis in the neutropenic patient and in patients with prosthetic devices in place.

THERAPY

Despite their high antibiotic resistance, these corynebacteria remain susceptible to vancomycin. Total effective duration of treatment has not been established. Clinical response must be followed, usually treating for 4 to 6 weeks. Newer fluoroquinolones, mainly ciprofloxacin, have also shown good results. Infected prosthetic material often requires removal.

Corynebacterium minutissimum

Infection with *C. minutissimum* usually involves the skin, and the classical disease entity is erythrasma. Erythrasma is a skin infection characterized by brownish-reddish macules that itch and when exposed to a Wood's lamp fluoresce. The most frequent location is the intertriginous areas.

Bacteremia with *C. minutissimum* has been described in patients with leukemia in blast crisis. There are also reports of trichomycosis axillaris associated with this corynebacterium.

Corynebacterium ulcerans

Corynebacterium ulcerans, like *C. diphtheriae*, produces diphtheria toxin by lysogeny but without apparent clinical consequences. However, there are documented reports of *C. ulcerans* bacteremias with cardiac and central nervous system involvement as well as pneumonia.

Corynebacterium pseudotuberculosis

Infection with *C. pseudotuberculosis* is associated with exposure to farm animals or consumption of raw milk. Clinically, it presents as a suppurative granulomatous lymphadenitis most likely related to the dermonecrotic toxin it produces. This organism responds to long-term treatment with erythromycin or tetracycline.

Corynebacterium bovis

Most infections reported with *C. bovis* are associated with central nervous system processes. There have been cases of meningitis, epidural abscesses, and shunt infections.

Corynebacterium pseudodiphtheriticum

Sites of infection caused by *C. pseudodiphtheriticum* include heart valves, wounds, urinary tract, and lungs, with pneumonia and necrotizing tracheitis. The susceptibilities of this microorganism are varied, with both susceptibility and resistance to erythromycin, clindamycin, and penicillin. There is a case of response to penicillin intravenously (12 million units daily for 14 days).

Corynebacterium striatum

Persons with an underlying immunosuppressive process are usually victims of *C. striatum*. There are reports of pneumonias, pulmonary abscesses, meningitis, and bacteremias with *C. striatum*. Most patients were treated with vancomycin.

Others

There have been reports of *Corynebacterium* CDC group A-4 associated with native valve endocarditis in immunocompetent patients as well as sepsis in immunocompromised hosts with infected Hickman catheters. *Corynebacterium aquaticum*, an environmental organism of fresh water, has been associated with septicemia in a neutropenic patient with an indwelling central venous catheter who used untreated stored rainwater to shower. *Corynebacterium afermentans* (CDC group ANF-1) was reported to cause endocarditis in a prosthetic valve.

Therapy

Some corynebacteria are susceptible to erythromycin, sulfonamides, chloramphenicol, gentamicin, imipenem, some of the newer fluoroquinolones, and vancomycin. For most serious and systemic infections, we prefer to use vancomycin at 1 g every 12 hours for at least 2 weeks in adults with normal renal function. In some patients, especially immunocompromised patients, combination therapy can be used with vancomycin plus imipenem at 500 mg intravenously every 6 hours, vancomycin plus rifampin at 600 mg daily orally, or vancomycin plus ciprofloxacin at 750 mg orally every 12 hours for 2 to 4 weeks. Erythromycin at a dosage of 2 to 4 g in divided doses can be used as an alternative regimen. The optimal effective therapy for these infections has not been determined, but 8 weeks of treatment are often required. For unresponsive cases, surgical consultation is recommended.

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134. Enterobacteriaceae

L. W. Preston Church

The Enterobacteriaceae comprise several genera commonly referred to as the enteric gram-negative bacilli and several species less commonly encountered in clinical practice (Table 134.1). The unique features of *Salmonella*, *Shigella*, and *Yersinia* are considered in separate chapters. These organisms are ubiquitous in the environment and are readily recovered from water and soil. The human reservoir for most species is the colon, although other muscosal sites may become colonized, particularly in healthcare-related settings. Members of the Enterobacteriaceae are important causes of community-acquired and hospital-acquired infections of almost any organ system, with hospital-acquired strains increasingly demonstrating resistance to multiple

Table 134.1 Medically important Enterobacteriaceae

Genus and species	Comments
Citrobacter diversus, *C. freundii*	Usually nosocomial, most frequently involving urinary tract
Edwardsiella tarda	Associated with freshwater ingestion causing diarrhea
Enterobacter aerogenes, *E. cloacae*, *E. sakasakii*	Intestinal colonizer typically surfaces as a pathogen in hospitalizad patients receiving antibiotics; antibiotic resistance common
Escherichia coli	Most common cause of urinary tract infection. Several diarrheal pathotypes. Pneumonia, particularly in alcoholics, diabetics, immunocompromised or nosocomial (HAP, VAP). Important in community and nosocomial infections of all types. High level antimicrobial resistance including ESBL increasing
Ewingella americana	Nosocomial infections, rare
Hafnia alvei	Rare
Klebsiella pneumoniae, *K. oxytoca*	Community and nosocomial pathogen. Common cause of urinary tract infection with bacteremia. Important cause of pneumonia as for *E. coli*. Liver abscess in diabetics in Asia. High level antimicrobial resistance including ESBL
Kluyvera species	Rare
Morganella morganii	Uncommon cause of nosocomial infections
Pantoea agglomerans	Environmental pathogen
Plesiomonas shigeloides	Associated with freshwater ingestion causing diarrhea
Proteus mirabilis, *P. vulgaris*	Urinary tract infections (frequently bacteremic), especially in presence of foreign body or urologic abnormalities
Providencia stuartii, *P. rettgeri*	Catheter-associated urinary tract infections
Salmonella enterica	See Chapter 150, *Salmonella*
Serratia marcescens	Environmental pathogen, antibiotic resistance common
Shigella species	See Chapter 155, *Shigella*
Yersinia species	See Chapter 160, *Yersinia*

Abbreviations: HAP = hospital-associated pneumonia; VAP= ventilator-associated pneumonia; ESBL = extended-spectrum β-lactamase.

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classes of antibiotics through a variety of resistance mechanisms. This growing dilemma underscores the need for accurate diagnoses and intelligent use of a diminishing antimicrobial arsenal.

URINARY TRACT INFECTION

The Enterobacteriaceae are the most important etiology of both community-acquired and nosocomial urinary tract infection, with *Escherichia coli* the most frequently encountered pathogen. The success of *E. coli*, in part, may be attributed to the adaptation of specialized adherence fimbriae which facilitate attachment to normal uroepithelium.

The symptoms of urinary tract infection are common to all uropathogens but may assist in defining the location and extent of infection. In women the three principal manifestations are urethritis, characterized primarily by dysuria; cystitis, characterized by frequency, urgency, dysuria, suprapubic tenderness with or without fever; or pyelonephritis, characterized by nausea and vomiting, fever, chills, flank pain, and costovertebral angle tenderness. In the male urinary tract additional structures may be involved as seen in epididymitis and acute or chronic prostatitis. In the elderly or the patient with an indwelling urinary catheter or a spinal cord injury many of the signs and symptoms may be absent and the lines separating infection from asymptomatic bacteruria may be blurred. Presenting features rarely distinguish the infecting agent with the exception of urinary tract infection with alkaline urine (pH8), often in the presence of staghorn renal calculi, which is strongly suggestive of *Proteus* species.

An important corollary of urinary tract infection is asymptomatic bacteriuria – the presence of a uropathogen in significant quantity, usually defined as $>10^5$ organisms/mL, with or without pyuria in the absence of symptoms. Although asymptomatic bacteriuria infrequently progresses to symptomatic infection, treatment is only indicated in pregnancy (done for the increased risk for pyelonephritis), young children, or prior to instrumentation of the urinary tract, as with insertion of a Foley catheter. Bacteriuria in the presence of symptoms defines urinary tract infection. Although $>10^5$ organisms/mL is often used as the cutoff for significant bacteriuria in defining a urinary tract infection, for a properly obtained sample yielding a likely pathogen in the presence of appropriate symptoms, $>10^4$ organisms/mL is a more sensitive measure. For samples obtained by suprapubic tap or other means of percutaneous drainage a lower threshold of $>10^3$ organisms/mL may be appropriate.

GASTROINTESTINAL AND INTRABDOMINAL INFECTION

Although many of the Enterobacteriaceae are part of the normal gut flora this group is the principal cause of intra-abdominal infections through a variety of mechanisms. Several strains of *E. coli* are associated with diarrheal disease of the small and large intestine (Table 134.2). Most, if not all, of those infections are self-limited illnesses although the severity varies. Enterotoxigenic *E. coli* (ETEC) is the most common cause of travelers' diarrhea and enjoys a long list of colorful synonyms such as Montezuma's revenge. Disease is the result of cholera-like toxins that result in excess secretion of water by the small bowel into the gut lumen, overwhelming the capacity of the colon to resorb water. For most of the enteropathogenic *E. coli* diagnostic testing is not routinely available although specific toxins or genes may be detected by PCR or DNA probes. The important exception is enterohemorrhagic *E. coli* (EHEC) and if suspected the stool should be cultured on sorbital-MacConkey agar to identify the

Table 134.2 Pathogenic *E. coli* of the gastrointestinal tract

Pathotype		Clinical illness	Comments
ETEC	Enterotoxogenic *E. coli*	Acute watery diarrhea, usually self-limited	Most common cause of travelers' diarrhea and in children worldwide
EAEC	Enteroaggregative *E. coli*	Mucoid diarrhea	May cause chronic diarrhea, emerging in travelers
EPEC	Enteropathogenic *E. coli*	Acute diarrhea and vomiting	Common in children in developing countries
EIEC	Enteroinvasive *E. coli*	Watery diarrhea or dysentery (fever, abdominal pain, tenesmus, blood)	Occurs in outbreaks
EHEC	Enterohemorrhagic *E. coli*	Watery and bloody diarrhea	Hemolytic-uremic syndrome

O157:H7 strain most commonly associated with this disease. EHEC typically manifests as acute bloody diarrhea accompanied by abdominal pain and cramping. Fever is notably absent. Most commonly associated with undercooked ground meat, outbreaks have been associated with unpasteurized apple cider and other uncooked or unpasteurized products. Hemolytic-uremic syndrome, characterized by acute renal failure and thrombocytopenia, complicates 7% to 15% of cases of EHEC with the greater proportion of cases occurring in the very young and the elderly.

Obstruction of diverticuli or the appendix may be part of the mechanism behind diverticulitis and appendicitis, both polymicrobial infections in which the Enterobacteriaceae have an active role. Gut flora may, through perforation of a viscus, form an abscess anywhere within the abdominal or pelvic cavities or result in peritonitis. Introduction of these organisms into the biliary system, especially in the content of obstruction, may result in cholecystitis. Liver abscess may result from extension of an infectious process in the biliary system or may be seeded from the gut via the portal venous system. These infections may be characterized by fever and abdominal pain which may or may not be localizing. Leukocytosis with a left shift may be an important clue to the diagnosis. In cholecystitis and cholangitis the total bilirubin is usually elevated if the common bile duct is involved but is only elevated 25% of the time if not obstructed. Alkaline phosphatase is elevated in two-thirds of liver abscess, usually with little to no elevation of bilirubin or aminotransferases. Recently, specific *Klebsiella* serotypes have been implicated as the etiology of liver abscess with metastatic infection to the eye and central nervous system; this syndrome affects predominantly diabetic patients and is well described in East and Southeast Asia, though recent reports identify it as an emerging global threat.

Infection of the pancreas or a pancreatic pseudocyst may be extremely troublesome to diagnose as the signs and symptoms of abdominal pain, nausea, vomiting, fever, and leukocytosis may all be manifestations of acute pancreatitis. Infection should be suspected with the appearance of a new febrile episode, especially after manipulation of the pancreas as during endoscopic retrograde cholangiopancreatography (ERCP).

Finally, the Enterobacteriaceae are the primary etiologic agent of spontaneous bacterial peritonitis (SBP). Despite the proximity to the gastrointestinal tract, SBP is a consequence of hematogenous seeding of pre-existing ascites, most commonly in the context of cirrhosis but occasionally complicating nephritic syndrome or severe right-sided heart failure. Clinical manifestations include presence of ascites by exam or imaging, which is usually new or clinically worse, abdominal pain and tenderness, and fever.

PNEUMONIA AND PLEURAL SPACE INFECTIONS

The Enterobacteriaceae account for 5% to 15% of all pneumonias for which an etiologic agent can be identified, regardless of whether the pneumonia is community or nosocomially acquired. Clinical findings are rarely helpful in determining the etiology of a bacterial pneumonia although aspiration, older age, and comorbid conditions such as heart failure, renal disease, or diabetes may favor a gram-negative etiology. Production of dark-red mucoid or "currant jelly" sputum suggests pneumonia due to *Klebsiella pneumoniae* but the other hallmarks of "Friedlander's" pneumonia are nonspecific. No pattern on chest radiograph is pathognomonic of gram-negative pneumonia but the diagnosis should be considered whenever necrotizing pneumonia, pneumatoceles, cavitation, or empyema are seen.

SKIN AND SOFT-TISSUE INFECTIONS

Enterobacteriaceae may be involved in a variety of skin and soft-tissue infections. Pure infections with one of these organisms may occur as surgical wound infections, especially in abdominal or pelvic locations or as a secondary infection of burns. More commonly these organisms are part of mixed infections, especially with anaerobic bacteria. In this context they may cause complicated and often destructive infections of decubitis ulcers or diabetic foot infections or present as part of a spectrum of rapidly progressive and destructive infections of soft tissue, including synergistic necrotizing cellulitis, gangrenous balanitis, perineal phlegmon (Fournier's gangrene), progressive bacterial synergistic gangrene, and necrotizing fasciitis. In general these infections complicate a pre-existing wound or trauma (which may be surprisingly trivial) or may arise from extension from an internal source such as a perforated viscus. Diabetes mellitus is a frequently encountered risk factor. All of these conditions, which differ primarily by location or depth of tissue involvement, are characterized

by moderate to severe pain, swelling, crepitus on exam or radiologic evidence of tissue gas, malodorous wound discharge, and evidence of skin necrosis. Affected individuals are usually systemically ill-appearing with fever and leukocytosis.

BONE AND JOINT INFECTIONS

Septic arthritis, osteomyelitis, and prosthetic joint infections may be seen with any of the Enterobacteriaceae. Overall they are considerably less frequent than infections of similar sites due to gram-positive cocci and account for 5% to 25% of these infections. Focal infections may result from extension of a localized soft-tissue infection, as in the diabetic foot, as early or late postoperative complications, particularly in the presence of orthopedic devices, or by contamination from penetrating injuries. Local vascular and lymphatic seeding from the prostate may lead to lumbar vertebral osteomyelitis and hematogenous seeding can affect any bone or joint. Clinical presentations will be the same as for any bacterial infection of these sites, varying from small draining sinuses with no associated symptoms to local pain, swelling, erythema, wound dehiscence, and fever. Vertebral infections may have pain in a localized or radicular pattern and may have associated focal neurologic abnormalities if concomitant epidural abscess is present.

Diagnosis rests upon clinical suspicion and may be augmented by imaging studies including conventional x-rays, radionuclide scanning, computed tomography (CT), or magnetic resonance imaging (MRI); the latter two modalities may be particularly useful in the evaluation of suspected vertebral infections. Elevated erythrocyte sedimentation rates or C-reactive protein are not useful for diagnosis but may be useful markers to follow response to therapy. In the context of these organisms, surface swabs are unreliable in identifying the agents of deep infection and sterilely obtained cultures of fluid, bone, or tissue are required for diagnosis.

CENTRAL NERVOUS SYSTEM INFECTIONS

Escherichia coli accounts for the majority of bacterial meningitis due to gram-negative bacilli, with the majority of cases occurring within the first few weeks of life or in the immunocompromised or elderly. Outside of these risk groups most infections are the result of trauma or other causes for bacteremia such as parenteral drug use. Hyperinfection with strongyloides may lead to bacteremia and meningitis as migrating larvae allow colonic bacteria to cross the gut lumen and possibly travel to different anatomic sites in association with larval invasion. Due to the nature of the host, classic signs of fever and nuchal rigidity may be absent and alteration of consciousness may be the only clue. Diagnosis hinges on analysis of the cerebrospinal fluid (CSF). Gram stains are positive in approximately 50% and may be misinterpreted as negative due to similar staining characteristics of the bacteria and the cellular and protein elements in the CSF. Latex agglutination for the *E. coli* K1 antigen, found on 75% of neonatal CSF isolates, may be a useful adjunctive test.

Focal suppurative infections of the central nervous system, including brain abscess, subdural empyema, and spinal epidural abscess, all occur to a limited extent with these organisms. As noted for vertebral osteomyelitis, chronic prostatitis may lead to seeding of the lower lumbar area with Enterobacteriaceae and produce both osteomyelitis and spinal epidural abscess in this location. One particularly problematic infection is ventriculitis due to ventricular shunt infections. *Enterobacter* species, which thrive in hospital environments, are frequently identified and may be difficult to treat due to intrinsic and acquired antimicrobial resistance.

BACTEREMIA, ENDOVASCULAR INFECTION, AND SEPSIS

A positive blood culture for one of the Enterobacteriaceae, when properly obtained in the evaluation of suspected infection, should always be regarded as a true-positive result and a source aggressively sought. Any of the previously described syndromes may include bacteremia but the majority of gram-negative bacteremias without a clinically apparent source will have originated in the urinary tract or as an intrabdominal infection. Intravascular catheters, particularly those used for parenteral nutrition or hemodialysis or those in a femoral vein location, are also important sources of gram-negative bacteremia. In this setting the line exit site and tunnel show no evidence of infection; the line as a source is suspected on the basis of positive blood cultures obtained through the line and ideally from the periphery as well. Some studies suggest that a differential time to positive culture of greater than 2 hours in favor of the culture obtained through the line signifies the line as the source, assuming

that equal volumes of blood were obtained for culture and the timing of the cultures was similar. Often the line as a source can be confirmed by culture of the catheter tip in a semiquantitative fashion by rolling it across an agar plate.

Other intravascular devices, including vascular stents, prosthetic vascular grafts, implanted transvenous pacemakers and defibrillators (AICD), are all at risk for infection and may only manifest as fever, leukocytosis, and bacteremia. The specific risk for stent infections exists until the shunt has endothelialized, a period that may now take up to a year for drug-eluting coronary artery stents and probably never completely occurs with large vessel stents. Infections of these devices are often very difficult to demonstrate. Tagged white cell scans may identify a stent or graft infection but negative scans do not preclude this diagnosis. Echocardiography, particularly by the transesophageal route, may identify abnormalities on the pacing wires or adjacent cardiac structures suggesting infection. Chest x-ray or chest CT findings of septic pulmonary embolism also support a diagnosis of infected pacemaker or AICD.

Despite the frequency of bacteremia due to the Enterobacteriaceae, they account for only 2% to 5% of both native valve and prosthetic valve endocarditis. Associated mortality of up to 50% is the norm. Injection drug use is a risk factor. Congestive heart failure and large valvular vegetations are typical findings.

Bacteremia with Enterobacteriaceae for any reason may progress rapidly to the complications of gram-negative sepsis or septic shock. Sepsis is defined as the presence of the systemic inflammatory response syndrome with a known pathogen; septic shock is sepsis plus hypotension that fails to respond to simple fluid administration and is usually accompanied by evidence of tissue hypoperfusion such as lactic acidosis, oliguria, or acute lung injury. Although the injection of purified lipopolysaccharides from Enterobacteriaceae produces a picture of septic shock with fever and refractory hypotension that may lead to organ failures, the role of endotoxin in the pathophysiology of sepsis and septic shock remains controversial, and how these organisms initiate the cytokine and neuroendocrine cascades that lead to the clinical picture of sepsis remains unclear.

PRINCIPLES OF ANTIMICROBIAL THERAPY

Suggested antibiotic regimens for the infections described in this chapter are outlined in Table 134.3. Under most circumstances final antibiotic selection needs to be determined by results of culture and susceptibility and fine tuned on the basis of medication allergies and toxicities, penetration into target tissues, suspected or proven presence of co-pathogens, renal and hepatic function, possible drug–drug interactions cost, convenience of dosing, and ease of administration.

Simple urinary tract infections respond well to short-course oral therapy; these choices can be made on the basis of local susceptibility patterns and culture is generally unnecessary. Community-acquired complicated urinary tract infections, including pyelonephritis with or without bacteremia, also respond to oral antibiotics as long as nausea and vomiting do not preclude their administration. Infections in chronically catheterized patients or acquired in healthcare or extended care settings are often resistant to oral agents and parenteral therapies are generally preferred for patients requiring hospitalization until culture results are available.

The antibiotic therapy of enteric infections is controversial. Most of these infections are self-limited and resolve without antibiotics, and in my practice I try to wait until an etiologic diagnosis is made – by the time stool cultures are positive, most patients have improved. In travel settings patients are frequently provided antibiotics to self-administer for the same syndromes, justified perhaps by limited access to medical care and the inconvenience of diarrhea on overseas journeys. In the case of EHEC some observational studies suggest a significantly greater risk of haemolytic-uremic syndrome with antibiotic administration.

Recent studies on the duration of therapy for hospital-acquired pneumonia have demonstrated equivalent results with 8 days of therapy compared with longer courses. Whether this can be applied to community-acquired gram-negative pneumonia, which has traditionally been treated for 3 weeks or longer, is unclear but would appear reasonable in the absence of postobstructive pneumonia, lung abscess, or empyema.

Gram-negative osteomyelitis and infections of orthopedic hardware generally require 6 weeks of antibiotics for acute infections and longer durations for chronic osteomyelitis. Fluoroquinolones have excellent bone penetration and work well against susceptible organisms, although concerns have been raised in animal models that suggest these agents may impede fracture healing and that long half-life parenteral cephalosporins may be preferable for an infected fracture

Table 134.3 Suggested antimicrobial regimens for selected infections

Infection	Typical pathogens	Recommended antibiotics	Alternatives	Treatment duration (days)
Urinary tract infection, uncomplicated	*E. coli, Klebsiella, Proteus*	Oral TMP–SMX, FQ	Ampicillin, cephalexin, nitrofurantoin	3
Urinary tract infection, complicated (including pyelonephritis, male UTI)	*E. coli, Klebsiella, Proteus*	Ceftriaxone, FQ	Pip/tazo, aminoglycosides, carbapenems, aztreonam	7–14
Urinary tract infection, recurrent catheter associated	All	Carbapenems, cefepime	Aminoglycosides	14
Diarrhea	*E. coli*	None	FQ, rifaximin, azithromycin	3–5
Spontaneous bacterial peritonitis	*E. coli, Klebsiella*	Cefotaxime	FQ, moxi, pip/tazo, ceph3, cefepime, carbapenems	10–14
Diverticulitis	*E. coli* + anaerobes	FQ or TMP–SMX + metronidazole, moxi	Pip/tazo, ceph3 + metronidazole	7–10
Cholangitis, cholecystitis, pancreatitis, other abdominal abscesses	All	Pip/tazo, cefepime + metronidazole, carbapenems	FQ + metronidazole, moxi, tigecycline	To resolution
Complicated skin/soft tissue	All	Pip/tazo, carbapenems	Tigecycline, FQ, moxi	To resolution + 2 days
Pneumonia, community acquired	*E. coli, Klebsiella*	Ceftriaxone, cefepime, FQ, moxi	Pip/tazo, carbapenems	≤21
Pneumonia, hospital or ventilator acquired	*E. coli, Klebsiella, Enterobacter, Serratia*	Carbapenems, cefepime, pip/tazo (usually with aminoglycoside or FQ as initial therapy)	Tigecycline	8
Meningitis	*E. coli*	Cefepime, ceftriaxone, meropenem		14
Meningitis/ventriculitis, shunt associated	*Enterobacter*	Cefepime or meropenem ± aminoglycoside	Ceph3	To normalization of CSF
Osteomyelitis, prosthetic joint infection	All	Ceftriaxone, cefepime	FQ, carbapenem, tigecycline	≥42
Bacteremia (line)	All	Cefepime	Carbapenem, pip/tazo, FQ, moxi	10–14
Endocarditis, intravascular device	All	Cefepime or ceftriaxone ± aminoglycoside	Pip/tazo ± aminoglycoside	42

Abbreviations: FQ = ciprofloxacin or levofloxacin; moxi = moxifloxacin; pip/tazo = piperacillin–tazobactam; ceph3 = ceftriaxone, cefotaxime, ceftazidime; TMP–SMX = trimethoprim–sulfamethoxazole; UTI = urinary tract infection; CSF = cerebrospinal fluid.

nonunion. If hardware is retained in an infected site, prolonged oral suppressive therapy should be considered until hardware can be removed.

Suspected or proven severe infections, such as bacteremia or necrotizing soft-tissue infections, are best initially treated with two parenteral antibiotics, usually a cell wall-active agent (antipseudomonal penicillins, cephalosporins, or carbapenems) plus an aminoglycoside or fluoroquinolone. The rationale for this combination approach is not for synergy or demonstration of improved efficacy, as commonly believed, but rather to maximize the probability that an antibiotic active against the infecting agent has been chosen. The choice of cell wall agent should depend upon local susceptibility patterns; in particular, if there is risk of infection due to extended-spectrum β-lactamase-producing organisms a carbapenem should be chosen. Once an organism has been identified and susceptibility determined, treatment can be reduced to a single effective agent, with the caveat that an aminoglycoside should not be used as a single agent for a gram-negative bacteremia due to demonstration of inferior outcomes.

Line-associated infections are most successfully managed if the line is removed, followed by 10 to 14 days of an appropriate antibiotic. Successful treatment with retention of the line can be achieved with parenteral administration of antibiotics through the line with or without antibiotic lock but risks recurrent bacteremia

and has the additional risk of metastatic complications of bacteremia.

Aspiration of abscesses may be both diagnostic and therapeutic and should be pursued when possible. Aggressive debridement is critical to the successful management of necrotizing skin and soft-tissue infections. Infected decubitus ulcers and burns may respond to local debridement and penetrating topical agents such as mafenide acetate (Sulfamylon). Adjunctive use of hyperbaric oxygen in these infections is controversial and expensive.

Focal central nervous system infections should be drained when possible and ventricular shunts removed. Third- and fourth-generation cephalosporins and meropenem have sufficient central nervous system penetration to treat most gram-negative infections as single agents although pairing with an aminoglycoside is generally recommended; intrathecal administration of antibiotics should be reserved for resistant organisms without other adequate treatment options. The role of steroids in gram-negative meningitis has not been specifically studied but analogy to studies of meningitis due to *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Salmonella typhi* suggest a benefit is possible when administered prior to or concurrent with the initial dose of antibiotics.

A discussion of adjunctive measures for treatment of sepsis and septic shock is beyond the scope of this chapter. (See Chapter 2, Sepsis, severe sepsis, and septic shock.)

CONCLUSION

The Enterobacteriaceae cause a broad array of infections and are prominent causes of urinary tract infection, pneumonia, skin and soft-tissue infection, and intra-abdominal infection. The complex resistance patterns emerging in nosocomial isolates create a challenge in constructing appropriate initial treatment regimens. Aggressive pathogen identification and the appropriate modification of antibiotics to a targeted approach remain keys to successful management.

SUGGESTED READING

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135. *Enterococcus*

Ronald N. Jones

Since the early 1970s, the enterococci have steadily emerged as major hospital-acquired (nosocomial) pathogens. In statistics from the National Nosocomial Infections Surveillance System (NNISS) and subsequent Centers for Disease Control and Prevention (CDC) programs, they are the second most common gram-positive cause of nosocomial infections overall and the third most common cause of nosocomial wound infections. In fact, enterococci rank first among gram-positive cocci in producing urinary tract infections (see Table 135.1). Increases in occurrence of this genus since the mid 1970s are related to patterns of general antimicrobial use in the hospital and in particular to widespread use of extended-spectrum cephalosporins, β-lactamase inhibitor/penicillin combinations, fluoroquinolones, and carbapenems as well as the emergence of resistances in the genus.

Cephalosporins are generally not active *nor* bactericidal against enterococci, and they may therefore result in a selective advantage for this organism. Fluoroquinolones are also only modestly active against these species. *Enterococcus faecalis* produce most human enterococcal infections (70% to 80%), and *Enterococcus faecium* accounts for most (10% to 16%) of the remainder. However, *E. faecium* may account for a greater proportion (>30%) of enterococcal bacteremias (see Table 135.2). Antimicrobial resistance is a particular problem among *E. faecium* isolates. Other species of interest are *Enterococcus casseliflavus* and *Enterococcus gallinarum*, not because of the frequency with which they are isolated (<5%), but because of the intrinsic low-level resistance to vancomycin (e.g., the *vanC* genotype and resultant generally intermediate susceptibility phenotype; minimum inhibitory concentrations [MICs], 4–8 μg/mL).

In addition to the problems posed by the increasing frequency of enterococcal infection, the therapy of these infections has become challenging as resistance to ampicillin, high-level resistance to aminoglycosides (preventing bacteriocidal combination therapy), and glycopeptides (vancomycin and others) have occurred; emerging linezolid (an oxazolidinone), daptomycin, tigecycline (a glycylcycline), and quinupristin/dalfopristin resistance have also narrowed the number of therapeutic regimens. In addition, the risk of failure of trimethoprim–sulfamethoxazole (TMP–SMX) in therapy even for urinary tract infection has become recognized regardless of in vitro susceptibility where some standard organizations recommend *not* testing TMP–SMX. All enterococci are intrinsically resistant to achievable in vivo levels of aminoglycosides; however, synergic killing can occur when

Table 135.1 Percentage of various gram-positive pathogens causing nosocomial infections in the NNISS (CDC) comparing 1975 to 2003

	Percentage for 1975/2003 by infection site			
Pathogen	**Bloodstream**	**Wounds**[a]	**Pneumonia**	**Urine**
Enterococci	8.1/14.5	11.9/13.9	3.0/1.3	14.2/17.4
S. aureus	16.5/14.3	18.5/22.5	13.4/27.8	1.9/3.6
CoNS	10.3/42.9	7.4/15.9	2.6/1.8	3.2/4.9
Other species	8.0/4.5	8.8/5.8	6.9/3.2	2.2/1.2

[a] Skin and skin structure infections (SSSI).

Abbreviations: CoNS = coagulase-negative staphylococci; NNISS = National Nosocomial Infections Surveillance System; CDC = Centers for Disease Control and Prevention.

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aminoglycosides are combined with a cell wall-active agent such as a penicillin or a glycopeptide. Strains resistant to high levels of aminoglycoside (>500 μg/mL of gentamicin or >1000 μg/mL of streptomycin) are not susceptible to the synergic co-drug effects of the aminoglycosides. It is clinically significant that cross-resistance to the synergic activity of the aminoglycosides is *not* complete between gentamicin (and the related compounds tobramycin, netilmicin, amikacin, kanamycin, and isepamicin) and streptomycin. Streptomycin may be used successfully in combination to treat some high-level gentamicin-resistant strains. The selection of the appropriate aminoglycoside co-drug should be directed by validated in vitro susceptibility tests and the availability of streptomycin for clinical use.

Resistance to vancomycin is much more common with *E. faecium* isolates than with *E. faecalis*. Reports in the United States in the late 1990s suggested that the overall vancomycin-resistant rate for enterococci was approximately 20% among bloodstream infections, and higher resistance rates for some other drugs and species limited therapeutic choices. These resistance rates have escalated through 2011 (Table 135.2). Acquired vancomycin resistance is often associated with resistance to teicoplanin (Van A phenotype or *vanA* gene) or may occur in the absence of cross-resistance to teicoplanin (Van B phenotype or *vanB* gene). This difference can be clinically significant in nations where teicoplanin has been clinically available since the 1980s, and could also be relevant in the United States as telavancin and dalbavancin (long-acting lipoglycopeptide) are marketed worldwide. Also, another investigational glycolipopeptide, oritavancin, retains activitity against VanA and VanB resistance phenotypes, as does daptomycin. Willems and colleagues have identified a hospital-adapted *E. faecium* clone (CC-17) that has evolved ampicillin-, vancomycin-, and fluoroquinolone-resistant patterns. This CC-17 has been documented in vancomycin-resistant enterococci (VRE) populations in the United States (Figure 135.1) and since 1999 in Europe

Table 135.2 Trends in VRE bacteremia rates in the SENTRY Antimicrobial Surveillance Program (USA; 2000–2011) hospitals, quantitating vancomycin resistance (VanA) patterns

	Vancomycin nonsusceptible rate (%VanA)[a]	
Surveillance year	***E. faecium***	***E. faecalis***
(no. tested)	(3018)	(5671)
2000	57.1 (84.2)	4.0 (42.5)
2001	60.0 (88.2)	1.4 (35.7)
2002	70.7 (86.4)	2.9 (55.2)
2003	70.5 (88.5)	4.6 (34.8)
2004	68.6 (94.9)	2.6 (50.0)
2005	70.5 (95.6)	4.3 (51.2)
2006	69.7 (99.0)	4.8 (87.5)
2007	71.6 (97.6)	3.9 (89.7)
2008	75.3 (97.9)	6.5 (75.4)
2009	76.3 (97.6)	3.2 (65.6)
2010	80.7 (97.0)	5.3 (77.4)
2011	77.7 (96.6)	4.1 (82.9)

[a] A total of 401 other *Enterococcus* spp. were tested (data not shown) for a total of 9090 US enterococcemias.

Modified from Arias *et al.*, *Clin Infect Dis.* 2012;54(Suppl 3):S233–238.

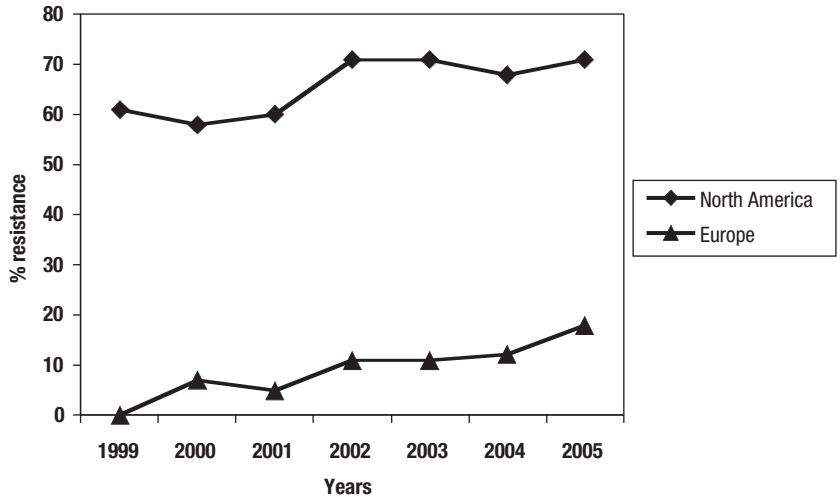

Figure 135.1 Progression of vancomycin resistance in *E. faecium* among bloodstream isolates studied in North America and Europe, including presence of isolates with antibiograms consistent with those of CC-17 (SENTRY Program, 1999–2005).

has progressively increased at rates comparable to those in the United States in the earlier years (1990s). Vancomycin resistance in *E. faecium* bacteremia isolates (SENTRY Program, 2008–2011, Table 135.2) now approaches 80%, dominantly VanA patterns.

For the clinician, the problems posed by the emergence of resistance have been exacerbated by the technical difficulties in reliable detection of these resistances. In vitro resistance to TMP–SMX as a result of the ability of the most prevalent enterococci to use thymidine or thymine in the susceptibility test medium (escapes bactericidal action) has been addressed by use of media free of or low in concentration for these antagonists. However, there can be significant amounts of antagonists in the urine, and therefore the meaning of in vitro test results performed in these "improved" test conditions is compromised. Routine testing against ampicillin without testing for organism β-lactamase production may result in false-susceptible results. However, β-lactamase production continues to be an exceedingly rare mechanism of resistance (≤0.1%) among *E. faecalis* isolates. A number of problems with the detection of high-level aminoglycoside resistance using the most prevalent automated and commercial broth microdilution susceptibility test systems (Vitek 2, MicroScan, BD Phoenix) have been reported, although in some cases these appear to have been resolved. Similarly, with vancomycin and other newer agent resistances reported from both automated susceptibility test systems, Etest and disk diffusion test interpretive criteria may continue to require modifications over time to enable consistent, accurate detection of resistant strains. Some newer agents now necessitate testing with surfactants (polysorbate-80) to prevent binding to plastic reagent panels.

Highly reliable, empiric therapy of enterococcal infection is not consistently satisfactory given the complexity and variability of resistance patterns; and therefore, availability of prompt, reliable susceptibility test results is critical. At present, disk diffusion susceptibility testing, Etest, Vitek or BD Phoenix Systems, and the reference broth microdilution or agar dilution methods are reliable methods for detection of important resistances. However, recent reports of false resistance have been reported for some newer agents, including linezolid, caused by fuzzy zone diameter edges and trailing end points by dilution test methods.

ENTEROCOCCAL BLOODSTREAM INFECTION

Isolation of enterococci from blood cultures may occur with or without endocarditis. In community-acquired enterococcal bloodstream infection approximately one-third of cases are concurrent with endocarditis, compared with fewer than 5% of nosocomial enterococcal bacteremias. These nosocomial infections are usually associated with urinary tract disease or instrumentation, intra-abdominal infection, infected intravascular devices, neoplastic disease, and significant neutropenia.

Infective endocarditis, even when caused by more susceptible strains of enterococci, is more difficult to achieve cures for than endocarditis due to viridans group streptococci. Only two-thirds of patients will have favorable outcomes if a penicillin is used alone. A combination of a cell wall-active agent (a penicillin, usually ampicillin, or a glycopeptide) with an aminoglycoside for 4 to 6 weeks continues to be a recommended guideline. In general, ampicillin (2- or 4-fold more active) is used in preference to penicillin. High-dose penicillins (ampicillin, 2 g every 4 hours, or penicillin G, 18 to 30 million U/day) are appropriate, combined with gentamicin, 1 mg/kg every 8 hours or the use of the less toxic infusion pattern of once-daily dosing. However, limited clinical information supports the use of once-daily aminoglycosides for endocarditis. Monitoring of aminoglycoside serum concentrations is essential to ensure adequate therapeutic levels and to minimize toxicity during the extended therapeutic course, as well as vancomycin monitoring if used (see also Chapter 37, Endocarditis of natural and prosthetic valves: treatment and prophylaxis). Very recently, combinations of ampicillin and ceftriaxone to minimize gentamicin-caused renal toxicity and preserve higher cure rates have been successful, and other cephalosporins may achieve comparable or better results due to greater potencies and lower serum protein binding (ceftaroline, ceftobiprole).

The choice of an aminoglycoside for combination therapy is between gentamicin and streptomycin (limited availability). Gentamicin is generally preferred because synergic killing is more consistent (see Table 135.3), ototoxicity is less frequent, and facilities to measure serum levels are more easily available. Enterococcal strains resistant to high levels of aminoglycoside in vitro are not susceptible to enhanced (synergistic) killing with a penicillin or vancomycin-like agents, and in such patients use of

Table 135.3 Susceptibility rates of all enterococcal strains from the SENTRY Antimicrobial Surveillance Program, hospital patients in 2007–2012 (27–30 medical centers in the United States)[a]

Antimicrobial agent	Percentage susceptible		
	All enterococci (9281)	*E. faecalis* (5820)	*E. faecium* (3096)
Ampicillin	69	>99	8
Chloramphenicol[b]	90	87	96
Ciprofloxacin	42	60	4
Daptomycin	>99	>99	>99
Linezolid	>99	>99	98
Quinupristin–dalfopristin	33	3	92
Tetracycline	30	24	39
Teicoplanin	73	97	25
Tigecycline	>99	>99	>99
Vancomycin	71	96	23
Gentamicin (HL)	75	70	81
Streptomycin (HL)	69	72	58

Abbreviation: HL = high-level resistance screen.

[a] Data on file, SENTRY Antimicrobial Surveillance Program (JMI Laboratories, North Liberty, IA).

[b] Data from 2003 to 2006 only.

aminoglycosides constitutes exposure to potential toxicity (otic and renal) without apparent clinical benefit. Optimal therapy is not well defined for strains resistant to high levels of both aminoglycosides. Prolonged therapy with high dosages of a penicillin or ampicillin, possibly by continuous infusion, may be successful. Combination therapy with vancomycin and a penicillin or ampicillin and a cephalosporin has also been reported successful; daptomycin alone has received an indication for bacteremia and right-side infectious endocarditis; and has also been used in β-lactam combinations. Linezolid, quinupristin–dalfopristin, chloramphenicol, or newer agents such as dalbavancin, oritavancin, and telavancin could also be a therapeutic option as more clinical information is published.

Enterococcal resistance will be increasingly encountered in hospital practice and possibly in clinic patients, as well. There is no established therapy for this group of organisms although several newer agents appear promising (see above). Monitoring for adequacy of trough levels of some agents may be important where feasible, although facilities for such monitoring may not be available. Similarly, close adherence to package insert recommendations is critical to success with daptomycin, linezolid, and quinupristin–dalfopristin. Serum inhibitory and bactericidal titers may be helpful to follow therapy of serious infections (sepsis with or without endocarditis or osteomyelitis).

Therapy with dalbavancin or telavancin is not an option for VanA VRE strains, and this is the predominant pattern (>80% strains) of vancomycin resistance in the United States. Various therapeutic approaches have been suggested. Older drugs such as chloramphenicol and doxycycline have demonstrated a variable degree of activity (>50% susceptible by Clinical Laboratory Standards Institute [CLSI] criteria; Tables 135.3 and 135.4) against the multidrug-resistant enterococci. Case reports indicate that these drugs used alone or with co-drugs can be successful in some cases, but each agent is only bacteriostatic. Even with eradication of enterococci from the bloodstream, mortality remains high (30% to 50%). Furthermore, fluoroquinolones (ciprofloxacin, levofloxacin, and moxifloxacin) may have limited value for strains tested as susceptible (see Tables 135.3 and 135.4), as a resistance may emerge rapidly when these drugs are used alone. Combinations of ampicillin and a fluoroquinolone or a cephalosporin have been found bactericidal for some strains in vitro. Quinupristin–dalfopristin is a generally bacteriostatic option available for use in therapy of *E. faecium* infection only (not *E. faecalis*). A variety of other agents, some still under consideration by regulators (see Table 135.4), are more active against enterococci and may have slightly expanded potential for future enterococcal treatment. Daptomycin (formerly LY-146032, a cyclic lipopeptide), dalbavancin, oritavancin, telavancin, oxazolidinones (linezolid), and a glycylcycline (tigecycline) are the most highly effective compounds in vitro (see Tables 135.3 and 135.4). However, several of these drugs demonstrate little bactericidal action against multidrug-resistant enterococci, and experience with their use alone or in combination awaits reports from structured clinical studies.

Therapy for enterococcal bloodstream infection in the absence of endocarditis follows the same general principles as for endocarditis except that bactericidal therapy may not be required. Bactericidal effect should be sought in the immunocompromised patient, and empiric therapy for such patients should be initiated with the broadest-spectrum anti-gram-positive agents (vancomycin or daptomycin), because patients likely to develop nosocomial enterococcal

Table 135.4 In vitro susceptibility of alternative antimicrobial agents for United States enterococcal isolates with resistance to glycopeptides (2696 VRE isolates in 2007–2012 SENTRY Program)[a]

	Percentage by category[b]		
Antimicrobial agent	**Susceptible**	**Intermediate**	**Resistant**
Glycopeptide-like			
Dalbavancin[b]	12	–	–
Daptomycin	>99	–	–
Oritavancin[b]	92	–	–
Telavancin[b]	2	2	96
Oxazolidinones			
Linezolid	98	1	1
Pristinamycins			
Quinupristin–dalfopristin	86	3	11
Glycylcyclines			
Tigecycline	>99	–	–
Fluoroquinolones			
Ciprofloxacin	1	1	98
Levofloxacin	2	0	98
Moxifloxacin	2	1	97
Cephalosporins			
Ceftaroline[b]	7	4	89
Ceftobiprole[b]	11	0	89
Others			
Chloramphenicol	94	5	1
Clindamycin	7	1	92
Doxycycline	46	17	37
Erythromycin	2	1	97
Imipenem	11	0	89
Rifampin	22	4	74
Trimethoprim–sulfamethoxazole[c]	8	0	92

[a] Modified from results of the SENTRY Antimicrobial Surveillance Program (JMI Laboratories, North Liberty, IA).

[b] Categorical criteria per Clinical Laboratory Standards Institute (CLSI) M100-S23 (2013) or $\leq$4 μg/mL (susceptible) for ceftobiprole and ceftaroline, $\leq$0.5 μg/mL for dalbavancin, and $\leq$0.12 μg/mL for oritavancin and telavancin.

[c] Trimethoprim–sulfamethoxazole (1:19 ratio), susceptible results of in vitro tests may be misleading.

infection are also at risk for infection with methicillin-resistant staphylococci. As with all other pathogens, removal of potential foci of infection, such as an indwelling vascular device, and drainage of an abscess as source control, is essential for successful therapy.

THERAPY OF NONSEVERE INFECTIONS AND URINARY TRACT DISEASE

In the absence of immediate susceptibility test results, ampicillin is a reasonable option for therapy of mild to moderate infections and particularly for urinary tract infections, given the high levels of ampicillin achieved in the urine. Nitrofurantoin is also active against most enterococci (>90%; data not shown including VRE), but is useful in therapy of urinary tract infection only.

Clearly, these approaches must be modified in the context of local epidemiology (antibiogram) and emergence of resistant strains. In centers with very high incidence of infection with ampicillin-resistant enterococci, usually *E. faecium*, this may not be appropriate empiric therapy. For infection with drug-resistant organisms, the options are similar to those discussed for bloodstream infection, except that synergic combinations are usually not advised.

ENTEROCOCCAL CARRIAGE

There is no general acceptance that fecal carriage or colonization by multidrug-resistant enterococci is an indication for therapy; however, given the risk to the patient of subsequent disseminated infection, there is high epidemiologic interest in this issue. Studies of the intestinal tract reservoir/source of VRE have greatly increased our knowledge of colonization and factors leading to persisting carriage. The third-generation cephalosporins have clearly been implicated in promoting enterococcal colonization, but not all other cephalosporins or β-lactams present similar risks. Examples of low-risk agents are aztreonam and cefepime, in contrast to cefoxitin and clindamycin that have promoted VRE colonization. Some antimicrobials such as piperacillin/tazobactam inhibit establishment of VRE in the gut during therapy, but promote overgrowth and persistence when exposed to VRE in the period of post-therapy recovery of normal flora. Data from clinical trials continue to be necessary to more adequately understand these complex interactions of antimicrobials, indigenous bowel flora, and colonizing resistant enterococci.

It seems reasonable to review the patient's therapy with a view toward discontinuation of any nonessential antimicrobials that might confer a selective advantage for the enterococci. However, relapses after discontinuation of selective intestinal tract decontamination remain high. The implications for infection control focus on (1) gastrointestinal selective decontamination; (2) antimicrobial use strategies (limit or restriction of selecting agents); (3) assuring persistence of the gastric acid barrier; (4) restoring indigenous colonic microflora; (5) assuring, where possible, decontamination of the hospital

environment or patient's cutaneous surfaces; and (6) preventing patient-to-patient transmission via promoting handwashing/gloving by healthcare workers.

COMMENTS

Therapy of enterococcal infections is one of the most challenging areas in the contemporary treatment of infectious disease. Quality laboratory support is essential to the management of these infections in the most appropriate manner while minimizing toxicity. Given the emerging inadequacies of our therapeutic armamentarium (ampicillin and glycopeptides) and the clear evidence that nosocomial spread of this pathogen can occur, an aggressive position with respect to hospital environment surveillance and infection control remains of critical importance. Also, more study will be required to develop new, safe therapeutic agents and to focus our treatments on existing or newer antimicrobial agents (daptomycin, oxazolidinones, newer glycolipopetides) used alone or in proven combinations that achieve acceptable enterococcus infection eradication with clinical safety.

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136. *Erysipelothrix*

W. Lee Hand

Erysipelothrix rhusiopathiae is a pleomorphic, nonspore-forming, gram-positive bacillus. This organism causes both a self-limited soft-tissue infection (erysipeloid) and serious systemic disease. *Erysipelothrix rhusiopathiae* is widespread in nature and infects many domestic animals. Swine are probably the major reservoir of *E. rhusiopathiae*. The microorganism is also found in sheep, cattle, horses, chickens, and dogs, as well as in birds, fish, crustaceans, seals, and dolphins. Infection in humans is usually due to occupational exposure. Butchers, abattoir workers, fishermen, farmers, and veterinarians are at risk for *Erysipelothrix* infections. The clinical spectrum of human infection includes localized cutaneous infection, diffuse cutaneous disease, and systemic bloodstream infection.

LOCALIZED CUTANEOUS INFECTION

Erysipeloid of Rosenbach, the localized cutaneous form of illness, is the most common type of human infection caused by *E. rhusiopathiae* (Figure 136.1). Fingers and/or hands (sites of exposure) are almost always involved in this soft-tissue infection.

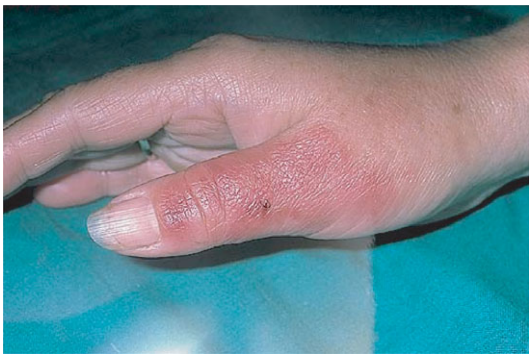

Figure 136.1 Erysipeloid. (From Gary M. White and Neil H. Cox, *Diseases of the Skin*, Philadelphia: WB Saunders; 1995.)

Mild pain may occur at the site of inoculation, followed by itching, throbbing pain, burning, and tingling. The characteristic skin lesion slowly progresses from a small red dot at the site of inoculation to a fully developed erysipeloid skin lesion, consisting of a well-developed purplish center with an elevated border. Patients often complain of joint stiffness and pain in the involved fingers, but swelling is minimal or absent. Small hemorrhagic, vesicular lesions may be present at the site of inoculation. Erysipeloid lesions do not resemble true cellulitis, as opposed to erysipelas, which is due to group A streptococcal infection. Thus, Rosenbach introduced the term *erysipeloid* for the human cutaneous disease caused by *Erysipelothrix*. Pain may be disproportionate to the degree of apparent involvement. Local lymphangitis and adenitis develop in 30% of patients. However, systemic symptoms such as high fever or chills are uncommon.

A provisional diagnosis is based on a history of contact with potentially contaminated materials or occupational exposure, plus compatible physical findings. Gram-stained smears and cultures of aspirated material from skin lesions are often negative because the organism is deep within the dermis.

DIFFUSE CUTANEOUS DISEASE

Most erysipeloid skin lesions resolve even without specific treatment. However, erysipeloid occasionally will progress to the diffuse cutaneous form in untreated patients. Eating of contaminated meat has also been reported as a cause of this clinical entity. The characteristic purplish skin lesions expand with gradual clearing of the center. Bullous lesions may appear at the primary site or at distant locations. These patients often have systemic symptoms such as high fever, chills, and arthralgias. Blood cultures are invariably negative.

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SYSTEMIC INFECTION (BACTEREMIA AND/OR ENDOCARDITIS)

Bacteremic infection caused by *E. rhusiopathiae* is generally a primary infection and not the result of dissemination from localized cutaneous disease. Nevertheless, one-third of patients with bloodstream infection have skin lesions suggestive of erysipeloid. Persistent bacteremia with *E. rhusiopathiae* has been reported after eating contaminated seafood. Cutaneous serpiginous lesions or multiple bullous lesions over the trunk and extremities may be seen. Many patients have fever for 2 to 3 weeks before presentation. Fever and chills may resolve spontaneously, but relapse is to be expected.

Patients with severe underlying heart disease or liver disease may present with a clinical picture resembling gram-negative sepsis. More than one-third of patients with disseminated infection are alcoholics, and chronic liver disease is a major predisposing factor. Bacteremia has also been reported in immunocompromised individuals, who often are receiving corticosteroid and/or cytotoxic drug treatment for collagen vascular disease or malignancy.

Erysipelothrix rhusiopathiae bacteremia is usually associated with a severe clinical course and is frequently complicated by endocarditis. *Erysipelothrix* endocarditis often results in extensive destruction of cardiac valves, especially the aortic valve. Previous reports were that approximately one-third of endocarditis patients die, and an additional one-third require cardiac valve replacement. However, there are no recent data on mortality. Absence of typical findings of endocarditis on initial physical examination or echocardiography does not exclude this diagnosis in patients with positive blood cultures. Reported complications of endocarditis have included proliferative glomerulonephritis with acute renal failure and visceral botryomycosis.

Earlier publications indicated that 90% of bacteremic infections were associated with endocarditis. This perceived high frequency may, at least in part, be a result of reporting bias because a number of bacteremic cases without endocarditis have been reported more recently.

Unusual reported infections due to *Erysipelothrix* include necrotizing fasciitis (after local inoculation), septic arthritis of native and prosthetic knees, peritoneal dialysis-associated peritonitis, acute and chronic meningitis, intra-abdominal abscesses, and empyema in the spinal canal with paravertebral abscesses.

The diagnosis of disseminated *E. rhusiopathiae* infection depends on identification of this organism in blood cultures. Commercial media are satisfactory for isolation from blood, and growth is usually recognized in 2 or 3 days. The organism may initially be misidentified as a *Lactobacillus* species.

THERAPY

Erysipeloid may resolve spontaneously within 3 weeks, but treatment with appropriate antibiotic therapy hastens the healing process and prevents relapse. Local therapy with rest and heat is helpful for patients with painful, swollen lesions or arthritis. The involved hand or finger should be carried in a sling or splint. Surgical incision or debridement of local lesions is not necessary.

Penicillin and imipenem are the most active antibiotics against *Erysipelothrix* with in vitro testing. Penicillin is a time-tested, effective agent for treatment of all forms of *E. rhusiopathiae*

Table 136.1 Antibiotic therapy for *Erysipelothrix rhusiopathiae* infection

	Antibiotics of choice		
Type of *Erysipelothrix* infection	**Drug**	**Dose and route**	**Duration**
Localized cutaneous			
Primary	Penicillin V	500 mg q6h PO	7 d
Alternatives	Ciprofloxacin (other fluoroquinolones may be used)	250 mg q12h PO	7 d
	Clindamycin	300 mg q8h PO	7 d
	Erythromycin (other macrolides may be used)	500 mg q6h PO	7 d
Severe bacteremic or endocarditis			
Primary	Penicillin G	2–4 million units q4h IV	4 wk
Alternatives	Ceftriaxone	2 g q24h IV	4 wk
	Imipenem	500 mg q6h IV	4 wk
	Ciprofloxacin (other IV fluoroquinolones may be used)	400 mg q12h IV	4 wk

infection. Other β-lactam antibiotics are also active against this organism. Fluoroquinolones and clindamycin demonstrate good in vitro activity. Macrolides, tetracyclines, and chloramphenicol have less predictable activity against *Erysipelothrix* and should not be used in the treatment of disseminated infection. *Erysipelothrix rhusiopathiae* is resistant to sulfonamides, trimethoprim–sulfamethoxazole, aminoglycosides, and vancomycin. Limited data indicated that daptomycin has good in vitro activity.

Antibiotic therapy should be based upon the clinical picture and results of blood cultures (Table 136.1). Oral antibiotic therapy is appropriate for localized cutaneous infection. Parenteral antibiotic treatment is indicated if patients have systemic infection or severe diffuse cutaneous disease. Penicillin G has been the historic drug of choice. Alternatives include ceftriaxone, imipenem, and fluoroquinolones. Patients with bacteremia or endocarditis should receive at least 4 weeks of intravenous antibiotic therapy.

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137. HACEK

Vivian H. Chu

The acronym HACEK describes a heterogeneous group of organisms that share three major characteristics. First, they are small gram-negative rods that are commonly present as part of normal oral–pharyngeal or respiratory flora. Second, they are relatively fastidious microorganisms. Third, they have a predilection to infect heart valves. The HACEK group includes *Haemophilus* species (except *Haemophilus influenzae*), *Aggregatibacter* (formerly *Actinobacillus*) species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species. These organisms are infamous for their ability to cause endocarditis although, rarely, they can also cause a variety of other infections (Table 137.1). For example, human bites can result in cellulitis or abscess formation resulting from HACEK organisms, especially *Eikenella* species, and various *Haemophilus* species can cause epiglottitis or brain abscesses.

Members of the HACEK group are normal indigenous flora of the oral cavity. Hematogenous seeding of the bloodstream may occur after dental manipulation, but is more likely to occur in the setting of ordinary daily activities, particularly among individuals with periodontal disease. Transient or sustained bacteremia puts individuals with underlying valvular heart disease at risk for developing infective endocarditis (IE). Antibiotic prophylaxis (AP) prior to dental manipulation has not been shown to protect against IE, therefore the guidelines for AP have been modified to include only individuals in the highest risk group. While millions of patients undergo dental procedures annually, cases of IE caused by HACEK group organisms are rare.

DIAGNOSIS

Bacteria in the HACEK group are commonly but often erroneously considered in the differential diagnosis for culture-negative endocarditis. In the past the traditional method of increasing the recovery of HACEK bacteria was to extend the incubation of blood culture bottles from 5 to 7 days to 2 to 3 weeks. However, with improvements in blood culture methods, this practice is no longer recommended. A recent multicenter study showed that the mean and median times to detection of HACEK isolates using current

Table 137.1 HACEK-associated infections

Haemophilus aphrophilus, Haemophilus haemolyticus, Haemophilus parahaemolyticus, Haemophilus parainfluenzae, Haemophilus paraphrophilus, Haemophilus segnis	Brain abscess, endocarditis, endophthalmitis, epiglottitis, hepatic abscess, intra-abdominal infection, meningitis, neonatal sepsis, necrotizing fasciitis, otitis media, pneumonia, sinusitis, septic arthritis, urinary tract infection
Aggregatibacter actinomycetemcomitans	Brain abscess, cellulitis, empyema, endocarditis, endophthalmitis, osteomyelitis, periodontal infection, parotitis, pericarditis, pneumonia, synovitis, thyroid abscess, urinary tract infection
Cardiobacterium hominis	Endocarditis, meningitis
Eikenella corrodens	Abscessed tooth, Bartholin's gland abscess, brain abscess, cellulitis, conjunctivitis, dacryocystitis, empyema, endocarditis, endometritis, gingivitis, intra-abdominal abscess, intravascular space infections, keratitis, liver abscess, mediastinitis, meningitis, mycotic aneurysm, otitis externa, parotitis, pericarditis, pneumonia, septic pulmonary emboli, subdural empyema, thyroid abscess, thyroiditis
Kingella dentrificens, Kingella indologenes, Kingella kingae	Abscess, endocarditis, epiglottitis, intervertebral diskitis, meningitis, oropharyngeal infections, osteomyelitis, septic arthritis

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laboratory methods and media were 3 and 3.4 days, respectively. In addition, none of the cultures that were held for prolonged incubation and terminal subculturing yielded additional growth. Several other studies have demonstrated that isolation of HACEK organisms usually occurs within 5 days, suggesting that prolonged incubation is no longer needed to detect HACEK bacteria.

HACEK organisms typically grow on 5% sheep blood and chocolate agar but not on MacConkey's agar. Because growth is often poor or absent in an unenhanced atmosphere, incubation in 5% to 10% carbon dioxide (CO_2) is recommended. After growth is observed, standard biochemical tests will identify individual HACEK species. The use of 16S ribosomal RNA (rRNA) gene analysis may be useful for HACEK organisms that are not readily identified with standard biochemical tests.

CLINICAL FEATURES

Endocarditis caused by members of the HACEK group typically occurs in individuals with preexisting valvular abnormalities and/or prosthetic valves. The results of a recent large, multicenter cohort showed that individuals with HACEK IE tend to be younger than those with non-HACEK IE with a median age of 47 years vs. 60 years, respectively. According to the afore-mentioned study, the most common members of the HACEK group identified were *Haemophilus* spp. (40%) followed by *Aggregatibacter* spp. (34%), *Cardiobacterium* spp. (14%), *Eikenella corrodens* (5%), and *Kingella* spp. (5%).

Endocarditis due to members of the HACEK group usually has a subacute course that may include frequent embolization due to the presence of large valvular vegetations. In the aforementioned cohort, stroke occurred in a significantly higher proportion of patients with HACEK IE compared to non-HACEK IE (25% vs. 17%, respectively; $p = 0.05$); however, the rates of in-hospital mortality (4% vs. 18%, respectively; $p < 0.01$) and 1-year mortality (11% vs. 39%, respectively; $p < 0.01$) were low. The high rate of stroke and paradoxically low rate of death is unique to HACEK IE.

THERAPY

There have been no large trials to evaluate the best therapy for IE caused by HACEK group organisms. Currently available information on treatment is derived from in vitro susceptibility testing and the results of small case series or individual case reports. In the past, ampicillin plus an aminoglycoside was widely recommended as the therapy of choice. This treatment was advocated because synergy between β-lactams and aminoglycosides could often be demonstrated in vitro, but such synergy has not been conclusively proven to occur in vivo. Moreover, a number of case reports have documented therapeutic failures of combined therapy with ampicillin and gentamicin in the treatment of infections caused by *Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans* and *Haemophilus*. In addition, authors of several recent reports have described β-lactamase production by numerous strains of HACEK group organisms. Because of their fastidious growth requirements, susceptibility testing for many members of the HACEK group is often difficult to obtain in routine microbiology laboratories. Taken together, HACEK group organisms should be considered ampicillin resistant unless proved otherwise; and the use of ampicillin as empiric or initial therapy for infections due to HACEK group organisms is not advised.

Most HACEK organisms, with the notable exceptions of *A. actinomycetemcomitans* and *E. corrodens*, are susceptible to first- and second-generation cephalosporins, and virtually all species are susceptible to third-generation cephalosporins. Therefore, cefotaxime or ceftriaxone is generally considered to be the best therapy for IE caused by HACEK group bacteria. The use of ceftriaxone, 2 g intravenously (IV) or intramuscularly (IM) once daily, is recommended because of its convenience and suitability for outpatient parenteral therapy (Table 137.2). The duration of therapy for native valve endocarditis should be at least 4 weeks; at least 6 weeks of therapy is recommended for prosthetic valve endocarditis.

HACEK group organisms are also susceptible in vitro to most fluoroquinolones and aztreonam. Thus one of these agents may be used in the

Table 137.2 Antibiotics recommended for serious infections

	Antibiotic	Dosage and route	Length of therapy
First choice	Ceftriaxone	2 g IV or IM daily	4–6 wk
Alternative	Ciprofloxacin	750 mg PO every 12 h	4–6 wk

β-lactam-intolerant patient. There is a growing body of evidence to support the use of ciprofloxacin as outpatient therapy for HACEK endocarditis.

A number of investigators advocate empirical therapy with either ceftriaxone along with an aminoglycoside or ciprofloxacin until sensitivities return. A fluoroquinolone such as ciprofloxacin is the preferred alternative for patients who are allergic to a β-lactam. Ciprofloxacin is an appropriate choice for the outpatient segment of therapy because of its high bioavailability after oral ingestion and excellent safety profile. However, because of the lack of published data about fluoroquinolone therapy for HACEK group bacterial infections, ceftriaxone would still be considered first-line therapy. Careful follow-up of all patients undergoing treatment is also recommended, including periodic assessment of clinical and microbiologic response using careful examinations and follow-up blood cultures. Careful monitoring for compliance is advised for all patients treated with oral therapy.

HACEK group organisms are usually susceptible to tetracycline and chloramphenicol; however, both of these agents are bacteriostatic and thus are poor choices for endovascular infections. Most HACEK group members are resistant to metronidazole, vancomycin, erythromycin, and clindamycin.

PROGNOSIS

Endocarditis caused by HACEK group organisms is associated with a favorable prognosis. Most infections can be cured with medical therapy or a combination of medical and surgical therapy.

NONENDOCARDIAL INFECTIONS

Nonendocardial infections caused by HACEK group organisms are rare. Such infections are usually responsive to short courses of antibiotic therapy. Surgical drainage is indicated for abscesses. Most authorities recommend 3 to 4 weeks of parenteral therapy followed by an additional 3 weeks of antibiotics by mouth for treatment of septic arthritis caused by *Kingella kingae* and other HACEK group organisms. Two to four weeks of parenteral therapy followed by 1 to 6 months of oral therapy is recommended for the treatment of osteomyelitis caused by HACEK organisms. Management plans should include a careful assessment of the need for surgical debridement and monitoring for clinical response.

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138. *Helicobacter pylori*

David Y. Graham and Emiko Rimbara

INTRODUCTION

Helicobacter pylori are gram-negative spiral shaped-bacteria that infect more than 50% of humans globally. *H. pylori* infection is a serious chronic transmissible infectious disease that causes inflammation and progressive damage to the structure and function of the stomach. *H. pylori* is a major cause of morbidity and mortality worldwide. The prevalence of *H. pylori* infection is inversely related to the general health and well-being of a society. As with other chronic infectious diseases, the infection remains clinically latent and only approximately 20% of infected individuals eventually develop clinically recognizable diseases. *H. pylori* infection causes progressive and destructive inflammation (e.g., gastritis) of the stomach and is the infection etiologically related to gastric and duodenal ulcer disease, gastric cancer, and primary B-cell gastric lymphoma.

DISCOVERY OF *H. PYLORI*

In the early 1980s, Robin Warren, a pathologist in Perth, Western Australia teamed up with a young trainee in internal medicine, Barry Marshall, to investigate small curved bacteria seen on gastric biopsies from patients with gastritis. In 1982, with a bit of luck, the organism was cultured and initially named *Campylobacter pyloridis*. It is now known as *Helicobacter pylori* and is a microaerophilic, gram-negative, spiral rod approximately 0.6×3.5 μm with approximately seven unipolar flagellae. Biochemical features that help identify it are the presence of urease, oxidase, and catalase.

Warren and Marshall showed that the organism was etiologically involved in gastritis and suggested it might also cause peptic ulcer and gastric cancer, both known to be tightly associated with gastritis. Proof required development of accurate tests to identify whether the infection was present and an effective therapy before one could test whether eradication resulted in healing of gastritis (i.e., whether the organisms caused peptic ulcer disease). By 1994 sufficient unequivocal data were obtained that a consensus conference held by the National Institute of Health concluded that *H. pylori* was a major cause of peptic ulcer disease and they recommended that ulcer patients with *H. pylori* infection receive antimicrobial therapy. That same year, the International Agency for Cancer Research declared that *H. pylori* was a Class I carcinogen for gastric cancer. *H. pylori* was subsequently shown to also cause gastric mucosa-associated lymphoid tissue lymphoma (MALToma). In 2005 the Nobel Prize for Physiology and Medicine was awarded to Warren and Marshall for culture of the organism and proof of its relation to peptic ulcer disease.

EPIDEMIOLOGY AND TRANSMISSION

H. pylori infection is typically acquired in childhood. *H. pylori* can be thought of as "a situational opportunist" as transmission may involve any route that allows bacteria from one person's stomach to gain access to another's. Fecal–oral transmission is perhaps the most common but oral–gastric is also likely as *H. pylori* has been cultured from stools and from vomit obtained from both infected young children and adults. In countries with generally poor sanitation and unclean water supplies there is also evidence for waterborne transmission. Oral–oral transmission is unlikely except in unusual situations (e.g., either oral–oral or gastro–oral transmission is likely responsible for the high rate of transmission associated with premastication of infant foods practiced in some societies). The major risk factors for *H. pylori* infection include: birth in a developing country, low socioeconomic status, crowded living conditions, large family size, unsanitary living conditions, unclean food or water, presence of infants in the home, and exposure to gastric contents of infected individuals. The

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major associations can be summarized as examples of poor household hygiene.

The prevalence of *H. pylori* infections varies by geographic location, ethnic background, socioeconomic condition, and generally age. In developing countries, by age 20 typically 70% to 90% of the populations are infected. In developed countries, the prevalence of infection is lower and the age-related increase in incidence is thought to represent a birth-cohort phenomenon due to the fall in incidence among successive birth cohorts. The *H. pylori* prevalence among middle-class White Americans born in the United States and whose parents were also born in the United States is now less than 15% and falling. Improved sanitation and standards of living have resulted in falling rates of transmission to children in most developed countries and is leading to the rapid disappearance of the infection in many groups. However, *H. pylori* infection remains common among disadvantaged populations and among immigrants from developing countries such that immigration is responsible for a pool of *H. pylori* infection and *H. pylori*-related diseases in even the most advanced societies.

PATHOGENESIS OF INFECTION

After gaining access to the stomach, *H. pylori*, being motile, are able to "swim" to and enter into the mucus layer overlying the gastric mucosa. *H. pylori* possess the necessary tools that allow the organism to colonize the gastric mucosa (e.g., flagella, urease, adhesions) as well as to evade host defense (urease, catalase, superoxide dismutase, and poorly reactive lipopolysaccharide). Flagellae allow the bacterium to burrow through the mucus to the mucosal surface where, bolstered by its urease activity, it is protected from acidic gastric contents. Although *H. pylori* can attach to superficial gastric mucus cells and thus resist clearance from the stomach, small numbers of *H. pylori* are also found within gastric epithelial cells which may serve as a sanctuary, allowing evasion of host defenses and may be in part responsible for the failure of topical antibiotic therapy. Attachment of *H. pylori* to the gastric mucosa is associated with local production of proinflammatory cytokines (e.g., interleukin-8), which induces infiltration of polymorphonuclear leukocytes and ultimately leads to the characteristic histologic pattern of an acute inflammatory reaction superimposed upon chronic inflammation with organized lymphoid follicles.

The clinical outcome of *H. pylori* infection is determined by a complex interaction of the host, bacterium, and environmental factors. A number of putative virulence factors have been described, including the *cag* pathogenicity island (PAI), the outer membrane inflammatory protein (OipA), a vacuolating cytotoxin (VacA), and a host of adhesins. The *cag* PAI region encodes a type IV bacterial secretion apparatus, which translocates or injects the CagA protein and possibly other proteins into host target cells. Phosphorylation of CagA activates a number of host signaling pathways that can subsequently influence host cellular functions, including proliferation, apoptosis, cytokine release, and cell motility. VacA is present in nearly all *H. pylori* strains but only about half of the *H. pylori* strains produce VacA toxin in vitro. Although VacA induces epithelial vacuolation in vitro, its function in vivo remains unclear but recent evidence suggests it may be critically involved in the intracellular survival of *H. pylori*.

A large number of descriptive epidemiologic studies have been done attempting to correlate *H. pylori* virulence factor genotypes and clinical outcome, especially in relation to *cagA* status and to genotypic variations in the *vacA* signal sequence (s1a, s1b, s1c) and mid-region of the *vacA* (m1, m2) gene. Generally, the risk of a clinically important outcome (e.g., peptic ulcer or gastric cancer) associates best with the severity of the inflammatory response. While scoring genotypes in terms of risk has merit, it is important to note that it only provides relative information as *H. pylori* lacking all of the currently recognized putative virulence have also been associated with the presence of inflammation, peptic ulcer disease, and gastric cancer. Thus, all *H. pylori* cause progressive destructive mucosal damage and are important human pathogens and testing for putative virulence factors has little or no utility clinically.

PATTERN OF GASTRITIS AND CLINICAL OUTCOMES OF *H. PYLORI* INFECTION

The outcome of an *H. pylori* infection is closely related to the severity and pattern of *H. pylori*-induced gastritis. The stomach is divided into two basic regions, an acid-secreting proximal portion, the corpus, and the distal non-acid-secreting antrum. Although *H. pylori* colonizes the entire surface of the stomach, the acid-secreting corpus is relatively resistant such that inflammation is less and both the organisms and the inflammation

tend to remain superficial. The organism is repelled from the gastric pits in the corpus because highly acidic (pH <1) fluid is ejected from the gastric parietal cells through the pits and into the lumen. This highly acid fluid restricts the bacteria to the most superficial mucosa where they can "hide" under the mucus layer. Inhibition of acid secretion associated with a highly selective vagotomy, use of antisecretory drugs, or a febrile illness releases this inhibition and allows the bacteria to interact with the mucosa in such a way as to produce more and deeper levels of inflammation. Interleukin-1β, a potent natural antisecretory agent, is produced in response to the bacteria and further reduces acid secretion, which may allow the infection to become established in the depths of the corpus, resulting in a pangastritis.

Antral inflammation is associated with up-regulation of the hormone gastrin as well as inhibition of somatostatin which is responsible for the normal acid inhibitory effect of antral acidity. Overall, this results in an increase in the amount and duration of gastric acid secretion in response to a meal. In patients with antral predominant gastritis, acid secretion from the corpus is uninhibited and such patients are at markedly increased risk of developing a duodenal ulcer. In contrast, in hosts with low acid secretory capacity due to a low number of parietal cells or whose parietal cells are being inhibited, the organism is capable of colonizing a wider niche, producing a pangastritis or even a corpus-predominant gastritis. Chronic active inflammation of the corpus mucosa may result in oxyntic gland atrophy with the normal corpus mucosa being replaced by pseudopyloric metaplasia often containing islands of intestinal metaplasia (chronic atrophic gastritis). This low acid-secreting state is the phenotype associated with the development of dysplasia and eventually gastric cancer.

The progression of *H. pylori*-related chronic gastritis to gastric cancer is modulated by bacterial, environmental, and host factors. For example, as noted above, the presence of the *cag* PAI signifies the presence of an infection with increased inflammation and thus an increased risk of cancer. Diets high in salt and low in fresh fruits and vegetables are also associated with rapid progression of damage and an earlier transformation from non-atrophic to atrophic gastritis. A number of host genetic factors, especially polymorphisms in the genes regulating the intensity of the inflammatory response to the infection, also influence outcome. For example, single-nucleotide polymorphisms in the genes encoding interleukin-1 that are associated with an increased inflammatory response are also associated with an increased risk of developing gastric atrophy and gastric cancer. *H. pylori* infection is a necessary but not sufficient cause of gastric cancer such that eradication of the organism can prevent gastric cancer if accomplished before irreversible changes occur despite the continuing presence of the environmental and host risk factors that promote the disease. After atrophic gastritis has developed, *H. pylori* eradication can prevent further damage and further increase in risk but cannot return the risk to zero.

Gastric atrophy/atrophic gastritis leading to hypochlorhydria or achlorhydria also allows gastric colonization by other enteric bacteria which in turn may be responsible for the formulation of carcinogenic substances (e.g., nitrosamines) from dietary and other sources. If parietal cells remain, *H. pylori* eradication can lead to a partial return in acid secretion and elimination or reduction in this form of bacterial overgrowth.

DIAGNOSIS OF *H. PYLORI* INFECTION

H. pylori infection can be reliably diagnosed by a wide variety of tests including noninvasive assays (i.e., those not requiring upper gastrointestinal endoscopy) and by those where it is necessary to obtain a sample of the gastric mucosa or contents (invasive or minimally invasive tests) (Table 138.1). The noninvasive methods

Table 138.1 Summary of diagnostic tests

Test	Sensitivity (%)	Specificity (%)	Cost
NONINVASIVE TESTS			
Serology			
Laboratory, serum, ELISA	86–95	78–95	$$
In-office, serum	88–94	74–88	$
In-office, whole blood	67–88	75–91	$
Urea breath test			
^{13}C-urea breath test[a]	90–96	88–98	$$$
^{14}C-urea breath test[b]	90–95	90–95	$$
Stool antigen test	83–98	81–100	$$
Invasive tests			
Rapid urease test	88–95	93–100	$
Histology	93–98	95–99	$$$
Culture	77–98	100	$$$

[a] No radiation exposure.
[b] Low radiation exposure.

Table 138.2 Indications for testing for *Helicobacter pylori* infection[a]

Duodenal or gastric ulcer (present or history of)
Evaluate success of eradication therapy
Gastric low-grade MALT lymphoma
Atrophic gastritis
After endoscopic resection of early gastric cancer
Uninvestigated dyspepsia
Non-ulcer dyspepsia
Chronic NSAID/aspirin therapy[b]
Chronic antisecretory drug therapy (e.g., Gastroesophageal reflux disease)[c]
Relatives of gastric cancer patients
Relatives of patients with duodenal ulcer
Relatives of patients with *H. pylori* infection
Patient desires to be tested

[a] All proven to have an active *H. pylori* infection should be treated.
[b] When planning long-term therapy.
[c] When planning long-term antisecretory therapy.
Abbreviations: MALT = mucosa-associated lymphoid tissue; NSAID = nonsteroidal anti-inflammatory drug.

include detection of an immune response to the infection (e.g., IgG serologic tests), urea breath tests, and stool antigen assays. More invasive methods include rapid urease tests, histology, and culture. In addition, there are a number of tests available that are used for research purposes such as detection of the presence of *H. pylori* using the polymerase chain reaction.

The method of choice clinically depends on availability, cost, and whether endoscopy is otherwise indicated. Because the diagnosis of an active *H. pylori* infection should always be followed by eradication therapy, the primary consideration for testing is the willingness to treat the infection. Currently, testing for *H. pylori* infection is indicated in patients with a wide variety of conditions, including active peptic ulcer disease, a past history of documented peptic ulcer, non-ulcer dyspepsia, gastric MALToma, and adenocarcinoma (Table 138.2).

According to guidelines of the European *H. pylori* Study Group, testing is recommended in dyspeptic patients without alarm symptoms or under 45 years of age, at low risk of malignancy as part of a "test and treat strategy" (Figure 138.1). Noninvasive testing (e.g., the urea breath or stool antigen test) is preferred. Stool antigen tests using monoclonal antibodies are superior to ones using polyclonal antibodies. Serologic testing is often the least expensive test. However, the sensitivity and specificity of serologic tests, particularly in-the-office tests, is typically lower than that of the urea breath test or stool antigen test. Nonetheless, IgG serologic testing remains useful in conditions of high or low pretest probability. For example, a positive test in a patient with a known high probability condition such as a peptic ulcer disease would be considered reliable as would a negative test in a low *H. pylori* prevalence region in a patient with a low-probability condition such as gastroesophageal reflux disease. In contrast, when one obtains an unexpected result (e.g., a negative serologic test in a patient with duodenal ulcer disease), it would be prudent to retest using a test for active infection. Because antibody titers fall slowly they cannot be relied upon to assess post-eradication status of *H. pylori* infection. IgA and IgM *H. pylori* serologic tests are typically inaccurate and not recommended.

When endoscopy is clinically indicated, the test of choice is a rapid biopsy urease test using preferably two specimens, one from the antrum and one from the corpus. Biopsy urease testing provides both a high sensitivity and specificity for the diagnosis of *H. pylori* infection. If a biopsy urease test is negative, absence of an *H. pylori* infection should be confirmed by histology. Histology has the advantages of providing a permanent record and allowing identification of the pattern and severity of gastritis. Prospective studies have consistently shown that hematoxylin and eosin (H&E) staining of gastric mucosal biopsies has poor sensitivity and specificity for diagnosis of active *H. pylori* infections, and a special stain such as immunohistochemistry, the Genta or El-Zimaity triple stains, or the combination of H&E and the Diff-Quik stains should be requested. Culturing *H. pylori* is often impractical as most clinical laboratories have not established this as a routine test. However, culture to establish drug susceptibility of *H. pylori* isolates is useful to choose therapy and is clearly indicated in patients who fail to eradicate *H. pylori* using standard antimicrobial regimens. Cultures can also be obtained using minimally invasive methods using a brush or string test.

CAUTIONS ABOUT FALSE-NEGATIVE DIAGNOSTIC TESTS

False-negative results are possible and even likely if the patient has taken drugs that reduce the bacterial load such as antibiotics, bismuth, or proton pump inhibitors (PPIs). In general, one

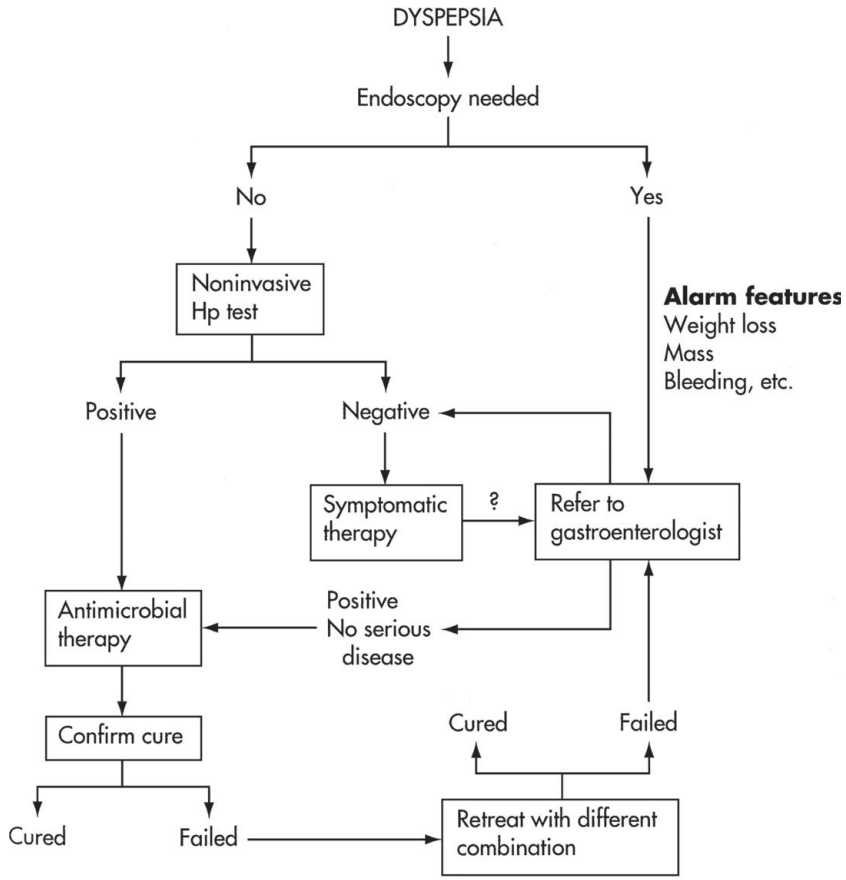

Figure 138.1 This algorithm shows one approach to the evaluation of patients presenting with dyspepsia. It has become apparent that in the United States where the incidence of gastric cancer is very low, noninvasive testing with serology, urea breath testing, or fecal antigen testing is sufficient and that endoscopy can be reserved for those with alarm symptoms. Referral to a gastroenterologist should be considered for those with alarm symptoms, those who have failure of symptoms to resolve after successful therapy, and those who fail one or more courses of therapy. The exception is those with clear-cut gastroesophageal reflux disease whose symptoms are not anticipated to resolve after successful cure of *H. pylori*. Those over the age of 50 with a long history of symptomatic gastroesophageal reflux would be one group where referral should be considered to exclude Barrett's esophagus.

should stop these drugs for 1 to 2 weeks before testing. H_2-receptor antagonists do not adversely affect any of these tests (although they apparently may adversely affect the ^{14}C-urea breath test) and can be used if needed to control symptoms. In clinical practice, post-eradication assessment for *H. pylori* infection should be conducted at least 4 weeks following the completion of eradication therapy to avoid false-negative results.

INDICATIONS FOR *H. PYLORI* ERADICATION

In developed countries, with a low incidence of gastric cancer, the rule is to cure all cases diagnosed, making the main issue whom to test. Table 138.2 lists conditions where a test and treat strategy is likely cost-effective despite the relatively low prevalence of the infection in the general population. Considering that humans are the only natural host, the infection causes gastric cancer, and that it universally causes progressive damage to the structure and functions of the stomach, it shares with smallpox, tuberculosis, polio, and syphilis the fact that the world will be better off when they are all eradicated. In March 2013 Japan approved universal *H. pylori* eradication and is thus leading the way toward population-wide *H. pylori* eradication. However, developing countries with poor sanitation remain a challenge because of the high prevalence of the infection and the high rate of reinfection after eradication therapy. Elimination of this important

pathogen will likely require an effective vaccine. However, progress in vaccine development has been slow.

GASTROESOPHAGEAL REFLUX DISEASE, BARRETT'S ESOPHAGUS, AND ADENOCARCINOMA OF THE ESOPHAGUS

One source of confusion and uncertainty has been confusion concerning whether *H. pylori* eradication might remove a beneficial effect of the infection. For example, atrophic gastritis (the precursor lesion for gastric cancer) leads to a reduction in the ability of the stomach to make acid such that even if an individual experienced gastroesophageal reflux, the material refluxing would have such a low acidity that symptoms and consequences would rarely occur. In developed countries, *H. pylori* infection and atrophic gastritis (and gastric cancer) have declined whereas the prevalence of symptomatic reflux esophagitis has increased. This change is reflected in adenocarcinoma of the esophagus increasing from being an extremely rare disease to simply a rare one while gastric cancer fell from an extremely common problem to an uncommon one. More recently, it has been suggested that *H. pylori* infection might protect against atopy and asthma in children. In this scenario *H. pylori* is part of the hygiene hypothesis and provides critical antigens that help regulate the immune response. However, studies in regions with poor hygiene and little or no *H. pylori* did not support (i.e., disproved) this hypothesis but rather supported the notion that *H. pylori* is rather a surrogate for poor household hygiene and is not directly involved itself. Current evidence is consistent with the notion that *H. pylori* infection provides no meaningful benefits and should be eliminated whenever the infection is found.

TREATMENT OF *H. PYLORI* INFECTION

H. pylori infection is common but is more difficult to cure than many other common bacterial infections. *H. pylori* occupy a number of different niches in the stomach including being intracellular such that therapy must be effective over the wide range of conditions where the organisms exist. The stomach is acid with the pH varying from near neutral at the cell surface to less than 1 in the lumen. Acidic conditions are hostile to antibiotics, which generally work best at near neutral pH.

The main impediments to successful treatment are the presence of antimicrobial resistance and poor patient adherence with the sometimes complicated regimens. The choice is easy if pretreatment susceptibility testing has been done. However, this is rarely available and one must frequently rely on empiric choices. Most successful regimens (defined as reliably curing at least 95% of infections with susceptible strains) include an antisecretory drug, most commonly a PPI, and two or three antimicrobials. In most places in the world the prevalence of clarithromycin resistance has increased to the point where the initially successful "triple therapy" consisting of a PPI, clarithromycin, and metronidazole or amoxicillin is no longer effective. Sufficient studies have now been published providing data in terms of outcome with different patterns of resistance to allow a rational choice of therapy provided one has an idea of the local pattern of resistance.

Because treatment success with 10-day sequential therapy (a PPI and amoxicillin dual therapy for 5 days, followed by a PPI, clarithromycin, and tinidazole/metronidazole triple therapy for a further 5 days) and traditional clarithromycin or metronidazole-containing triple therapies is negatively affected (e.g., treatment success falls greatly) in the presence of either clarithromycin or metronidazole resistance (e.g., 75% success rate with sequential therapy in the presence of metronidazole resistance) the best choice for an empiric clarithromycin-containing regimen is 14-day concomitant therapy consisting of twice a day administration of a PPI, amoxicillin, metronidazole/tinidazole, and clarithromycin for 14 days (Table 138.3). Concomitant therapy and hybrid sequential–concomitant therapy (Table 138.3) are negatively affected only by dual clarithromycin–metronidazole resistance. Traditional triple or sequential regimens are now known to be inferior choices as empiric therapy and should be reserved for targeted therapies which are based on pretreatment susceptible testing.

Basically, the choices for empiric therapy are four-drug regimens, the non-bismuth concomitant or hybrid therapies or bismuth quadruple therapy (consisting of a PPI twice a day, metronidazole/tinidazole three times daily, plus a bismuth and tetracycline four times daily, preferably for 14 days) (Table 138.3). For reliable success it is important to pay attention to doses and durations as the regimen is affected by metronidazole resistance unless given at full dose and duration. Generally, the non-bismuth

Table 138.3 Recommended antibiotic combinations for *H. pylori* infections

Treatment	Drugs, dosages, and duration
Empiric therapies	
Concomitant therapy	Amoxicillin (1 g), clarithromycin (500 mg), and tinidazole (500 mg) or metronidazole (500 mg) plus a PPI (40 mg omeprazole equivalent per dose) all given twice daily for **14 days**
Sequential–concomitant hybrid therapy	Amoxicillin (1 g) plus a PPI twice daily (40 mg omeprazole equivalent per dose) for 7 days, followed by amoxicillin (1 g), clarithromycin (500 mg), and tinidazole (500 mg) or metronidazole (500 mg) for a further 7 days (total 14 days)
Bismuth quadruple therapy	Bismuth subsalicylate or bismuth subcitrate 2 tablets and tetracycline hydrochloride (500 mg) both four times daily with meals and at bedtime plus metronidazole/tinidazole (500 mg) three times daily with meals and a PPI twice daily for 14 days.
For prepackaged bismuth quadruple therapy	PYLERA® for 14 days, add a PPI BID Helidac® for 14 days, add a PPI BID. For this formulation we recommend increasing the metronidazole to 500 mg TID (either give the extra 250 mg at night or use it with one of the TID doses)
Tailored therapy	(based on known susceptibility testing)
Triple therapy when *H. pylori* infection is known to be susceptible to clarithromycin	Amoxicillin (1 g) and either clarithromycin (500 mg), or tinidazole (500 mg) or metronidazole (500 mg) plus a PPI all given twice daily for 14 days
Fluoroquinolone therapy when *H. pylori* is known to be susceptible to fluoroquinolones	Fluoroquinolone (e.g., levofloxacin 500 mg once daily), plus a PPI and amoxicillin 1 g twice daily for 14 days Or amoxicillin (1 g) plus a PPI twice daily for 5 days, followed by a fluoroquinolone (e.g., levofloxacin 500 mg once daily) and tinidazole (500 mg) or metronidazole (500 mg) plus a PPI all twice daily for a further 5 days (total 10 days)
Fluoroquinolone concomitant therapy	Esomeprazole or omeprazole 40 mg twice daily, amoxicillin 1 g twice daily, levofloxacin 500 mg twice daily, and tinidazole/metronidazole 500 mg twice daily; all for 5 days
Empiric salvage therapy	
Furazolidone quadruple therapy	Bismuth subsalicylate or bismuth subcitrate 2 tablets and tetracycline hydrochloride (500 mg) both four times daily with meals and at bedtime plus furazolidone 100 mg TID, with meals and PPI twice daily for 14 days
Rifabutin triple therapy	Rifabutin (150 mg daily or bid), amoxicillin (1.5 g q8h, and pantoprazole 80 mg (or an equivalent PPI) q8h for 12 to 14 days
High-dose PPI-amoxicillin dual therapy	PPI (e.g., omeprazole [40 mg] or lansoprazole [30 mg]) plus amoxicillin (500 mg) all four times daily at approximately 6-h intervals for 14 days (can be used at 8-h interval at night)

regimen is better tolerated; however, because the bismuth regimen does not contain amoxicillin and can overcome metronidazole resistance, it is especially useful when penicillin allergy is present or when dual metronidazole–clarithromycin resistance is suspected.

The likelihood of dual resistance should preclude any clarithromycin-containing regimen. The major issue with bismuth quadruple therapy is compliance as side effects are common and should be discussed (including the likelihood of black stools) before use. Studies are needed to test simplified bismuth-containing regimens such as twice-a-day therapy instead of more frequent dosing. Bismuth quadruple regimens shorter than 14 days are markedly less effective in the presence of metronidazole resistance and we recommend 14 days unless the infection is known to be susceptible to metronidazole.

MULTIPLE TREATMENT FAILURES OR SALVAGE THERAPIES

The best approach is to choose the regimen based on susceptibility testing, which often requires referral to a *H. pylori* specialist. Alternate successful regimens use a fluoroquinolone (e.g., levofloxacin), rifabutin, or furazolidone. Fluoroquinolone resistance has rapidly increased and any prior quinolone use typically signifies resistance; pretreatment susceptibility testing is recommended. Fluoroquinolone and rifabutin-containing regimens are best when given for 14 days as part of a PPI, amoxicillin, triple therapy (Table 138.3). Furazolidone is generally unavailable but where available is most often used as part of a 14-day bismuth-containing regimen (i.e., replacing the metronidazole) and given as 100 mg three times daily. It is highly effective but side effects are common as are drug interactions.

CONFIRMATION OF CURE

The risks related to the presence of untreated *H. pylori* are unaffected following treatment failures, requiring that treatment success be confirmed (i.e., therapy should be followed by confirmation of cure). The confirmatory test should be delayed until 4 to 6 weeks after the end of antimicrobial therapy to allow the bacteria, if still present, an opportunity to repopulate the stomach. Drugs that inhibit *H. pylori* such as PPIs should not be allowed for 1 and preferably 2 weeks prior to testing. The urea breath test is the ideal method of evaluating the outcome of therapy for those in whom follow-up endoscopy is not needed. An alternate approach would be to use the stool antigen test but in that case testing should be delayed for 6 to 8 weeks.

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139. Gonococcus: *Neisseria gonorrhoeae*

Amy J. Mathers and Michael F. Rein

Neisseria gonorrhoeae is the second most common sexually transmitted bacterial pathogen after *Chlamydia trachomatis*, resulting in an estimated 600 000 infections per year in the United States. The gonococcus causes disease by attaching primarily to columnar or cuboidal epithelial cells (Table 139.1) via pili and outer membrane proteins. It then penetrates between and through the cells to submucosal areas, where it elicits a neutrophilic host response. The clinical spectrum of primary infection with *N. gonorrhoeae* mirrors that of *C. trachomatis*, which is the most important etiologic differential diagnosis.

Acute urethritis, manifesting as some combination of urethral discharge and dysuria, is the most common presentation of disease in men, although some infected men are asymptomatic. Gram stain of urethral discharge may be used for presumptive diagnosis of gonococcal urethritis. Polymorphonuclear neutrophils (PMNs) with gram-negative, intracellular diplococci (GNID; Figure 139.1) are observed in 95% of infected, symptomatic men, and the finding is 98% specific. Observing PMN without GNID supports a diagnosis of nongonococcal urethritis (see Chapter 59, Urethritis and dysuria), but the sensitivity of GNID in asymptomatic men is only about 75%, and Gram stain cannot be used to rule out gonorrhea in these patients.

In women, the primary site of infection is the endocervix, although the organism can be recovered from the urethra and periurethral (Skene's) and Bartholin's glands in adults and from the vagina itself in prepubescent girls. Asymptomatic infection is more common in women than men. Gram stains of cervical smears from infected women are 97% specific for the disease when GNID are observed but only 25% to 70% sensitive.

Anorectal gonorrhea occurs in up to 40% of women with endocervical disease. It can also be an isolated finding in homosexual men who practice receptive anal intercourse. Most patients are asymptomatic, but acute proctitis may occur. Most patients with pharyngeal infection, acquired from fellatio, are also asymptomatic, but pharyngitis may occur. Gonococcal conjunctivitis in adults, usually acquired by autoinoculation from a genital focus, produces varying degrees of inflammation.

Disseminated gonococcal infection is increasingly uncommon, occurring historically in perhaps 0.5% to 3% of infected patients. It usually presents as the arthritis–dermatitis syndrome, manifesting as asymmetric, migratory polyarthritis, arthralgias, or tenosynovitis. In 75% of cases, disseminated disease is accompanied by small papules or by vesicles or pustules with an erythematous base.

Table 139.1 Sites of primary infection by *Neisseria gonorrhoeae*

Urethra
Pharynx
Cervix
Conjunctiva
Rectum
Vagina (in prepubescent girls)

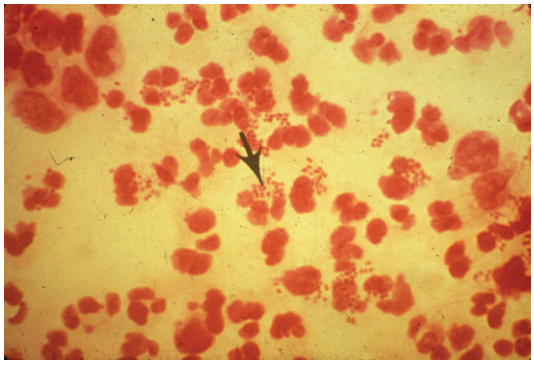

Figure 139.1 Gram stain of urethral discharge, showing gram-negative intracellular diplococci diagnostic of gonorrhea. Coincident nongonococcal urethritis cannot be ruled out. (Courtesy of Centers for Disease Control and Prevention.)

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Hereditary deficiency of the terminal components of complement or infection with organisms resistant to the bactericidal activity of serum predisposes to dissemination. Endocarditis and meningitis are very rare complications.

DIAGNOSIS

Definitive diagnosis requires demonstrating the presence of the organism. This is traditionally accomplished by culture of infected material, but culture has been largely supplanted by molecular techniques. Nucleic acid amplification tests (NAATs) are those most widely used clinically in the United States. The ligase chain reaction is highly specific and sensitive when used on a urethral, cervical, or vaginal specimen. However, studies on urine suggest an unacceptably low sensitivity of about 60% in women. Disadvantages of such molecular technology include the ability of the tests to detect dead organisms for perhaps as long as 2 weeks after successful treatment, lack of licensure for use on anal or pharyngeal specimens, and inability to provide a specimen for testing of antimicrobial sensitivity. As new data develop, the clinician should review the material provided with these tests for indication of their appropriate use. Although culture requires specialized collection apparatus, it is important to obtain appropriate cultures and susceptibility testing on all patients who do not improve on therapy, once reinfection and nonadherence to medication have been ruled out.

THERAPY

There are several important and unique general principles to consider regarding treatment of gonococcal infections. Ideal treatment of uncomplicated infection should be: single dose, affordable, possessing a low side effect profile, and, when possible, oral. Unfortunately, due to increases in antimicrobial resistance, there is no longer a recommended first-line oral option for therapy. The treatment for uncomplicated infection is almost always empirical and performed without knowledge of antimicrobial susceptibility. There are suprisingly few bacterial infections for which in vitro resistance correlates so tightly with clinical treatment failure. Resistance has emerged to all antimicrobial classes used for treatment of gonorrhea. Historically, one can follow the rapid appearance and dissemination of organisms resistant to penicillins, sulfonamides, tetracyclines, fluoroquinolones (FQ), and, most recently, cephalosporins. The genetic chronicle of gonococcal resistance has been mediated by a series of chromosomal mutations and by acquisition of readily dissmeninated plasmids that encode for resistance genes and have the ability to transfer between strains and even genera.

The rapid rise of penicillin and tetracycline resistance was first identified in the 1970s. Resistance to both classes has been driven by chromosomal mutations and dissemination of plasmids carrying genes which encode for a β-lactamase and a protein which modifies the ribosomal target of tetracycline. Although the spread of plasmid-mediated resistance has waned over the last decade, chromosomal resistance remains an issue and, ultimately, neither drug can be reliably used for routine treament.

In the mid 1980s a single, oral dose of FQ successfully treated gonococcal urethritis in men. However, as early as 1990, resistance to ciprofloxacin was detected in *N. gonorrhoeae*. The prevalence of FQ resistance and the incidence of treatment failures continued to rise throughout the 1990s, initially in Southeast Asia and then in Hawaii and California. *N. gonorrhoeae* has many mechanisms which may contribute to FQ resistance. The primary mechanism of FQ resistance is mutation in one or both genes (*parC* or *gyrA*) encoding differing topoisomerases. Reduced permeability through the cytoplasmic membrane and increase in an efflux pump may also contribute to FQ resistance. In 2011, the Gonococcal Isolate Surveillance Project, which performs sensitivity testing on about 3% of male urethral isolates around the United States, reported that 13.3% of strains were resistant to the FQ, more commonly in the Western states and among men who have sex with men (MSM). Fluoroquinolones are no longer recommended for the treatment of gonorrhea in the United States.

Due to increased resistance to other drug classes, late-generation cephalosporins have become the only recommended, first-line treatment for gonococcal infection. Cephalosporin resistance is mediated through accumulation of chromosomal mutations that alter binding by the drug's target. Although cephalosporin resistance remains relatively low level, the steep rise in the rate of decreased cefixime susceptibility does cause concern. Because of this rate of increase and concerns around increasing number of failures with oral cephalosporins, the only recommended treatment is intramuscular administration of 250 mg (formerly 125 mg) of ceftriaxone.

Treatment of gonococcal disease is further complicated by frequent anogenital coinfection with *C. trachomatis* or other agents of nongonococcal urethritis (NGU), such as *Mycoplasma genitalium* and *Ureaplasma urealyticum* (see Chapter 59, Urethritis and dysuria). Thus patients with gonorrhea should be treated simultaneously for coincident nongonococcal infection. In addition, dual therapy may slow the emergence of resistance if the gonococcal isolate is also susceptible to the second agent. Therapy recommended for gonorrhea therefore also includes either oral azithromycin 1 g or doxycycline 100 mg twice daily for 7 days. Although either of these regimens is reasonably effective for chlamydial infection, azithromycin is more effective for the mycoplasmas and for gonorrhea itself.

Management of sexual partners should probably extend back for 60 days prior to the onset of symptoms or date of diagnosis. All patients with gonorrhea should be advised to undergo testing for infection with human immunodeficiency virus. The recommended antigonococcal regimens are sufficiently effective that test of cure is not necessary, but retesting at 3 months should be encouraged to detect reinfection.

In some settings, medication or prescriptions may be provided for patients to deliver to their sexual partners. Since such therapies must be oral, they can no longer be considered first-line, and partners so treated should be advised to present for test of cure.

Standard therapy

Intramuscular ceftriaxone is highly effective, and a 250-mg regimen is recommended by the Centers for Disease Control and Prevention (CDC). The drug is often diluted in 1% lidocaine to reduce discomfort. Other single-dose parenteral regimens (ceftizoxime or cefotaxime, 500 mg IM) offer no advantage over ceftriaxone. Resistance to cefoxitin, often in association with high-level tetracycline resistance, mandates that this drug should no longer be used in the treatment of uncomplicated gonorrhea.

Oral cephalosporins have recently been shown to be less effective and failure was associated with relative increases in in vitro resistance. Due to this increase in resistance any oral cephalosporin should not be used unless ceftriaxone is unavailable. Fluoroquinolones should no longer be used to treat uncomplicated gonorrhea (see above). Azithromycin, 2 g, has the putative advantage of treating coincident chlamydial infection, but it is expensive, elicits gastrointestinal intolerance, and is subject to increasing resistance; it is not recommended as primary therapy except in the setting of severe (IgE-mediated) β-lactam allergy. Likewise, the aminocyclitol spectinomycin was previously listed by the CDC as an alternative for patients who are pregnant or for children who have a history of immediate hypersensitivity to ß-lactams. Earlier data support the use of gentamicin (see Table 139.2), which may be effective in the same settings, but a meta-analysis found a 92% cure rate with this strategy, which does not meet the criterion for cure rate of ≥95% required for CDC approval. Historically however, widespread use of spectinomycin was soon followed by aminoglycoside resistance. The use of any of these drugs mandates a test of cure 1 week after treatment.

Nonstandard therapy

The monobactam aztreonam and the carbapenems imipenem–cilastatin, meropenem, and ertapenem are uniformly effective against *N. gonorrhoeae* but are costly and available only

Table 139.2 Regimens for uncomplicated gonorrhea (urethritis, cervicitis, proctitis)

Drug	Dose	CDC recommended	Safe in pregnancy	Effective in pharynx	Comments
Ceftriaxone	250 mg IM	Yes	Yes	Yes	Most effective
Cefixime	400 mg PO	Secondary	Yes	Uncertain	Resistance developing
Cefpodoxime	400 mg PO	Secondary	Yes	Uncertain	Resistance developing
Ciprofloxacin	500 mg PO	No	Yes	Uncertain	Significant resistance, not recommended, see text
Other fluoroquinolones	Various	No	No	Uncertain	Significant resistance, not recommended, see text
Azithromycin	2 g PO	Secondary	No	Yes	In severe β-lactam allergy
Spectinomycin	2 g IM	No	Yes	No	Unavailable in USA
Gentamicin	280 mg IM	No	Yes	No	Old regimen, test of cure required, see text

Note: Always add a second drug for coincident infection with an agent of NGU and to forstall the development of gonococcal resistance (see text).

Table 139.3 Initial regimens for disseminated gonococcal infection[a]

Drug	Dose	CDC recommended	Safe in pregnancy	Comments
Ceftriaxone	1 g IV q24h	Yes	Yes	Most effective
Ceftizoxime	1 g IV q8h	Secondary	Yes	No advantage over ceftriaxone

[a] Intravenous therapy should be continued for 24 to 48 hours after improvement begins. Thereafter the patient can be switched to an oral regimen based on susceptibility testing.

Table 139.4 Follow-up regimens for disseminated gonococcal infection

Drug	Dosage	CDC recommended	Comments
Cefixime	400 mg PO, 2× daily	Yes	No data
Cefpodoxime	400 mg PO, 2× daily	No	No data

in intravenous form. These drugs are never primary therapy for gonorrhea. Recently, gentamicin 240 mg plus azithromycin 2 g PO or gemifloxacin 320 mg plus azithromycin 2 g PO demonstrated excellent efficacy against uncomplicated anogenital and pharyngeal gonorrhea. These regimens might be useful in treating infection with cephalosporin-resistant infections or in β-lactam-allergic patients.

Extragenital disease

A single dose of ceftriaxone, 1 g IM, in adults apparently cures gonococcal conjunctivitis, but clinical data are extremely limited. A single saline flush of the conjunctiva should be considered, but topical antibiotics have no proven additional benefit.

Elimination of *N. gonorrhoeae* from the oropharynx is particularly challenging. Prior to the recent era with increasing drug resistance, regimens which would work on uncomplicated local genital infection have not necessarily been effective for pharyngeal disease. A single center study found azithromycin superior to doxycycline as a second agent for treatment of the oropharynx.

No prospective studies on the treatment of disseminated gonococcal infection have been performed since 1976; hence, recommendations are empiric, because the worldwide spread of resistant gonococci occurred after that time. The gonococcal arthritis–dermatitis syndrome should be treated with ceftriaxone (Table 139.3). Regimens employing other third-generation cephalosporins were equally effective in the past; however, this has not been examined in the more recent era of increasing cephalosporin resistance. If frank septic arthritis is not present, the patient can be switched to an oral regimen (Table 139.4), preferably with a cephalosporin, to complete 7 to 10 days of therapy. Prior to transition to oral therapy susceptibility testing of isolates is strongly recommended. The optimal duration of therapy is unknown. Spectinomycin, if available, is an alternative for pregnant women, children, and those who are allergic to β-lactams. Gonococcal endocarditis should be treated with 4 weeks and meningitis with 2 weeks of an appropriate parenteral regimen, preferably ceftriaxone or another third-generation cephalosporin. There are no current studies of extended courses of FQ as treatment for extragenital disease, and in the face of recent increases in resistance, these drugs should not be used.

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140. *Haemophilus*

Timothy F. Murphy

HAEMOPHILUS INFLUENZAE

Haemophilus influenzae is an exclusively human pathogen whose ecologic niche is the human respiratory tract. The species *H. influenzae* includes strains with six antigenically distinct polysaccharide capsules designated a through f. Serotype b strains cause serious invasive disease in infants, including meningitis and bacteremia. Polysaccharide–protein conjugate vaccines have virtually eliminated disease caused by type b strains in countries where the vaccine is widely used. However, invasive disease caused by *H. influenzae* type b is still a significant problem worldwide in countries where the vaccine is not used.

Strains of *H. influenzae* that lack a polysaccharide capsule are called nontypeable because they are nonreactive with the typing sera directed at each of the six capsular polysaccharides. Nontypeable strains of *H. influenzae* demonstrate enormous genetic diversity and are an important cause of human respiratory tract disease.

Because type b and nontypeable strains of *H. influenzae* differ from one another in epidemiology, clinical manifestations, and treatment, they are considered separately in each section of this chapter.

Epidemiology and respiratory tract colonization

H. INFLUENZAE TYPE B

Prior to the widespread use of the *H. influenzae* conjugate vaccines, approximately 3% to 5% of infants were colonized in the nasopharynx by type b strains, with higher rates observed in day-care centers. The conjugate vaccines have resulted in a marked decrease in the colonization rate, contributing to the dramatic decrease in invasive type b infections in the United States.

NONTYPEABLE *H. INFLUENZAE*

Nontypeable strains of *H. influenzae* frequently colonize the nasopharynx of healthy children, with higher rates in day-care centers. Nasopharyngeal colonization begins in infancy and essentially every child is colonized at some time. Frequent transmission of strains occurs among children in day-care centers and colonization with nontypeable *H. influenzae* in the first several months of life is associated with recurrent otitis media. Different antibiotics have different effects on the dynamics of colonization. The widespread use of pneumococcal conjugate vaccines is changing patterns of nasopharyngeal colonization with "replacement" of pneumococcal vaccine serotypes by nonvaccine serotypes and possibly by nontypeable *H. influenzae* and *Moraxella catarrhalis*. Such changes in colonization patterns may change the distribution of pathogens that cause otitis media.

Nontypeable *H. influenzae* colonizes the upper respiratory tract of healthy adults and adults with chronic obstructive pulmonary disease (COPD). The airways of adults with COPD are colonized by nontypeable *H. influenzae*, even during clinically stable periods. This colonization is a dynamic process with new strains replacing old strains periodically; acquisition of a new strain is associated with an exacerbation of the COPD.

Clinical microbiology laboratories do not accurately distinguish *H. influenzae* from commensal *Haemophilus haemolyticus* because not all strains of *H. haemolyticus* demonstrate hemolysis. Thus, *H. haemolyticus* are frequently misidentifed as *H. influenzae*.

Clinical manifestations

H. INFLUENZAE TYPE B

Type b strains cause invasive infections predominantly in children under the age of 6 years. Meningitis is the most serious manifestation of infection by *H. influenzae* type b in children and occurs mostly under the age of 2 years. Nuchal rigidity may or may not be present. Epiglottitis is a life-threatening infection involving the epiglottis and supraglottic tissues. Cellulitis, pneumonia,

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and bacteremia are less common manifestations of *H. influenzae* type b infections. All forms of infection due to type b strains are uncommon in countries where the conjugate vaccines are used.

NONTYPEABLE *H. INFLUENZAE*

Nontypeable *H. influenzae* causes 25% to 35% of episodes of acute otitis media in children and is the most common bacterial cause of recurrent otitis media. Approximately three-quarters of all children experience an episode of otitis media by the age of 3 years, and otitis media is the most common reason that children receive antibiotics. Up to 10% of children in developed countries are *otitis prone* and experience recurrent or persistent otitis media, which are associated with a delay in speech and language development. As noted above, changing nasopharyngeal colonization patterns due to widespread use of conjugate vaccines is changing the distribution of pathogens that cause otitis media, resulting in a relative increase in cases caused by nontypeable *H. influenzae*.

Nontypeable *H. influenzae* is an important cause of lower respiratory tract infection in adults with COPD and is the most common bacterial cause of exacerbations. Clinically, exacerbations are characterized by increased sputum production, increased sputum purulence, and increased dyspnea. Exacerbations cause missed work time, office visits, emergency room visits, hospital admissions, and respiratory failure requiring mechanical ventilation and are thus associated with enormous morbidity, mortality, and healthcare costs.

In addition to exacerbations of COPD (which are characterized by an absence of infiltrate on chest x-ray), nontypeable *H. influenzae* causes community-acquired pneumonia, particularly in the elderly and in those with COPD.

A small proportion of sinusitis is caused by bacterial infection. Based on studies in which sinus aspirates were cultured, nontypeable *H. influenzae* causes sinusitis in adults and children.

Nontypeable strains of *H. influenzae* are unusual causes of a variety of invasive infections that are documented primarily by small series and case reports.

Treatment

H. INFLUENZAE TYPE B

Initial treatment should be a third-generation cephalosporin, either ceftriaxone or cefotaxime (Table 140.1). Administration of corticosteroids to patients with *H. influenzae* type b meningitis reduces the incidence of neurologic sequelae. The mechanism appears to be a reduction in inflammation that results from release of bacterial cell wall fragments when bacteria are killed by antibiotics. Dexamethasone should be administered to children, who are 2 months of age or older, with meningitis due to *H. influenzae* type b (Table 140.1). In addition to antimicrobial and corticosteroid therapy, patients require supportive care, including treatment of hypotension, acidosis, and respiratory failure that can be associated with meningitis.

Table 140.1 Treatment of *H. influenzae* type b meningitis

Therapeutic agent	Intravenous dose	Duration
Ceftriaxone or Cefotaxime	75 to 100 mg/kg daily in 2 divided doses 200 mg/kg daily in 4 divided doses	1 to 2 wk 1 to 2 wk
Alternative: Ampicillin plus Chloramphenicol	200 to 300 mg/kg daily in 4 divided doses 75 to 100 mg/kg daily in 4 divided doses	1 to 2 wk 1 to 2 wk
Dexamethasone[a]	0.6 mg/kg daily in 4 divided doses	2 d

[a] Recommended for children >2 months of age.

Other invasive infections caused by *H. influenzae*, including epiglottitis, are treated with the same antibiotics as meningitis, but the doses are somewhat lower. Maintaining an airway is critical in patients with epiglottitis.

NONTYPEABLE *H. INFLUENZAE*

Many infections caused by nontypeable *H. influenzae*, such as otitis media and exacerbations of COPD, can be treated with oral antimicrobials. Approximately 30% of strains of *H. influenzae* produce β-lactamase and are therefore resistant to amoxicillin. Alterations in penicillin-binding proteins are a more recently recognized mechanism of resistance. These β-lactamase-negative ampicillin-resistant strains are common in Japan and are increasing in frequency in Europe, although they are still uncommon in the United States.

Many episodes of otitis media and exacerbations of COPD are treated empirically. In these circumstances, the antimicrobial agent should be active against *Streptococcus pneumoniae* and *M. catarrhalis* because these bacteria also cause otitis media and exacerbations of COPD.

Oral antibiotics active against most strains of nontypeable *H. influenzae* include amoxicillin–clavulanic acid, fluoroquinolones, macrolides (e.g., azithromycin, clarithromycin), and various extended-spectrum cephalosporins.

Parenteral antibiotic therapy is indicated for more serious infections caused by nontypeable *H. influenzae* such as bacteremia and pneumonia that require hospital admission. Parenteral antimicrobial agents that are active include third-generation cephalosporins, ampicillin–sulbactam, fluoroquinolones, and the newer macrolides (azithromycin, clarithromycin).

Prevention

H. INFLUENZAE TYPE B

Conjugate vaccines are highly effective in preventing invasive infections due to type b strains. Three vaccines are currently licensed and commercially available in the United States (Table 140.2). All children should receive a series of *H. influenzae* type b conjugate vaccines. The first dose is given at 2 months of age and the primary series is given between 2 and 6 months of age. A booster is administered between 12 and 15 months. Specific recommendations vary for the different vaccines. Details are outlined in the recommendations of the American Academy of Pediatrics (www.aap.org).

Table 140.2 Conjugate vaccines for prevention of *H. influenzae* type b infections

Generic name	Trade name	Manufacturer	Content
PRP-OMPC[a,b]	PedvaxHIB	Merck	Native PRP[a] conjugated to an outer membrane complex of *Neisseria meningitidis*
PRP-T[c]	ActHIB HIBERIX[d]	Aventis Pasteur GlaxoSmithKline	Native PRP[a] conjugated to tetanus toxoid

[a] PRP: polyribitol ribose phosphate, the capsular polysaccharide of *H. influenzae* type b.

[b] PRP-OMPC is also marketed as Comvax, which also includes hepatitis B vaccine.

[c] PRP-T is also marketed as TriHIBit, which contains diphtheria, tetanus, and acellular pertussis vaccines (DTaP). TriHIBit is approved only for the fourth dose of the DTaP and Hib series, not for use as the primary series at 2, 4, or 6 months of age.

[d] HIBERIX is approved only for the booster dose (age 15 months to 4 years) of the *H. influenzae* type b series.

NONTYPEABLE *H. INFLUENZAE*

A pneumococcal polysaccharide vaccine in which the carrier protein is protein D of nontypeable *H. influenzae* has been approved for use in Europe and in many regions of the world. The vaccine shows efficacy in preventing otitis media due to *S. pneumoniae* and partial efficacy against *H. influenzae* otitis media (~30%). Although no vaccines specifically for nontypeable *H. influenzae* are currently licensed, such vaccines are likely to be available in the future.

HAEMOPHILUS DUCREYI

Haemophilus ducreyi is the etiologic agent of chancroid, a sexually transmitted disease characterized by genital ulcer and inguinal lymphadenopathy. Although uncommon in the United States, chancroid is more common in developing countries and facilitates the transmission of human immunodeficiency virus (HIV). Transmission is primarily heterosexual with more males than females affected. Many infections in males are associated with commercial sex workers.

The typical lesion begins as a papule and evolves into an ulcer that is painful and well circumscribed with ragged edges. Half of patients have inguinal lymphadenopathy. The primary differential diagnoses include primary syphilis and genital herpes. In the setting of HIV infection, chancroid can be more severe, including multiple ulcers and longer duration of ulcers. The diagnosis is best established by culturing the ulcer. However, because the organism is difficult to grow and requires selective media, the diagnosis is often made clinically. No US Food and Drug Administration (FDA)-approved polymerase chain reaction (PCR)-based assays are available in the United States. However, some laboratories have developed their own tests that have undergone Clinical Laboratory Improvement Amendment (CLIA) verification studies.

A probable diagnosis of chancroid can be made using these criteria: (1) one or more painful genital ulcers; (2) no evidence of *Treponema pallidum* by dark-field examination of an ulcer scraping or a negative serologic test for syphilis performed at least 1 week after the onset of the ulcer; (3) typical presentation for chancroid; and (4) a negative test for herpes simplex virus on the ulcer.

The preferred treatment of chancroid is a single 1-g oral dose of azithromycin. Alternative regimens are listed in Table 140.3. Contacts of

Table 140.3 Treatment regimens for chancroid[a]

Antibiotic	Dose and route	Duration
Azithromycin	1 g PO	Single dose
Ceftriaxone	250 mg IM	Single dose
Ciprofloxacin	500 mg PO 2× daily	3 d
Erythromycin base	500 mg PO 3× daily	7 d

[a] Recommendations of the Centers for Disease Control, August 4, 2006.

patients with chancroid should be treated if sexual contact occurred within the 10 days preceding the onset of symptoms in the patient, whether or not symptoms are present in the contact.

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141. Legionellosis

Thomas J. Marrie

ETIOLOGIC AGENTS

The genus name *Legionella* was derived from the fact that the first recognized outbreak of infection due to these microorganisms affected members of the American Legion. *Pneumophila* ("lung loving") was the species designation for the first isolate. There are now 50 species and 70 serogroups in the family Legionellaceae and about half of these have caused disease in humans. *Legionella pneumophila* serogroup 1 accounts for 80% to 90% of cases of Legionnaires' disease (LD) (Table 141.1). However, in Australia and New Zealand *Legionella longbeachae* accounts for 30% of the cases. Legionellaceae are gram-negative, aerobic, non-spore-forming bacilli that measure 0.3 to 0.9 μm wide and 2 to 20 μm long. These organisms require special media for growth. Charcoal yeast extract agar buffered to pH 6.9 and containing α-ketoglutarate along with cefamandole, polymyxin B, and anisomycin to prevent growth of other microorganisms is the primary medium used for isolation of these organisms. Addition of α-ketoglutaric acid to the medium promotes growth of *Legionella* likely by stimulation of oxygen-scavenging enzymes.

These organisms are visualized poorly if at all by Gram stain. In tissue, silver impregnation stains such as the Dieterle or Warthin–Starry method allow visualization of the organisms.

To date the genomes of 6 strains of *L. pneumophila* have been sequenced. They range in size from 3.34 to 2.52 MB. The GC content ranges from 86% to 88% and 86% to 87% of the genes are coding genes. Recently whole genome sequencing has been applied to the investigation of an outbreak of LD.

Table 141.1 Legionellaceae that have been reported as causing pneumonia

Legionella pneumophila serogroups 1–15 (serogroup 1 most commonly; also 3, 4, 6, 13)
Legionella micdadei
Legionella bozemanii
Legionella dumoffi
Legionella sainthelensi
Legionella longbeachae
Legionella anisa
Legionella maceachernii
Legionella waltersii
Legionella feelei
Legionella wadsworthii
Legionella parisiensis
Legionella hackeliae
Legionella jordanis
Legionella lansingensis
Legionella cincinnatiensis

EPIDEMIOLOGY AND PATHOGENESIS

Legionellae are aquatic microorganisms and thus the epidemiology of infections due to these organisms is linked to water systems that are contaminated with these bacteria. The earliest known outbreak of LD occurred in 1965 at St. Elizabeth's Hospital in Washington, DC. The outbreak that gave this illness its name and led to the isolation of the causative microorganism was associated with the 58th Annual Convention of the American Legion held at a hotel in Philadelphia from July 21 to July 24, 1976. One hundred and eighty-two of the attendees at the convention developed pneumonia. One hundred and forty-seven (81%) were hospitalized, and twenty-nine (16%) died. This outbreak of pneumonia of apparent unknown cause triggered an extensive epidemiologic and microbiologic investigation by the Centers for Disease Control and Prevention (CDC), culminating in the isolation of a new microorganism, *Legionella pneumophila*, about 6 months later.

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We now know that legionellosis can occur as sporadic (endemic) cases or as outbreaks in the community or in healthcare facilities. We have learned a lot about legionellosis by studying outbreaks. Outbreaks have varied in size from a few cases to the largest outbreak yet reported of 800 suspected and 449 confirmed cases in Murcia, Spain, in July 2001. A study from Europe from 2000 to 2002 indicated that there were 10 322 cases of LD with infection rates among the reporting countries from 0 to 34.1 cases per million population. Thirty-six outbreaks involving 211 persons were linked to hospitals; 38 outbreaks with 1059 cases occurred in community settings; 2 outbreaks were linked to private homes; and 113 outbreaks were travel-associated clusters involving 315 persons. Travel within Europe accounted for 88% of the cases. The remainder were associated with travel to the Americas, Caribbean, Far East, Africa, and Middle East. Continuing studies show that 20% of legionellosis in Europe is travel related. In 2009 there were 607 cases of LD possibly associated with 825 accommodation sites for an overall risk of 0.3 cases/million nights. Travel to Greece was associated with the highest risk.

With the use of geographic information systems it has been shown that the dispersion distances of *Legionella* from a contaminated cooling tower is about 11.6 km.

When data on 3254 patients with LD reported to the CDC from 1980 through 1989 were analyzed, investigators found that disease rates did not vary by year but were higher in northern states and during the summer. The mean age of patients with LD was 52.7 years compared with 34.7 years for the US population. In contrast to earlier reports, persons with LD were now more likely to be black. They were also more likely to be smokers, or have diabetes, cancer, acquired immunodeficiency syndrome (AIDS), or end-stage renal disease. Indeed, the observed number of cases among patients with AIDS was 42-fold higher than expected. Twenty-three percent of the cases were nosocomially acquired.

Some of the features noted in a review of the first 1000 cases of LD in the United States were that 71% of the cases were male and states with the highest attack rates were east of the Mississippi River. In addition, in the 2 weeks before onset of illness 37% of the patients had traveled overnight; 29% had been a hospital visitor, and 5% had been hospitalized for 2 days or fewer before onset of illness. The most recent update on LD in the United States in 2012 shows that legionellosis increased 217% from 2000 to 2009 with a total of 22 410 cases being reported to the CDC. The highest rates were in mid Atlantic States, lowest in West and South Central States. The rate was higher in males than in females and higher in African Americans. The highest rates were in those $\geq$80 years of age at 2.66/100 000 compared with 0.13/100 000 for those in the 20- to 29-year age group.

Only 5% of the cases were confirmed by culture, the rest by urinary antigen. Cases peaked in July and August, and were lowest in January through April.

Other risk factors for LD in the setting of an outbreak are cigarette smoking (relative risk 1.7 to 3.4) (smoking cannabis and tobacco may be a risk factor for severe LD) and consumption of three or more drinks of alcohol per day (confers a relative risk of 3.5). More recently investigators have begun to combine studies of traditional risk factors with a dissection of host susceptibility using molecular biology tools. A mutation leading to a stop codon at position 392 results in a dysfunctional toll-like receptor (TLR) 5 protein unable to recognize flagellin and is a risk factor for *L. pneumophila* infection in nonsmokers. Reduced interferon-γ release has been noted in patients who have recovered from LD. More recently it has been observed that treatment with a tumor necrosis factor antagonist can predispose to LD, with now more than 22 cases reported. It is interesting in light of the above information about the role of cell-mediated immunity in LD that patients with human immunodeficiency virus (HIV) infection who have a defect in cell-mediated immunity are relatively infrequently infected with *Legionella* spp. However, when they do develop *Legionella* infection, they take longer to become afebrile, have more respiratory symptoms, and have a higher rate of respiratory failure and mortality when compared with patients with *Legionella* but without HIV infection.

Outbreaks provide an opportunity to learn about the mechanisms of transmission of LD. In most instances, *Legionella* is transmitted to humans by inhalation of aerosols containing the bacteria. Outbreaks have been associated with exposure to a variety of aerosol-producing devices, including showers, a grocery store mist machine, cooling towers, whirlpool spas, decorative fountains, and evaporative condensers. Other water sources implicated in transmission of LD include showers and spas in wellness centers, water on trains, birthing pools, dental units, asphalt paving machines, and windscreen wiper fluid without added screen wash. New reservoirs

for *Legionella* continue to be identified such as compost facilities. It is also likely that aspiration of contaminated potable water by immunosuppressed patients is a mechanism whereby infection with *Legionella* is acquired. Legionellosis is believed to occur worldwide, but data are limited or nonexistent for many countries. It is likely that legionellosis is uncommon in areas without hot-water heaters and complex water distribution systems. However, even in these areas, aspiration of contaminated natural water, as, for example, following boating accidents, can result in LD. Legionnaires' disease has been found throughout North America, Europe, the United Kingdom, Argentina and Brazil in South America, Singapore, Thailand, and Australia. A few cases of LD have been reported from India.

PATHOGENESIS

Our knowledge of the pathogenesis of *Legionella* infections in humans is still incomplete. The alveolar macrophage is the target cell for *Legionellae* in the lower airways. Both E-cadherin and b1 integrin receptors mediate filamentous *L. pneumophila* attachment to lung epithelial cells. Only virulent strains of *Legionella* are capable of initiating parasite-directed endocytosis. Following phagocytosis or endocytosis, there is abrogation of phagosome–lysosome fusion, which is essential for the intracellular growth of this microorganism. The replicative phagosome becomes associated with the endoplasmic reticulum.

Following a latent period of about 12 hours, the bacteria start dividing. During this latent period, there is synthesis of up to 35 proteins and repression of 32 proteins. Iron must be available in the phagosome for growth. Virulent *L. pneumophila* strains are sensitive to sodium chloride.

Once the replicative phagosome has been established, the bacteria begin to multiply with a doubling time of 2 hours. Heat shock protein 60 (Hsp 60), a chaperone protein, is a dominant protein during this intracellular phase, suggesting that it has an essential role in the viability of the microorganism. Several morphologic changes occur as the number of bacteria increase: They become shorter and accumulate intracytoplasmic membranes and vesicles.

It is likely that *Legionella* behave differently while multiplying in macrophages than they do while multiplying in amebae, their natural hosts. Because airborne amebae have been found in water aerosols, this finding may have implications for LD in humans.

INFECTIOUS SYNDROMES

Pneumonia is the most common manifestation of infection with *Legionella* spp. It may occur in the community as sporadic cases or as outbreaks. In addition, *Legionella* is one of the agents of healthcare-associated pneumonia. There may be a variety of extrapulmonary manifestations and sometimes the clinical picture is dominated by these.

Pontiac fever is a syndrome related to inhalation of *Legionella* spp. lipopolysaccharide.

In the Philadelphia outbreak, fever was present in 97% of the patients, malaise in 89%, cough in 86%, chills in 74%, dyspnea in 59%, myalgias in 55%, headache in 53%, chest pain in 52%, sputum production in 50%, and diarrhea in 41% at presentation. Sixty percent had a white blood cell count $>10\ 000/mm^3$, and 34% had bilateral pulmonary opacities on chest radiograph.

When patients with LD are compared with those with community-acquired pneumonia due to other agents, the patients with LD are more likely to have myalgias, headache, diarrhea, and a higher mean oral temperature at the time of presentation. They also present to hospital sooner after the onset of symptoms – 4.7 days vs. 7.7 days ($P = 0.02$). When patients with LD were compared with patients with bacteremic pneumococcal pneumonia, the following features were associated with *Legionella* pneumonia: male sex, odds ratio (OR) 4.6, 95% confidence interval (CI) 1.48–14.5; heavy alcohol consumption, 4.8 (1.39–16.42); previous β-lactam therapy, 19.9 (3.47–114.2); axillary temperature $>39^{\circ}C$, 10.3 (2.71–38.84); myalgias, 8.5 (2.35–30.74); gastrointestinal symptoms, 3.5 (1.01–12.18). Negative associations included pleuritic chest pain, previous upper respiratory tract infection, and purulent sputum.

In a study comparing the radiographic features of LD, pneumococcal pneumonia, mycoplasma pneumonia, and psittacosis it was noted that radiographic deterioration following diagnosis was a particular feature of LD, occurring in 30/46 (65%) compared with 14/27 (52%) patients with bacteremic pneumococcal pneumonia. It should be noted that this study was done at a time when erythromycin was the standard therapy for LD. In general, several days were required before a therapeutic effect was evident with this agent. With current therapies the same

degree of radiographic deterioration is unlikely. About half the patients with LD have unilateral pneumonic involvement throughout the course of their illness. The lower lobes are involved most commonly, and pleural effusions are seen in about 35%. The severity of the radiographic findings correlated significantly with the presence of *L. pneumophila* in sputum by direct fluorescent antibody. Lung abscess, empyema, and bulging fissure sign are other radiographic features that are occasionally seen in patients with LD.

Relative bradycardia is seen in about two-thirds of patients with LD. Most patients appear acutely ill. Crackles are generally present on auscultation of the chest. Many experts feel that LD cannot be distinguished from other causes of pneumonia on the basis of clinical features.

One of the remarkable things about LD is the range of extrapulmonary manifestations. Although they occur in about 30% of patients, they can dominate the clinical picture and determine the outcome: There can be a variety of central nervous system manifestations. These include lethargy, confusion, delirium, stupor, coma, seizures, hallucinations, slurred speech, fine or coarse tremors, hyperactive reflexes, absence of deep tendon reflexes, and signs of cerebellar dysfunction, including nystagmus and gait disturbance. There is some evidence that the central nervous system manifestations of legionellosis are due to an autoimmune mechanism and case reports indicate that treatment with high-dosage intravenous immunoglobulin is of benefit. Peripheral neuropathy and cranial nerve palsies, incontinence, or urinary retention are other manifestations. Myocarditis, pericarditis, and endocarditis have all been reported, albeit uncommonly, as extrapulmonary manifestations of LD. Acute renal failure, tubulointerstitial nephritis, tubular necrosis, and rapidly progressive glomerulonephritis are renal manifestations of LD. Reactive arthritis and osteomyelitis are uncommon rheumatologic manifestations.

The clinical course of LD with currently available treatments seems to be different now than what it was when erythromycin was the treatment of choice. This is exemplified by a study of 25 patients with LD who were treated with azithromycin. These patients were all diagnosed by using an assay for *Legionella* urinary antigen and thus early diagnosis (results are available in a few hours in contrast to several days for culture of the microorganism or weeks for a serologic diagnosis) may have accounted for the very favorable outcomes. Twenty-two of twenty-three evaluable patients were cured. At the 10-day follow-up, 45% had signs and symptoms, whereas at the 4- to 6-week follow-up period 35% had signs and symptoms. It is also apparent that different strains of *Legionella* may vary in virulence. Thus in the Murcia, Spain, outbreak involving 800 suspect and definite cases the mortality was 1.1% for definite and 0.9% for suspect cases.

Pontiac fever

In July 1968, an explosive epidemic of acute febrile illness occurred at a county health department facility in Pontiac, Michigan. This self-limiting illness of 2 to 5 days' duration was characterized by fever, headache, myalgia, and malaise. It affected 144 persons. The mean incubation period was approximately 36 hours. Later it was shown that Pontiac fever was due to *L. pneumophila* endotoxin. There has been speculation that Pontiac fever is due to inhalation of free-living amebae that are commonly present in environmental sites containing *Legionella*. Subsequently many outbreaks of Pontiac fever have occurred. It has been associated with exposure to *L. pneumophila* serogroups 1, 6, and 7; *L. feelei*; *L. micdadei*; and *L. anisa*. Most commonly, exposure to contaminated whirlpools, cleaning evaporative condensers, and water fountains has resulted in Pontiac fever. The pathogenesis is still incompletely understood, although some investigators feel it is exposure to *Legionella* endotoxin that results in the symptoms. In support of this is the finding of high concentrations of *Legionella* endotoxin in contaminated water associated with Pontiac fever. One hundred and seventy people who had visited a hotel and leisure complex in Lochgoilhead, a village on the west coast of Scotland, became ill with headache, fever, arthralgia, myalgia, cough, and breathlessness. This illness was initially labeled Lochgoilhead fever but because *L. micdadei* was isolated from the whirlpool spa and 60 of 72 persons with symptoms seroconverted to *L. micdadei*, this was really Pontiac fever. An outbreak of Pontiac fever and legionellosis at a hotel in Oklahoma from March 15 to March 21, 2004, is instructive because the sensitivity and specificity of the *Legionella* urinary antigen test were 35.7% and 100%, respectively, and for serology 46.4% and 90%. Because the urinary antigen test detects *L. pneumophila* serogroup 1 lipopolysaccharide (endotoxin) this outbreak adds to the evidence that *Legionella* endotoxin is the cause of Pontiac fever. In the

Oklahoma outbreak, 3 of 101 (2.9%) persons with Pontiac fever were hospitalized.

Nosocomial (healthcare-associated) Legionnaires' disease

The clinical features of nosocomial LD are not different from those of nosocomial pneumonia due to any bacterium. Immunocompromised patients, especially those receiving corticosteroid therapy, are most susceptible to *Legionella* if it is contaminating the hospital water supply. Indeed, nosocomial LD is all about contamination of the hospital's potable water: if there is no *Legionella* in the potable water there are usually no cases of nosocomial LD. This has led to a debate about whether to conduct routine surveillance for *Legionella* in the potable water and if it is found to eradicate it. However, there are those who maintain that if you do not have a problem with nosocomial LD you should not do routine surveillance. Having battled nosocomial LD for many years my opinion is that all hospitals should carry out routine surveillance of their water for *Legionella*. If it is present, all cases of nosocomial pneumonia should be investigated for *Legionella* and, if found, measures to control or eradicate *Legionella* from the hospital water supply should be taken (Table 141.2).

More recently some investigators have proposed that there is a risk of nosocomial LD if ≥30% of water samples are positive for *Legionella* species. A review of available data suggests that this number has sensitivity of 59% and a specificity of 74%.

Immunocompromised patients should not drink the hospital water (if it is contaminated with *Legionella*) nor should they shower in it. Only sterile water should be used to flush nasogastric tubes. Occasionally unusual sources of nosocomial LD such as contaminated esophageal probes are found. The CDC have issued guidelines for the prevention of healthcare-associated pneumonia but have not made any firm recommendations on the measures outlined in Table 141.2 for eradication or control of *Legionella* in potable water. Copper–silver disinfection and point-of-use filters have proven effective in control of nosocomial LD in some institutions.

Table 141.2 Control of *Legionella* in hot water systems

1.	**Physical measures**
	Maintain water temperature above 55°C
	Ultraviolet irradiation
	Sonication
	Terminal tap water filters
2.	**Chemical measures**
	Prevent scale formation in the pipes
	Biocides: sodium hypochlorite, ozone
	Charcoal filters
	Copper–silver ionization
3.	**Maintain good plumbing practices**
	Dead spaces in calorifiers should be removed
	Dead legs should be removed
	Regular flushing of outlets
	Pumps and calorifiers should be in series not in parallel

DIAGNOSIS

A high index of suspicion is necessary for the diagnosis of sporadic cases of LD. Outbreaks of pneumonia usually trigger a workup for *Legionella* so these are easier to diagnose.

Isolation of the organism from respiratory secretions or other specimens is the definitive diagnostic test. Detection of *Legionella* antigen in urine by enzyme-linked immunosorbent assay is about 80% sensitive and >95% specific. This test is readily available for *L. pneumophila* serogroup 1. Diagnostic kits are also available for detection of antigens of *L. pneumophila* 1 to 6. Legionella antigen is excreted in the urine for days to weeks (rarely up to 1 year) after the onset of pneumonia. It should be noted that the antigen test positivity rate varies with the severity of the disease, being positive in 40% to 53% of mild cases and 88% to 100% of severe cases.

Demonstration of a 4-fold rise in antibody titer between acute and convalescent serum samples using an indirect immunofluorescence whole-cell assay can also be used to diagnose LD. Up to 12 weeks may be required to demonstrate a 4-fold rise in antibody, so serology is not useful for the acute management of this disease. A single or static titer of 1:256 or greater is no longer considered satisfactory for the diagnosis of LD. Polymerase chain reaction applied to respiratory secretions, pulmonary tissue, or pleural fluid is also useful.

TREATMENT (TABLE 141.3)

In the original outbreak of LD it was observed that those who were treated with the macrolide erythromycin had a lower mortality rate than individuals who were treated with other antibiotics. Subsequently a newer macrolide, azithromycin, was shown to have a bactericidal effect in the guinea pig alveolar macrophage model and it had a 5-day post-antibacterial

Table 141.3 Antibiotic treatment of Legionnaires' disease

1. Fluoroquinolones
   Levofloxacin, 750 mg IV (PO for mild cases) once daily
   Moxifloxacin, 400 mg IV or PO once daily (only available PO in most countries)
   Ciprofloxacin, 750 mg IV or PO q12h
2. Macrolides
   Azithromycin, 1 g IV or PO, as a loading dose and then 500 mg IV or PO (due to the long half-life) of azithromycin; only 5 days necessary for treatment of mild cases; 7–10 days for more severe cases
   Erythromycin, 1 g q6h IV; phlebitis is problematic at this dosage (unless infused through a central line); transient deafness, especially in patients who are receiving treatment with diuretics, also occurs at this dosage level
   Clarithromycin, 500 mg q12h IV or PO (IV formulation not available in all countries)
3. Doxycycline, 200 mg loading dose, and then 100 mg q12h IV or PO
4. Rifampin, 300 to 600 mg q12h PO (IV formulation available in some countries). Rifampin should only be used in combination with a macrolide. There are no data supporting a synergistic role when it is used with other classes of antimicrobials. Recent data indicate that treatment with rifampin is associated with longer length of stay and higher bilirubin levels

Note: For cases of mild to moderately severe disease in immunocompetent patients treatment for 7 days is usually sufficient. For immunocompromised patients, treatment for 21 days or longer may be necessary. In these instances individual decisions are necessary and are based on the underlying process that requires the immunosuppression, degree of immunosuppression, and response to therapy. Close follow-up is necessary once treatment is discontinued as relapse is not infrequent.

effect when it was removed from the system, whereas erythromycin in the same model was bacteriostatic and had no post-antibacterial effect. These observations have been confirmed in clinical trials wherein 20 of 21 patients treated with azithromycin were cured.

It is noteworthy that because β-lactam antibiotics do not penetrate into host cells they are ineffective in LD even though they show activity in vitro. Data from a prospective, nonrandomized study indicate that levofloxacin is superior to macrolides for the treatment of severe LD. In this study carried out in Murcia, Spain, 3.4% of the patients receiving levofloxacin had complications compared with 27.2% of those receiving macrolides; the levofloxacin patients had a shorter length of stay: 5.5 vs. 11.3 days. Addition of rifampin to levofloxacin provided no additional benefit. In a study of 139 cases of *L. pneumophila* pneumonia from a prospective series of 1934 consecutive cases of community-acquired pneumonia the overall mortality rate was 5%. Eighty patients received initial therapy with a macrolide and 40 with levofloxacin. Patients who received levofloxacin had a shorter time to defervescence, 2 vs. 4.5 days, and to clinical stability, 3 vs. 5 days. The complication rates were the same in both groups at 25%. The case-fatality rate for those treated with levofloxacin was 2.5% vs. 5% for those treated with macrolides ($p = 0.906$). The median length of stay was 8 days for the levofloxacin-treated group and 10 days for those who received macrolides ($p = 0.014$). In a study of 33 patients admitted to an intensive care unit with LD, fluoroquinolone administration within 8 hours of intensive care unit arrival was associated with decreased mortality. This is not surprising in that there are now several studies showing that administration of antibiotics to elderly patients with community-acquired pneumonia within 4 to 8 hours of presentation to an emergency room is associated with lower mortality than administration of the first dose of an antibiotic at a later time.

In a recent study from Spain the authors compared monotherapy, 11 patients treated with clarithromycin, to combination therapy with clarithromycin and rifampin, 21 patients. All patients were cured; however, the patients who received rifampin had a 50% longer length of stay and a trend toward higher bilirubin levels. A review of the data on rifampin in LD led to the conclusion that it should be considered only for patients with severe disease or significant comorbid conditions including immunocompromised hosts and those refractory to conventional monotherapy regimens.

Many factors should be considered when deciding on the duration of therapy. Immune status and severity of the infection are probably the two most important factors. In mild to moderate cases of LD in immunocompetent subjects with a rapid response to therapy, a duration of 10 days is sufficient. Indeed in this setting a 5-day course of azithromycin, given its long half-life, is probably sufficient. In patients with severe disease and/or immunocompromised state a 3-week course of treatment with either fluoroquinolones or macrolides (other than azithromycin) is necessary to avoid relapse. Careful follow-up of immunocompromised patients to identify relapse of infection early is necessary. One should also remember that in some patients with legionellosis polymicrobial infection may be present.

It is likely, given the small numbers of patients with LD, that we will never get evidence from randomized trials to guide our therapeutic choices and we will have to depend on evidence such as summarized above.

Patients who are seriously ill with LD require management in an ICU. In this setting (sepsis and septic shock) there is evidence that low-dose corticosteroid therapy is beneficial to those who are relatively adrenal insufficient ($\leq$9 μg/mL response in cortisol level to a dose of adrenocorticotropic hormone).

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142. Leprosy

Eduardo Castro-Echeverry, Thomas Lee, Travis Vandergriff, and Clay J. Cockerell

EPIDEMIOLOGY

Leprosy is an ancient disease that has been the cause of great morbidity and mortality for centuries. A 4000-year-old skeleton with evidence of lepromatous leprosy was found in India, and DNA from the causative agent, *Mycobacterium leprae*, has been isolated from a Byzantine skeleton from Israel dated to 300–600 AD. *Mycobacterium leprae* is an unculturable, obligate intracellular, gram-positive, acid-fast bacillus. It multiplies very slowly in the host and grows best at 33°C (91.4°F), which accounts for its predilection for cooler parts of the body such as the skin, testis, anterior segment of the eye, mucous membranes of nasal passages, and ear lobes and extremities.

Leprosy appears to have originated in a single clone in East Africa and then spread to Asia, the Middle East, Europe, and by way of the slave trade into West Africa. Phylogenetic studies using medieval European and modern bacterial DNA suggest a European origin of leprosy in the Americas as well as a paleogeographic relationship between Europe and the Middle East. The disease is now endemic in a number of regions, mainly in Asia, Africa, South America, and the Pacific. It is especially prevalent in India and Brazil. India alone accounts for more than 50% of the global leprosy burden of disease. Isolated pockets of disease are found in many parts of the world, and as a consequence of international travel, affected individuals may be encountered in any location. In the United States, infected patients may be found in any state, but most are in California, Hawaii, Florida, Texas, and Louisiana. Most cases encountered in the United States are seen in immigrants born in endemic regions.

The primary mechanism of transmission is thought to be via nasal inhalation of aerosolized organisms. *Mycobacterium leprae* cannot breach intact skin. Armadillos are known to harbor *M. leprae*, and a number of cases have been traced to exposure to these animals, although direct transmission of the organism to humans has not been definitively demonstrated. Polymerase chain reaction (PCR) studies indicate that nasal carriage of *M. leprae* can occur in persons without clinical evidence of infection and is transient. Serologic studies suggest that most people in endemic areas have been exposed to the organism, resulting in development of mucosal immunity that prevents progressive infection. However, transmission of the organism is likely to occur during subclinical infection. Very few exposed persons ultimately go on to develop clinical disease. The incubation period ranges from 9 months to 20 years. Risk factors for the development of clinically apparent leprosy include high bacterial load of the index case and close (household) contact with, and genetic relatedness to, the index cases. Genetic studies have identified abnormalities in innate and acquired immunity, increasing our knowledge of the genetic predisposition of some individuals to the disease. A locus within the gene *PARK2/PACRG* located on chromosome 6q25–q27 has been associated with susceptibility to leprosy, but the exact mechanism by which it exerts this influence is unclear.

PATHOPHYSIOLOGY

Much like tuberculosis, leprosy is a chronic infectious disease which develops as a consequence of both the host's immune reaction to *M. leprae* as well as from direct effects of bacillary spread and multiplication. Schwann cells infected with bacilli have been shown in mouse models to undergo reprogramming and transformation into progenitor/stem-like cells (pSLC). These reprogrammed cells promote bacterial dissemination by differentiation into other cell types such as muscle and later become incorporated into other body tissues. Those susceptible to infection demonstrate an impaired cell-mediated immune response to the organism. This is thought to result from a genetic predisposition because cases

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cluster in families, and there is a high concordance rate in identical twins.

Mycobacterium leprae has a tropism for nerves that are then damaged as a consequence of immune response to intraneural bacilli as well as physical effects induced by proliferation of bacilli within the nerves. As a result, many of the clinical manifestations are due to peripheral nerve damage with loss of motor and sensory function leading to ulcers, contractures, and loss of tissue substance. Other tissues, such as the skin, may harbor innumerable organisms in some forms of the disease, and deforming cutaneous nodules may develop. Immune response to organisms in skin leads to severe forms of vasculitis with extensive cutaneous necrosis.

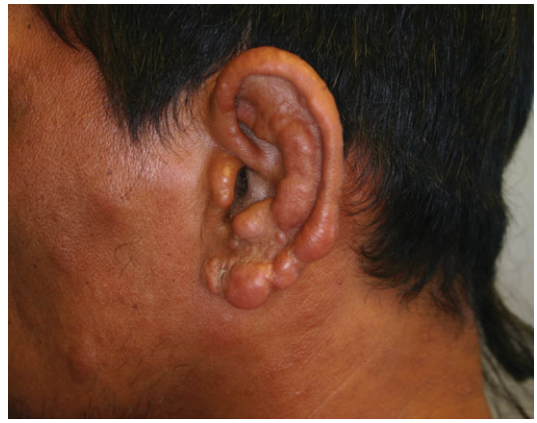

Figure 142.1 Lepromatous leprosy on the ear.

CLASSIFICATION AND CLINICAL PRESENTATION

There may be a number of different clinical presentations in patients with leprosy, depending on the level of immunity and the duration of the disease. Individuals with the early indeterminate form present with one or more scaly hypopigmented anesthetic macules of the skin appearing initially on the face, although the limbs, trunk, or buttocks may be involved. If untreated, this may progress to any form of the disease. Others present only with sensorimotor neuropathy with enlargement of the peripheral nerves without skin lesions. Nerves affected most commonly include the ulnar and median nerves, the common peroneal nerve, the posterior tibial nerve, and the facial and great auricular nerves. Other areas of the body, such as the nasopharynx, eyes, and testicles, may also be involved.

Classically, patients present with symptoms that can range from one pole (tuberculoid) to another (lepromatous) or anywhere in between (borderline tuberculoid, borderline, or borderline lepromatous). Tuberculoid leprosy presents with a small number of asymmetric skin lesions that are hypopigmented, have sharp borders, and are associated with anesthesia. Commonly, cutaneous nerves are enlarged and few bacilli are present on biopsy (paucibacillary form). Lepromatous leprosy presents as widely distributed symmetric skin lesions that can manifest as macules, papules, plaques, or nodules, which are red to brown (Figure 142.1). Biopsy shows many bacilli (multibacillary form). Borderline cases may present anywhere between these two extremes.

The World Health Organization (WHO) schema is the most commonly used classification system and is based on the number of skin lesions and number of bacilli present in smears. Patients with five or fewer skin lesions without evidence of bacilli on skin smears are considered paucibacillary, whereas those with six or more skin lesions with or without bacilli on skin smears are considered to be multibacillary. Classification of patients into multibacillary and paucibacillary groups determines the duration of their treatment.

Leprosy in reaction refers to clinical disease produced when there is a change in the host's immune response to *M. leprae*. There are two forms of reactional leprosy. Type 1 reactions are induced by cell-mediated immunity and are referred to as *upgrading* and *downgrading* reactions. Upgrading reactions are characteristically seen in patients with borderline lepromatous disease who undergo a shift toward more tuberculoid (paucibacillary) forms. These may develop after induction of therapy. Downgrading reactions occur with transformation from a tuberculoid to a more lepromatous (multibacillary) form and often develop in the absence of treatment. Both may appear similar clinically and are manifest by erythema and edema of existing skin lesions associated with painful neuropathy and ulceration.

Type 2 reactions are immune complex mediated and include erythema nodosum leprosum (ENL) and Lucio's phenomenon. Both of these are manifestations of immune complex-mediated vasculitis that lead to prominent inflammation and often ulceration with acute damage to nerves. Patients present with fever; multiple erythematous tender nodules; and varying degrees of neuritis, edema, arthralgias, leukocytosis, iridocyclitis, pretibial periostitis, orchitis, and nephritis.

Patients infected with human immunodeficiency virus (HIV) do not have an increased incidence of leprosy, and coinfection with *M. leprae* and HIV appears to have minimal effect on the course of either leprosy or HIV.

DIAGNOSIS

The diagnosis is primarily clinical and is based on the presence of one of three cardinal findings: hypopigmented or reddish patches with definitive loss of sensation, thickened peripheral nerves, and demonstration of acid-fast bacilli.

Definitive diagnosis of *M. leprae* is difficult, as the organism cannot be cultured in vitro. The gold standard for the diagnosis of leprosy is a skin biopsy specimen obtained from the advancing edge of an active lesion and detection of bacilli in tissue sections using the Fite–Faraco staining method. The slit skin smear has a high specificity but a low sensitivity (10%–50% of all leprosy patients are smear negative). Slit skin smears may be useful as an adjunctive procedure to semiquantitate acid-fast organisms in infected skin for monitoring the response of patients during and after treatment.

Serologic tests have been developed to detect IgM antibodies to phenolic glycolipid I (PGL-I), a glycolipid unique to *M. leprae*. The sensitivity of these tests depends on the type of leprosy, and these tests are most useful in distinguishing those individuals with lepromatous leprosy from those with paucibacillary or tuberculoid leprosy after diagnosis. Although individuals positive for PGL-I have approximately an 8-fold risk for developing clinically apparent leprosy, it is not a useful screening test in the general population, as a positive test does not necessarily predict development of the disease.

Another major recent advance in the laboratory diagnosis of leprosy is the development of PCR assays that have reported specificity of 100% and a sensitivity ranging from 34% to 80% in patients with paucibacillary forms of the disease to greater than 90% in patients with multibacillary forms of the disease.

TREATMENT

Treatment depends on whether the individual has paucibacillary or multibacillary disease. Virtually all patients are treated with multidrug therapy with monthly supervision as first implemented by the WHO in 1981 (Table 142.1), which has been modified several times since then.

Table 142.1 World Health Organization-recommended drug therapy

	Paucibacillary	Multibacillary
Monthly, supervised	600 mg rifampin	600 mg rifampin and 300 mg clofazimine
Daily, unsupervised	100 mg dapsone	100 mg dapsone and 50 mg clofazimine
Duration of therapy	6 mo	12 mo
Follow-up	2 yr	5 yr

Dapsone and clofazimine are weakly bactericidal when used alone, although they are mycobactericidal and kill more than 99% of bacilli when used in combination. Rifampin is highly bactericidal alone. No antileprosy drugs should be prescribed in isolation because of the likelihood of developing resistance. Administration of antibiotics renders the patient noninfectious in a matter of weeks.

Paucibacillary patients (fewer than five lesions) receive a supervised dose of rifampin, 600 mg orally once per month for 3 months, and a daily unsupervised dose of dapsone, 100 mg orally for 6 months. At the end of 6 months, therapy is discontinued. Multibacillary patients receive a supervised dose of rifampin, 600 mg orally once monthly, a 300-mg dose of clofazimine, an unsupervised daily dose of dapsone, 100 mg orally, and a 50-mg daily oral dose of clofazimine for 12 months. Relapses should be treated in the same manner as the initial disease, providing there is no drug resistance.

Where only a single lesion is present, the WHO recommends treatment with a single oral dose combination of rifampin, 600 mg, ofloxacin, 400 mg, and minocycline, 100 mg. The cure rate at 18 months of follow-up in patients receiving a single dose is slightly less than in those who receive 6 months of treatment (47% versus 55%), and relapse rates appear to be slightly higher in these patients. However, the simplicity of this regimen and the fact that the overwhelming majority of these patients show clinical improvement makes this a feasible treatment option in the appropriate clinical context.

All patients are evaluated for relapse at least monthly. Most programs continue inspections for 5 to 10 years in all patients. Relapse rates vary between 1% and 3% in both paucibacillary and multibacillary patients. Patients should be instructed to recognize the signs and symptoms of recurrent disease as well as adverse reactions to medications. It may take up to 5 years for

Table 142.2 Recommended treatment of reversal reactions

	Type I reaction	Erythema nodosum leprosum
Mild	Symptomatic	NSAIDs, symptomatic
Severe	40–60 mg prednisone	40–60 mg prednisone or 300 mg clofazimine (chronic) or 300–400 mg thalidomide
Duration	Slowly taper as tolerated	Slowly taper prednisone as tolerated Taper clofazimine to 100 mg in 12 months Taper thalidomide as tolerated to 100 mg, discontinue as soon as indicated

Note: All patients should receive prednisone in the presence of neuritis.
Abbreviation: NSAIDs = nonsteroidal anti-inflammatory drugs.

bacilli to be completely cleared in patients with multibacillary disease. Although many of the neurologic problems may be permanent, skin lesions usually disappear within 1 year of treatment, and reappearance of skin lesions is highly suggestive of relapse.

Major drug side effects are relatively uncommon with present regimens. Clofazimine may cause gastrointestinal symptoms and a purplish skin discoloration, both of which clear with discontinuation of the drug. Dapsone often causes mild anemia, although severe anemia may result in patients with glucose-6-phosphate dehydrogenase deficiency, so all patients should be tested for this enzyme before initiation of therapy. Other side effects include agranulocytosis, cutaneous eruptions, peripheral neuropathy, gastrointestinal distress, and nephrotic syndrome. Rifampin rarely causes adverse effects but may cause orange discoloration of the urine, stool, and other body fluids. Pregnant women have safely taken dapsone and clofazimine, but experience with rifampin is limited.

TREATMENT OF REVERSAL REACTIONS

Reversal reactions occur in up to 25% of patients, usually during therapy. Early diagnosis and prompt treatment of reversal reactions is of great importance to prevent many of the deforming complications of leprosy (Table 142.2).

Mild reactions can be treated symptomatically; however, severe type 1 reactions with neuritis or silent neuropathy require prompt initiation of systemic glucocorticoid therapy, starting at a minimum dose of 40 to 60 mg of prednisone, tapering once the reaction is controlled. In patients with nerve damage from reactional leprosy that is present for 3 to 6 months, the response to therapy is less than 67%. When present for longer than 6 months, the response to therapy is even poorer.

Mild to moderate type 2 reactions can be treated with nonsteroidal anti-inflammatory drugs and other symptomatic modalities. Severe ENL or the presence of neuritis requires prednisone (as prescribed in type 1 reactions). Clofazimine is useful for chronic reactions, and its use has been credited with the overall decrease of ENL in leprosy. Thalidomide, 300 to 400 mg orally, will suppress ENL within 48 hours and is considered the drug of choice for young men with severe ENL. Its high teratogenic potential has prevented its widespread use. Azathioprine, methotrexate, and cyclosporine have been used to treat type 2 reactions; results have been mixed. More controlled studies are needed to evaluate efficacy of these medications.

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143. Meningococcus and miscellaneous neisseriae

Chuen-Yen Lau and Edmund C. Tramont

Meningococcal infection, first recognized over 2 centuries ago as epidemic cerebrospinal fever, occurs worldwide as endemic sporadic cases but with the potential to spread and expand into an epidemic. Humans are the only natural host for the bacteria. Transmission of the organism occurs from person to person by direct contact with colonized respiratory secretions or airborne droplets with subsequent colonization of the nasopharynx. Nasopharyngeal carriage approximates 5% to 15% in non-epidemic periods but may approach 50% to 95% during epidemics. The carriage rate is also increased when there is crowding, such as in military barracks, dormitories, prisons, convocations, and sporting events. The oropharyngeal and nasopharyngeal carriage may persist for several weeks to several months as part of the normal nasopharyngeal flora. Sexual transmission of meningococci in women and homosexual men may result in anogenital carriage.

Most cases of disease (e.g., bacteremia, meningitis) occur in children between 6 months and 5 years of age (Figure 143.1). However, case-fatality rates are highest in the 15- to 24-year age group. With rare exceptions, invasive meningococci have a polysaccharide capsule that forms the basis for serogrouping of strains, and, except for serogroup B, is the principal bacterial antigen to which protective immunity develops (see below). Invasive disease occurs almost exclusively in persons who lack specific bactericidal anti-meningococcal antibody to the invading meningococcal strain.

However, there are four known situations where antibodies may not be protective: (1) individuals with complement component or properdin deficiencies are at an increased risk for developing invasive meningococcal infections because their serum loses the ability of complement-antibody-mediated lysis (bactericidal activity) of the meningococcal organism; hence, complement deficiency, most often of the terminal components, or properdin deficiency should be considered in persons with recurrent episodes of invasive meningococcal infection; (2) asplenic individuals are also at increased risk for suffering invasive meningococcal disease because of decreased efficiency of clearing of the encapsulated invading microorganisms from the blood; on rare occasions, persons may (3) develop serum immunoglobulin A (IgA) antibodies that block the bactericidal action of immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies or (4) possess genetic upper airway surfactant protein mutations that result in an impaired local first-line innate immune defense. All of these individuals should be periodically vaccinated (see below) to maintain as high a titer of anti-meningococcal antibodies as possible.

CLINICAL FEATURES

As with most other invasive gram-negative bacteria, the clinical consequences of meningococcal infection are primarily the result of meningococcal endotoxin (lipopolysaccharide) release and subsequent activation of the procoagulation, anticoagulation, fibrinolysis, complement, and kallikrein–kinin cascades resulting in the excessive release of various inflammatory mediators ("cytokine storm"). The clinical manifestations of meningococcal infection range from a mild transient bacteremia to fulminant meningococcemia, also referred to as Waterhouse–Friderichsen syndrome or purpura fulminans (Figure 143.2), with or without concurrent bacterial meningitis. Unless treated early, the mortality rate of the latter is high.

Most often, *Neisseria meningitidis* acquisition results in asymptomatic colonization of the nasopharynx and oropharynx. The mildest form of invasive disease, a transient bacteremia, begins insidiously with fever, malaise, and symptoms of an upper respiratory tract infection. A few petechial skin lesions may appear, but neither signs nor symptoms of sepsis or meningitis

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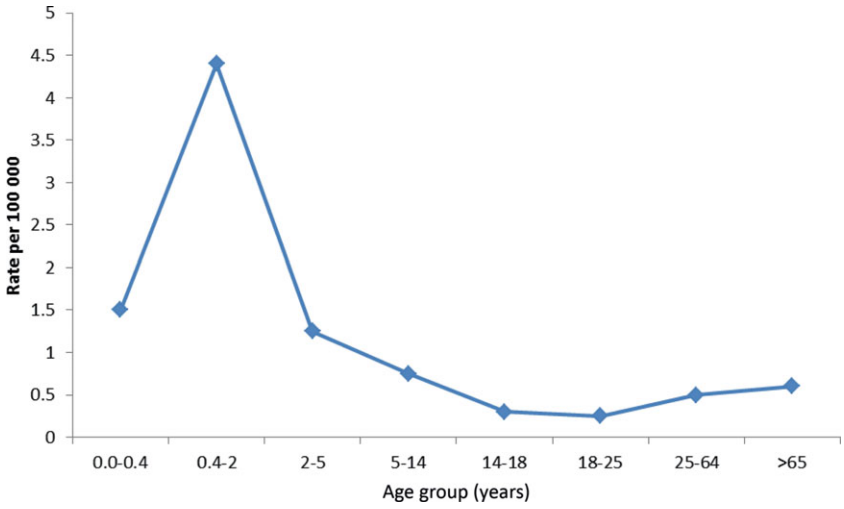

Figure 143.1 Rates of meningococcal disease by age group.

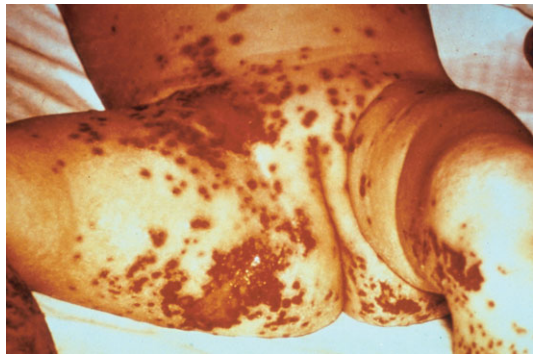

Figure 143.2 Purpura fulminans (Waterhouse–Friderichsen syndrome or severe ecchymotic rash).

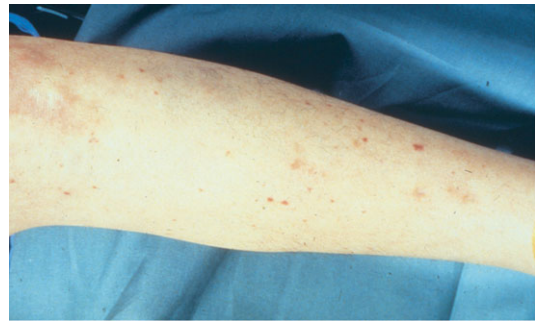

Figure 143.3 Petechial rash lower extremity.

develop. Signs and symptoms usually resolve spontaneously within 24 to 48 hours. However, the transient bacteremia may progress to acute meningococcemia heralded by fever, chills, malaise, weakness, headache, myalgias, and nausea and/or vomiting.

Skin manifestations, especially a petechial rash (Figure 143.3), should raise the index of suspicion for invasive meningococcal infection. They commonly appear in crops on the ankles, wrists, axilla, arms, legs, trunk, and mucous membranes, whereas the palms, soles, neck, and face are usually spared. The rash may also be urticarial, maculopapular, ecchymotic, or gangrenous depending on the degree of vascular pathology. In severe invasive meningococcal disease, the rash rarely fails to develop. Fulminant meningococcemia complicates acute meningococcemia in 5% to 15% of cases and is associated with the rash progressing into massive skin and mucosal hemorrhage, disseminated intravascular coagulopathy (DIC), and vascular collapse (Waterhouse–Friderichsen syndrome). Adrenal hemorrhage may occur despite appropriate antibiotic therapy.

Meningitis usually occurs along with the manifestations of meningococcemia but not always. Clinically, meningococcal meningitis resembles acute meningitis of any cause, presenting with fever, headache, altered sensorium/cognition, and nuchal rigidity.

On rare occasions, a chronic meningococcemia develops. This is characterized by intermittent febrile episodes, lasting 2 to 10 or more days, accompanied by a variety of skin lesions (macular, maculopapular, petechial, ecchymotic, or pustular), arthralgias or arthritis, myalgias, and splenomegaly. This manifestation may last for months and is sometimes fatal, but it usually

resolves spontaneously. Occasionally, *N. meningitidis* may cause oropharyngitis, sinusitis, pneumonia, conjunctivitis, endophthalmitis, proctitis, urethritis, cervicitis, immune-mediated arthritis, endocarditis, myocarditis, pericarditis, or pelvic inflammatory disease (PID). Nonspecific helpful laboratory abnormalities include an elevated white blood cell count, C-reactive protein and/or procalcitonin levels.

CULTURE AND LABORATORY FINDINGS

N. meningitidis is an aerobic, oxidase-positive, gram-negative diplococcus (coffee bean shape) that grows best at 35°C to 37°C (95°F to 98.6°F) in a moist environment of 5% to 7% carbon dioxide (candle jar). The gold standard for diagnosis of systemic meningococcal infection is the isolation of *N. meningitidis* by culture from a usually sterile body fluid such as blood and/or cerebrospinal fluid (CSF) (most common), or synovial, pleural, or pericardial fluid. For culture of a normally sterile site, nonselective culture media are standard but a selective antibiotic-containing culture medium, such as Thayer–Martin, Martin–Lewis, or New York City culture medium, is necessary to reduce the overgrowth of commensals when the culture specimen is obtained from a nonsterile site such as the oropharynx, urethra, or rectum.

In meningococcal meningitis, the frequency of positive blood cultures is 50% to 60% and the frequency of positive CSF cultures is 80% to 90%. Isolation of the organism by culture not only confirms the etiology, but also allows antibiotic susceptibility testing, which has become important in light of increased antibiotic resistance, especially to the penicillins. Gram stain and culture of a skin lesion can increase the diagnostic yield, although a negative result does not exclude *N. meningitidis*. As mentioned earlier a number of rapid diagnostic tests (RDTs) are available ranging from PCR to simple dipstick and agglutination tests.

Chemistry and cytologic findings suggestive of bacterial meningitis include a CSF glucose concentration below 45 mg/dL (2.5 mmol/L), a protein concentration above 500 mg/dL, and a white cell count above 1000/μL. The CSF is generally cloudy with a leukocytosis consisting predominantly of polymorphonuclear neutrophils associated with hypoglycorrhachia. However, one or more of the classic findings is often absent in meningococcal meningitis. The Gram stain of the CSF is positive in about 75% of cases (Figure 143.4).

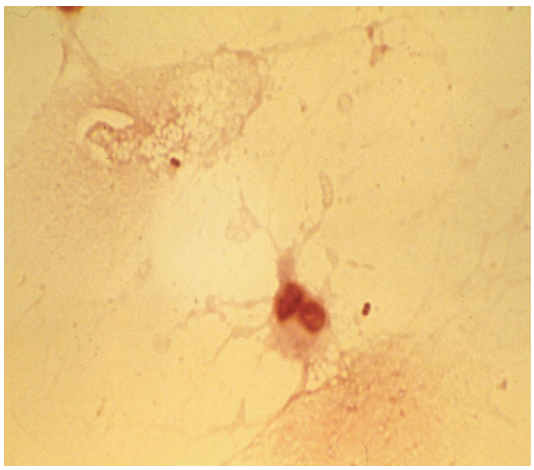

Figure 143.4 Gram stain of CSF: note gram-negative diplococci and polymorphonuclear leukocyte.

Nonspecific helpful laboratory abnormalities include an elevated serum white blood cell count, C-reactive protein, and/or procalcitonin levels.

N. meningitidis is serogrouped based on the distinct chemical composition of its polysaccharide capsule. The meningococcus has been classified as serogroups A, B, C, D, 29E, H, I, J, K, L, W (W-135), X, Y, Z, and nontypeable (indicates organism is nonencapsulated). Serogroups A, B, C, W, and Y are responsible for the vast majority of cases of invasive disease. With rare exceptions, invasive meningococci are encapsulated, attesting to the virulence conveyed by the polysaccharide capsule. In contrast, meningococci colonizing mucous membranes are usually not encapsulated.

Commercial latex agglutination kits, which can also be used on body fluids such as CSF and urine, utilize latex beads coated with antibodies to meningococcal capsular antigens to detect five capsular types: A, B, C, Y, and W, but the sensitivity for serogroup B is relatively low.

A number of rapid diagnostic tests (RDTs) are available ranging from PCR to simple dipstick and agglutination tests. Advantages of these tests over culture are rapidity, reliability in the setting of concomitant antibiotics, and in the case of PCR, simultaneous testing for infection due to *N. meningitidis, Streptococcus pneumoniae, Haemophilus influenzae*, or other microorganisms.

THERAPY

Ceftriaxone is the drug of choice for meningococcal disease. Ceftriaxone therapy should be administered within 30 minutes of considering the diagnosis of meningococcal meningitis and is

Table 143.1 Treatment of meningococcal meningitis

Antibiotic	Scenario	Dosing	Comment[a]
Ceftriaxone	Preferred treatment	Adults: 2 g IV q12h Children: 100 mg/kg IV (up to 4 g) in 1–2 doses per day	Good CNS penetration
Chloramphenicol	Beta-lactam allergy	Adults: 12.5 mg/kg IV (up to 6 g/day) q6h Children: 75–100 mg/kg IV (up to 2–4 g/day) in 1–2 doses per day	Concentrates in CSF; potential to cause irreversible aplastic anemia; rare resistance
Meropenem[b]	Alternative	Adults: 2 g IV q8h	Limited data for use in children
Moxifloxacin[b,c]	Alternative	Adults and adolescents with skeletal maturity: 400 mg q24h	Resistant isolates have been encountered
Penicillin G	Penicillin MIC <0.1 μg/mL	Adults: 300 000 U/kg/day IV divided q4h Children: 250 000–300 000 U/kg/day IV divided q4h	Limit 24 million U/day; penicillin resistance has been reported since 1988

[a] Treatment is 7 days, but may be extended based on clinical scenario or if the organism is not fully sensitive to the selected regimen.
[b] Option for ceftriaxone, penicillin, and other β-lactam allergic patients.
[c] Other quinolones have been successful. Abbreviations: MIC = minimal inhibitory concentration; CNS = central nervous system; CSF = cerebrospinal fluid.

administered intravenously (IV), at least initially. Infected persons should receive 2 g IV every 12 hours for at least 7 days. Those who are β-lactam allergic should receive a fluoroquinolone or chloramphenicol. Chloramphenicol- and fluoroquinolone-resistant isolates have been encountered, but are rare. Although use of penicillin G has been limited since reports of resistance in the late 1980s, meningococcal meningitis is well treated with penicillin G once the isolate is proven to be penicillin susceptible (minimum inhibitory concentration [MIC] < 0.1 μg/mL). Seven days of therapy is usually sufficient but may be lengthened based on clinical judgment regarding the severity of illness, patient response, or if testing demonstrates reduced sensitivity to the selected regimen (Table 143.1).

Since exact etiology is typically unknown upon presentation, initial treatment must cover potential causes of meningitis beyond *N. meningitidis*. Empiric antimicrobial therapy is usually given for cases of presumed bacterial meningitis based on age and immune status. For immunocompetent infants less than 1 month of age, empiric treatment is chosen to also cover group B streptococcus, *Escherichia coli* and listeria. For immunocompetent patients between 1 month and 50 years of age, penicillin-resistant *S. pneumoniae, H. influenzae*, and *N. meningitidis* need to be covered. Infections with these three organisms have significantly decreased with increased vaccine coverage.

Without a specific etiologic diagnosis, immunocompetent persons between 1 month and 50 years of age should receive initial empirical therapy with a broad-spectrum cephalosporin antibiotic, especially ceftriaxone or cefotaxime, plus vancomycin. Meropenem may be substituted for the cephalosporin if neither cefotaxime nor ceftriaxone can be administered. Dexamethasone may be added when neurologic deficits and sequelae of inflammation are of concern. Although dexamethasone has not been specifically shown to be of benefit in meningococcal meningitis, it is usually added during empiric therapy to reduce central nervous system inflammation.

Supportive care is extremely important in all cases of meningitis. Potential complications such as purpura fulminans, DIC, acute respiratory distress syndrome (ARDS), neurological/cognitive sequelae, myocardial involvement, volume depletion, acidosis, and adrenal insufficiency should be anticipated.

Long-term sequelae include hearing loss, other cranial palsies, and cognitive dysfunction. Treatment of myocardial failure can help to ameliorate pulmonary edema and poor peripheral perfusion. Adjunctive steroid therapy is indicated when acute adrenal insufficiency is a possibility, especially when the patient has progressed into the Waterhouse–Friderichsen syndrome or is obtunded. The primary treatment of DIC is aimed at the underlying cause, in this case *N. meningitidis*. Protein C concentrate has been investigated as a potential strategy to treat coagulopathy and purpura fulminans.

PREVENTION

Methods of prevention for meningococcal infection include respiratory droplet precautions, disease surveillance, antimicrobial chemoprophylaxis after identification of an index case, vaccination prior to possible exposure, e.g., military recruits, college freshmen, etc., and avoidance of risk factors, e.g., crowding. Routine young adult and adult immunization is not warranted because most cases of *N. meningitidis* are sporadic. Most often, *N. meningitidis* is harbored in the nasopharynx and/or oropharynx as a commensal in asymptomatic carriers. The organism is spread through direct contact, especially respiratory droplets. The risk of contracting a symptomatic *N. meningitidis* infection is approximately 4 cases per 1000 among persons who have had "close contact" with a known carrier or patient with a virulent strain (defined as causing invasive disease). Close contacts are defined as persons living in the same household, dormitory, or barrack; attending a day-care center; handling clinical specimens or cultures; or anyone who has spent >4 hours with the index case from 10 days prior to the onset of illness through 24 hours after initiation of appropriate antibiotic therapy. This is to cover the 1- to 10-day incubation period for groups such as airline passengers, cruise shipmates, nursing home residents, and healthcare workers (Table 143.2).

Table 143.2 Considered close contact of an index case

All household members
Day-care and preschool classmates, attendees, and workers
Healthcare workers with contact with oral and/or respiratory secretions from the index case
Workers and classmates in boarding schools or camps
Living in a common military barrack
Sharing an aircraft or boat cabin, especially if sitting next to the index case
Cruise shipmates with >4 hours contact with the index case
Laboratory workers handling culture from an index case

Antimicrobial chemoprophylaxis

The risk of developing secondary invasive disease after exposure to a close contact is greatly diminished by chemoprophylaxis: administering prophylactic antibiotics to individuals who have had close contact to an index case, e.g., dormitory, barracks, living in the same house, prison, etc. Antibiotics should be administered as early as possible, ideally within 24 hours of identification of the index case. Chemoprophylaxis more than 14 days after exposure is not necessary unless reexposure occurs. Since pharyngeal cultures of the exposed individual are not helpful for determining the need for prophylaxis, obtaining cultures should not delay administration of prophylactic antibiotics.

Ceftriaxone and rifampin are the drugs most often used for chemoprophylaxis. Effective alternatives include ciprofloxacin and azithromycin, although ciprofloxacin-resistant group B meningococcus has been reported (Table 143.3).

Vaccine immunoprophylaxis

Several meningococcal vaccines are available, but only recently has a group B vaccine been developed. Menomune (MPSV4), a serogroup A, C, W, and Y unconjugated polysaccharide

Table 143.3 Antibiotics used for chemoprophylaxis of *Neisseria meningitidis*

Antibiotic (route)	Age group	Dose	Duration	Comments
Ceftriaxone (IM)	Children <15 years Older children and adults	125 mg 250 mg	Once	A regimen of choice
Rifampin (oral)	Children < 1 month Children ≥ 1 month Adults	5 mg/kg q12h 10 mg/kg q12h 600 mg q12h	2 days	A regimen of choice Not recommended for pregnant women May reduce reliability of oral contraceptives Causes reddish-orange discoloration of bodily fluids
Ciprofloxacin (oral)	Adults	500 mg	Once	Not recommended for persons <18 years or pregnant/lactating women Can be used in children if no alternative available
Azithromycin (oral)	Children < 15 years Children > 15 years	10 mg/kg 500 mg	Once	• Not routinely recommended • May be used in areas with ciprofloxacin resistance

Table 143.4 Vaccination recommendations in the USA

Age group	Vaccine	Series/regimen
6 wk–18 mo	Conjugated bivalent HibMenCY (MenHibrix)	4 doses at 2, 4, 6, and 12–15 mo; quadrivalent vaccines (conjugated MenACWY-D [Menactra] or MenACWY-CRM [Menveo]) can be substituted
9 mo–24 mo	Conjugated quadrivalent MenACWY-D (Menactra)	2 doses recommended
>2 yr	Conjugated quadrivalent MenACWY-D (Menactra) or MenACWY-CRM (Menveo) or Unconjugated quadrivalent MPSV4 (Menomune)	Single dose
10–25 yr	Serogroup B (Trumenba)	3 doses at 0, 2, and 6 mo

1. Persons at increased risk (complement deficiency, asplenia, inherited surfactant protein deficiency, unique social situations, i.e., MSM, homelessness, travel to endemic areas such as sub-Saharan Africa, Mecca) should receive booster vaccinations on or about every 5 years.
2. These safe vaccines can be given as a booster at any time, regardless of previous vaccine history.
Adapted from Advisory Committee on Immunization Practices (ACIP) 2012.

vaccine, has been available in the United States for several decades. Menactra (MCV4), a quadrivalent meningococcal polysaccharide vaccine conjugated to diphtheria toxoid, became available in 2005. Another quadrivalent meningococcal polysaccharide vaccine conjugated to a mutant diphtheria toxin, Menveo (CRM197), was approved by the US Food and Drug Administration (FDA) in 2010. MenHibrix/HibMenCY combination conjugate vaccines against meningococcus serogroups C and Y and *H. influenzae* type b were approved in 2012 for infants and children aged 6 weeks to 18 months. In 2013, the European Commission approved a meningococcal serogroup B vaccine, Bexsero, for use in individuals over 2 months of age in the European Union; and in 2014 the US FDA followed suit with Trumenba, for persons aged 10 to 25 years. The major challenge in the development of the meningococcal serogroup B vaccine has been that the serogroup B polysaccharide is a poor immunogen.

In the United States, meningococcal vaccination against serogroups A, C, W, and Y is appropriate for persons over 6 weeks of age. The specific vaccine and schedule depend upon age, host factors, e.g., complement deficiency, asplenia, inherited surfactant protein abnormalities, unique social situations (e.g., men who have sex with men [MSM], homelessness, travel to high risk areas such as sub-Saharan Africa, Mecca), and prior history of vaccination. Recommendations are presented below (Table 143.4).

Since vaccine immunoprophylaxis cannot be relied on to prevent meningococcal disease after exposure to an index case because of the 4- to 10-day lag time to develop a protective antibody titer, it is recommended primarily for high-risk groups with an increased chance of future exposure, such as persons moving into a dormitory or military barracks, and high-risk individuals with an increased chance of developing invasive disease, such as persons with terminal complement component deficiencies, those who have anatomic or functional asplenia, and MSM. Immunization is also recommended for travelers to areas in which *N. meningitidis* is hyperendemic (Nepal, India [New Delhi], Mecca, and the "meningitis belt" of sub-Saharan Africa, which stretches from Senegal in the west to Ethiopia in the east), particularly if their stay is prolonged.

As with the other polysaccharide-based vaccines, *H. influenzae* and *S. pneumoniae*, the concern that vaccination with these four serogroup vaccines would lead to replacement by other serogroups has not materialized.

INFECTIONS WITH OTHER *NEISSERIA* SPECIES

The nonpathogenic *Neisseria* species (*N. bacilliformis, N. lactamica, N. sicca, N. flava, N. subflava, N. mucosa, N. flavescens, N. cinerea, N. macacae, N. elongata*, and *N. polysaccharea*) are usually commensals of the oropharynx and nasopharynx. Infections caused by these organisms are extremely rare, occurring primarily in immunosuppressed hosts, especially those who are hypogammaglobulinemic or have defective antibody production (i.e., chronic lymphocytic leukemia). The relative lack of virulence of these organisms is attributed to the absence of encapsulation, and hence they have no predilection to resist bacterial lysis by nonspecific components of the

blood or to invade the meninges. Thus they are easily controlled by normal innate host defense mechanisms.

Because these organisms normally reside in the oropharynx, local extension occurs most often as part of a mixed infection, most commonly to the ear, sinuses, and lung. Conjunctivitis, meningitis, endophthalmitis, endocarditis, and urethritis have also been reported, attesting to the common tissue tropism that these sites share with the nasopharynx. These nonpathogenic *Neisseria* are easily treated with penicillin, cephalosporins, or quinolone antibiotics.

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144. *Listeria*

Bennett Lorber

INTRODUCTION

Listeria monocytogenes is an infrequent cause of illness in the general population, but, in certain groups, including neonates, pregnant women, elderly persons, and those with impaired cell-mediated immunity, whether due to underlying disease or immunosuppressive therapy, it is an important cause of life-threatening bacteremia and meningoencephalitis. Increasing interest in this organism has arisen from concerns about food safety following lethal foodborne epidemics.

MICROBIOLOGY

Listeria monocytogenes is a small, facultatively anaerobic, nonsporulating, catalase-positive, oxidase-negative, gram-positive rod that grows readily on blood agar, producing incomplete β-hemolysis. It possesses polar flagellae and exhibits a characteristic tumbling motility at room temperature (25°C). Optimal growth occurs at 30°C to 37°C, but, unlike most bacteria, *L. monocytogenes* also grows well at refrigerator temperature (4°C to 10°C), and, by so-called cold enrichment, it can be separated from other contaminating bacteria by long incubation in this temperature range. Selective media are available to isolate the organism from specimens containing multiple species (food, stool) and are superior to cold enrichment.

In clinical specimens, the organisms may be gram variable and may look like diphtheroids, cocci, or diplococci. Routine growth media are effective for growing *L. monocytogenes* from normally sterile specimens (cerebrospinal fluid [CSF], blood, joint fluid), but media typically used to isolate diarrhea-causing bacteria from stool cultures inhibit listerial growth. Laboratory misidentification as diphtheroids, streptococci, or enterococci occurs all too often, and the isolation of a "diphtheroid" from blood or CSF should always alert one to the possibility that the organism is really *L. monocytogenes*.

Seven listerial species are recognized (*Listeria monocytogenes*, *Listeria seeligeri*, *Listeria welshimeri*, *Listeria innocua*, *Listeria ivanovii*, *Listeria grayi*, and *Listeria marthii*), but *L. monocytogenes* is almost exlusively responsible for human infection. There are at least 13 serotypes of *L. monocytogenes*, based on cellular O and flagellar H antigens, but almost all disease is due to types 4b, 1/2a, and 1/2b, limiting the utility of serotyping for epidemiologic investigations. A number of newer molecular techniques, including pulsed-field gel electrophoresis, ribotyping, and multilocus enzyme electrophoresis, have been employed to separate isolates into distinct groups and have proved useful for investigating epidemics.

EPIDEMIOLOGY

Listeria monocytogenes is an important cause of zoonoses, especially in herd animals. It is widespread in nature, being found commonly in soil and decaying vegetation and as part of the fecal flora of many mammals. The organism has been isolated from the stool of approximately 5% of healthy adults with higher rates of recovery reported from household contacts of patients with clinical infection. Many foods are contaminated with *L. monocytogenes*, and recovery rates of 15% to 70% or more are common from raw vegetables, raw milk, fish, poultry, and meats, including fresh or processed chicken and beef available at supermarkets or deli counters. Ingestion of *L. monocytogenes* must be a very common occurrence.

Listeriosis was made a nationally reportable disease in 2000 in the United States. Two active surveillance studies performed by the Centers for Disease Control and Prevention (CDC) in the 1980s indicated annual infection rates of 7.4 per million population, accounting for approximately 1850 cases per year in the United States, with 425 deaths. By 1993, following food industry regulations instituted to minimize the risk of foodborne

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listeriosis, the annual incidence had declined to 4.4 cases per million. From 1996 through 2003 the crude incidence decreased 26%; estimated cases in the United States were 2228 and 1803 in 1996 and 2003, respectively, and deaths were 462 and 378.

The highest infection rates are seen in infants ≤1 month and in adults >60 years of age. Pregnant women account for about 30% of all cases and 60% of cases in the 10- to 40-year age group. Almost 70% of nonperinatal infections occur in those with hematologic malignancy, acquired immunodeficiency syndrome (AIDS), bone marrow or solid organ transplants, or in those receiving corticosteroid therapy, but seemingly healthy persons may develop invasive disease, particularly those older than 60 years.

Nonperinatal listeriosis is almost always the result of foodborne infection. Listeriosis is a relatively rare foodborne illness (~1% of US cases) but is associated with a case-fatality rate of 16% to 20% (second only to *Vibrio vulnificus* at 35% to 39%) and causes approximately 19% to 28% of all foodborne disease-related deaths. Mortality risk factors include nonhematologic cancers, steroid medication, and renal disease.

Numerous foodborne outbreaks resulting in invasive disease (e.g., bacteremia, meningitis) have been documented, with vehicles including milk, soft cheeses, butter, smoked fish, ready-to-eat pork products, hot dogs, deli-ready turkey, sprouts, taco or nacho salads, and cantaloupes. A 2002 outbreak due to contaminated turkey deli meat resulted in the recall of more than 30 million pounds of food products, one of the largest meat recalls in US history. In 2011, *L. monocytogenes*-contaminated cantaloupes were responsible for the deadliest foodborne outbreak in US history, with 28 states reporting illness in 146 persons and death in 30 (21% mortality). The importance of food as a source of sporadic listeriosis was illuminated by two CDC studies in which 11% of all refrigerator food samples were contaminated, 64% of patients had at least one contaminated food, and, in 33% of instances, the patient and food isolates had identical strains. Delicatessen-style ready-to-eat meats, especially chicken, had the highest rates of contamination. Cases were more likely than were controls to have eaten soft cheeses or deli-counter meats, and 32% of sporadic cases could be attributed to these foods.

Human listeriosis is typically acquired through ingestion of contaminated food, but other modes of transmission occur. These include transmission from mother to child transplacentally or through an infected birth canal and cross-infection in neonatal nurseries. Contaminated mineral oil used for bathing infants was the source of one outbreak. Localized cutaneous infections have occurred in veterinarians and farmers after direct contact with aborted calves.

The CDC has established PulseNet (http://www.cdc.gov/pulsenet/), a network of public health and food regulatory laboratories that use pulsed-field gel electrophoresis to subtype foodborne pathogens to detect promptly disease clusters that may have a common source. This system has proved effective in the early detection of listeriosis outbreaks.

PATHOGENESIS

Except for vertical transmission from mother to fetus and rare instances of cross-contamination in the delivery suite or neonatal nursery, human-to-human infection has not been documented.

Infection most often begins after ingestion of contaminated food. The oral inoculum required to produce clinical infection is unknown; experiments in healthy mammals indicate that $\geq 10^9$ organisms are required. Alkalinization of the stomach by antacids, H_2 blockers, proton pump inhibitors, or ulcer surgery may promote infection. The incubation period for invasive infection is not well established, but evidence from a few cases related to specific ingestions points to a mean incubation period of ~30 days, with a range from 11 to 70 days. In one report, two pregnant women, whose only common exposure was attendance at a party, developed listerial bacteremia with the same uncommon enzyme type; incubation periods for illness were 19 and 23 days.

Listeria monocytogenes can cause disease without promoter organisms, but, on occasion, intercurrent gastrointestinal infection with another pathogen may enhance invasion in individuals colonized with *L. monocytogenes*. Evidence for this is found in the common history of antecedent gastrointestinal symptoms in patients and household contacts, the long incubation period from ingestion to clinical illness, and two instances in which clinical listeriosis closely followed shigellosis. Both listerial meningitis and bacteremia have occurred shortly after colonoscopy, sigmoidoscopy, and upper endoscopy.

In the intestine, *L. monocytogenes* crosses the mucosal barrier aided by active endocytosis of organisms by endothelial cells. Once in the

bloodstream, hematogenous dissemination may occur to any site; *L. monocytogenes* has a particular predilection for the central nervous system (CNS) and the placenta. It is generally believed that listeriae reach the CNS by a bacteremic route, but animal experiments suggest that brainstem infection may develop by intra-axonal spread of bacteria from peripheral sites to the CNS.

Several virulence factors have been identified that enable *L. monocytogenes* to function as an intracellular organism. The bacterium possesses the cell surface protein internalin, which interacts with E-cadherin, a receptor on macrophages and intestinal lining cells, to induce its own ingestion. A membrane lipoprotein appears to promote entry into nonmacrophage cells. The major virulence factor, listeriolysin O, along with phospholipases, enables listeriae to escape from the phagosome and avoid intracellular killing. Once free in the cytoplasm, the bacterium can divide and, by inducing host cell actin polymerization, propel itself to the cell membrane. Subsequently, by means of pseudopod-like projections, it can invade adjacent macrophages. The bacterial surface protein Act A is necessary for the induction of actin filament assembly and cell-to-cell spread and, therefore, is a major virulence factor. Through this novel life cycle, *L. monocytogenes* moves from cell to cell, evading exposure to antibodies, complement, or neutrophils.

Iron, which is essential for the life of virtually all bacteria, appears to be an important virulence factor of *L. monocytogenes*. Siderophores of the organism enable it to take iron from transferrin. In vitro, iron enhances organism growth, and, in animal models of listerial infection, iron overload is associated with enhanced susceptibility to infection and iron supplementation with enhanced lethality, whereas iron depletion results in prolonged survival. Attesting to the importance of iron acquisition as a virulence factor in humans are the clinical associations of sporadic listerial infection with hemochromatosis and of outbreaks with transfusion-induced iron overload in patients receiving hemodialysis.

IMMUNITY

Resistance to infection with the intracellular bacterium *L. monocytogenes* is chiefly dependent on T-cell lymphokine activation of macrophages but involves both innate and adaptive immune responses. The adaptive response is predominantly cell mediated as evidenced by the overwhelming clinical association between listerial infection and conditions of impaired cell-mediated immunity, including lymphoma, pregnancy, AIDS, corticosteroid immunosuppression, and tumor necrosis factor-α (TNF-α) neutralizing agents. The production of nitric oxide by activated macrophages may play a role in natural immunity to listeriosis independent of T-cell function. The role of humoral immunity is unknown, although both immunoglobulin M (absent in neonates) and classical complement activity (low in neonates) have been shown to be necessary for efficient opsonization of *L. monocytogenes*.

Although listeriosis is 100 to 1000 times more common in patients with AIDS compared with the general population, it is somewhat surprising that it is not seen more commonly, given the ubiquity of the organism. The use of trimethoprim–sulfamethoxazole (TMP–SMX) for prophylaxis against *Pneumocystis jirovecii* (*carinii*) provides protection against listeriosis. Frequency of listeriosis is not increased in those with deficiencies in neutrophil numbers or function, splenectomy, complement deficiency, or immunoglobulin disorders.

CLINICAL MANIFESTATIONS

The species name derives from the fact that an extract of the *L. monocytogenes* cell membrane has potent monocytosis-producing activity in rabbits, but monocytosis is a very rare feature of human infection.

Infection in pregnancy

Mild impairment of cell-mediated immunity occurs during gestation, and pregnant women are prone to developing listerial bacteremia with an estimated 17- to 100-fold increase in risk. Listeriae proliferate in the placenta in areas that appear to be unreachable by usual defense mechanisms, and cell-to-cell spread facilitates maternal–fetal transmission. For unexplained reasons, CNS infection is extremely rare during pregnancy in the absence of other risk factors. Bacteremia manifests clinically as an acute febrile illness, often accompanied by myalgia, arthralgia, headache, and backache. Illness may occur at any time during pregnancy but usually occurs in the third trimester, probably related to the major decline in cell-mediated immunity seen at 26 to 30 weeks of gestation. Twenty-two percent of perinatal infections result in stillbirth or neonatal death; premature labor and spontaneous abortion

are common. Untreated bacteremia is generally self-limited, although if there is a complicating amnionitis, fever may persist in the mother until the fetus is aborted. Early diagnosis and antimicrobial therapy can result in the birth of a healthy infant.

There is no convincing evidence that listeriosis is a cause of habitual abortion in humans.

Neonatal infection

When in utero infection occurs, it can precipitate spontaneous abortion. The fetus may be stillborn or die within hours of a disseminated form of listerial infection known as granulomatosis infantiseptica and characterized by widespread microabscesses and granulomas that are particularly prevalent in the liver and spleen. In this entity, abundant bacteria are often visible on Gram stain of meconium.

More commonly, neonatal infection manifests similar to group B streptococcal disease in one of two forms: (1) early-onset sepsis syndrome, usually associated with prematurity and probably acquired in utero, or (2) late-onset meningitis, occurring at about 2 weeks of age in term infants, who most likely acquired organisms from the maternal vagina at parturition. Cases have occurred after cesarean delivery, however, and nosocomial transmission has been suggested.

In early-onset disease, *L. monocytogenes* can be isolated from the conjunctivae, external ear, nose, throat, meconium, amniotic fluid, placenta, blood, and, sometimes, CSF; Gram stain of meconium may show gram-positive rods and provide early diagnosis. The highest concentrations of bacteria are found in the neonatal lung and gut, which suggests that infection is acquired in utero from infected amniotic fluid rather than via a hematogenous route. Purulent conjunctivitis and a disseminated papular rash have rarely been described in neonates with early-onset disease, but clinical infection is otherwise similar to that due to other bacterial pathogens.

Bacteremia

Bacteremia without an evident focus is the most common manifestation of listeriosis after the neonatal period. Clinical manifestations typically include fever and myalgias; a prodromal illness with nausea and diarrhea may occur. Because immunocompromised patients are more likely than healthy persons to have blood cultures during febrile illnesses, transient bacteremias in healthy persons may go undetected.

Central nervous system infection

Organisms that cause bacterial meningitis most frequently (*Streptococcus pneumoniae, Neisseria meningitidis*, and *Haemophilus influenzae*) rarely cause parenchymal brain infections such as cerebritis and brain abscess. By contrast, *L. monocytogenes* has tropism for the brain itself (particularly the brainstem), as well as for the meninges. Many patients with listerial meningitis experience altered consciousness, seizures, or movement disorders and truly have meningoencephalitis. Ventriculoperitoneal shunt infection has been reported.

MENINGITIS

Active surveillance studies of bacterial meningitis conducted by the CDC indicate that *L. monocytogenes* accounts for 20% of bacterial meningitis cases in neonates as well as in those older than 60 years and carries a mortality of 22%. Worldwide, *L. monocytogenes* is one of the three major causes of neonatal meningitis, is second only to pneumococcus as a cause of bacterial meningitis in adults older than 50 years, and is the most common cause of bacterial meningitis in patients with lymphoma, patients with organ transplants, or those receiving corticosteroid immunosuppression for any reason. Twenty percent of bacterial meningitis in those older than 50 years is caused by *L. monocytogenes*; therefore, empiric therapy for bacterial meningitis in all adults older than 50 years with a negative CSF Gram stain should include an antilisterial agent (either ampicillin or TMP–SMX), especially in the absence of associated pneumonia, otitis, sinusitis, or endocarditis, which would suggest an alternative etiology.

Clinically, meningitis due to *L. monocytogenes* is usually similar to that due to more common causes; features particular to listerial meningitis are summarized in Table 144.1.

BRAINSTEM ENCEPHALITIS (RHOMBENCEPHALITIS)

An unusual form of listerial encephalitis involves the brainstem. In contrast to other listerial CNS infections, this illness usually occurs in healthy older children and adults; neonatal cases have not been reported. The typical clinical picture is one of a biphasic illness with a prodrome of fever, headache, nausea, and vomiting lasting about 4 days, followed by the abrupt onset of

Table 144.1 Distinctive features of listerial meningitis compared with more common bacterial etiologies

Feature	Frequency (%)
Presentation can be subacute (>24 hours)	~60
Stiff neck is less common	15–20
Movement disorders (ataxia, tremors, myoclonus) are more common	15–20
Seizures are more common	~25
Fluctuating mental status is common	~75
Positive blood culture is more common	50–75
Cerebrospinal fluid (CSF)	
Positive Gram stain is less common	30–40
Normal CSF glucose is more common	>60
Mononuclear cell predominance is more common	~30

asymmetrical cranial nerve deficits, cerebellar signs, and hemiparesis or hemisensory deficits or both. Nuchal rigidity is present in about 50%, CSF is only mildly abnormal, and CSF culture is positive in about 40%; almost two-thirds are bacteremic. Respiratory failure develops in about 4% of cases. Magnetic resonance imaging is superior to computed tomography for demonstrating rhombencephalitis. Mortality is high, and serious sequelae are common in survivors.

CEREBRITIS AND BRAIN ABSCESS

Parenchymal brain infection may occur without true abscess formation and is referred to as cerebritis; concomitant meningitis may or may not be present. Macroscopic brain abscesses account for about 10% of CNS listerial infections (Figure 144.1). Bacteremia is almost always present, and concomitant meningitis with isolation of *L. monocytogenes* from the CSF is found in 25%; both of these features are rare in other forms of bacterial brain abscess. About 50% of cases occur in known risk groups for listerial infection. Subcortical abscesses located in the thalamus, pons, and medulla are common; these sites are exceedingly rare when abscesses are due to other bacteria. Mortality is high, and survivors usually have serious sequelae.

Endocarditis

Listerial endocarditis may account for as much as 7.5% of adult listerial infections, produces both native valve and prosthetic valve disease, and has a high rate of septic complications and a mortality of 48%. Listerial endocarditis, but not bacteremia per se, may be an indicator of underlying gastrointestinal tract pathology, including cancer.

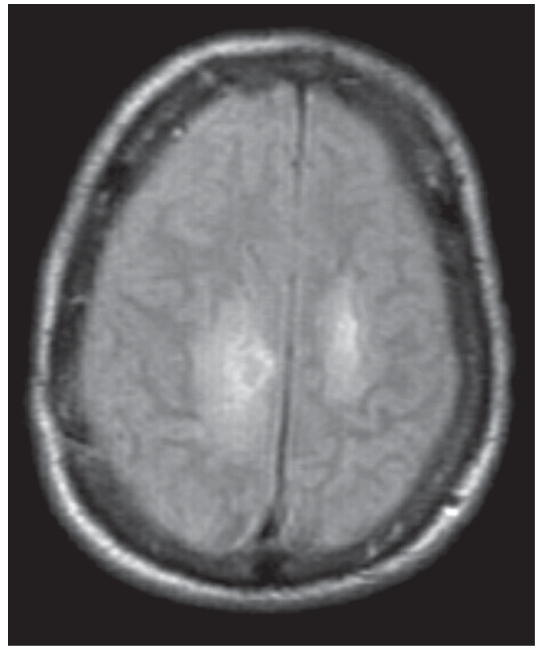

Figure 144.1 A magnetic resonance image (MRI) of the brain showing bilateral frontoparietal lesions with ring enhancement (abscess) on the right. The patient was a 70-year-old man with multiple myeloma who presented with difficulty walking followed by inability to stand and progressive quadriparesis. An aspirate of the abscess grew *Listeria monocytogenes*.

Localized infection

Focal infections from which *L. monocytogenes* has been isolated include direct inoculation resulting in conjunctivitis, skin infection, and lymphadenitis. Bacteremia can lead to hepatic infection, cholecystitis, peritonitis, splenic abscess, pleuropulmonary infection, septic arthritis, osteomyelitis, pericarditis, myocarditis, arteritis, necrotizing fasciitis, and endophthalmitis. Complications, including disseminated intravascular coagulation, adult respiratory distress syndrome, and rhabdomyolysis with acute renal failure, have been documented. There is nothing clinically unique about these localized infections; many, but not all, have occurred in those known to be at risk for listeriosis. Joint infection typically involves prosthetic joints in compromised hosts and requires prosthesis removal for cure.

Febrile gastroenteritis

Many patients with invasive listeriosis give a history of antecedent gastrointestinal illness, often accompanied by fever. Although isolated cases of gastrointestinal illness due to *L. monocytogenes* appear to be quite rare, at least seven outbreaks of foodborne gastroenteritis due to *L. monocytogenes* have been documented. In the largest outbreak to date 1566 individuals, most of them children between the ages of 6 and 10, became ill after eating caterer-provided cafeteria food at two schools, and 19% were hospitalized. Illness typically occurs 24 hours after ingestion of a large inoculum of bacteria (range 6 hours to 10 days) and usually lasts 1 to 3 days (range 1–7 days); attack rates have been quite high (52%–100%). Common symptoms include fever, watery diarrhea, nausea, headache, and pains in joints and muscles. Vehicles of infection have included chocolate milk, cold corn and tuna salad, cold smoked trout, and delicatessen meat. *Listeria monocytogenes* should be considered to be a possible etiology in outbreaks of febrile gastroenteritis when routine cultures fail to yield a pathogen.

DIAGNOSIS

Listeriosis should be a major consideration as part of the differential diagnosis in any of the following clinical settings:

1. Septicemia or meningitis in infants younger than 2 months.
2. Meningitis or parenchymal brain infection in: (a) patients with hematologic cancer, AIDS, organ transplantation, corticosteroid immunosuppression, or those receiving anti-TNF agents; (b) patients with subacute presentation; (c) adults >50 years; and (d) those in whom CSF shows gram-positive bacilli.
3. Simultaneous infection of the meninges and brain parenchyma.
4. Subcortical brain abscess.
5. Fever during pregnancy.
6. Blood, CSF, or other normally sterile specimen reported to have "diphtheroids" on Gram stain or culture.
7. Foodborne outbreak of febrile gastroenteritis when routine cultures fail to identify a pathogen.

Diagnosis requires isolation of *L. monocytogenes* from clinical specimens (e.g., CSF, blood) and identification through standard microbiologic techniques. Antibodies to listeriolysin O have not proved useful in invasive disease, nor have polymerase chain reaction (PCR) probes. Antibodies to listeriolysin O may be useful during investigation of outbreaks of febrile gastroenteritis. *Listeria monocytogenes* DNA in CSF and tissue has been specifically detected by PCR assays. Real-time PCR of CSF for the *hly* gene, which encodes listeriolysin O, has been useful in diagnosing CNS listeriosis, including cases in which routine bacterial cultures were negative, but this test is not yet commercially available.

Magnetic resonance imaging is superior to computed tomography for demonstrating parenchymal brain involvement, especially in the brainstem.

TREATMENT

No controlled trials have established a drug of choice or duration of therapy for listerial infection. Recommendations for treatment of invasive infections are presented in Table 144.2.

Ampicillin is generally considered the preferred agent. Based on synergy in vitro and in animal models, most authorities suggest adding

Table 144.2 Intravenous therapy for invasive listeriosis

Syndrome	Antibiotic[a]	Dosage[b]	Interval	Minimum duration
Meningitis	Ampicillin plus gentamicin	200 mg/kg 5 mg/kg	q4h q8h	3 wk
Brain abscess or rhombencephalitis	Ampicillin plus gentamicin	200 mg/kg 5 mg/kg	q4h q8h	6 wk
Endocarditis	Ampicillin plus gentamicin	200 mg/kg 5 mg/kg	q6h q8h	6 wk
Bacteremia	Ampicillin	200 mg/kg	q6h	2 wk

[a] Penicillin-allergic patients without endocarditis can be treated with trimethoprim–sulfamethoxazole alone, using 15 mg/kg of trimethoprim daily at 6- to 8-hour intervals. Patients with endocarditis should be desensitized to ampicillin and treated as above.

[b] Maximum daily dose of ampicillin should not exceed 15 g.

gentamicin to ampicillin for treatment of bacteremia in those with severely impaired cell-mediated immunity and in all cases of meningitis and endocarditis. In one uncontrolled study, the combination of TMP–SMX plus ampicillin was associated with a lower failure rate and fewer neurologic sequelae than ampicillin combined with an aminoglycoside.

For those intolerant of penicillins, TMP–SMX is believed to be the best alternative. Early transition to oral TMP–SMX has been used effectively and may be considered in selected patients with likely good adherence. No currently available cephalosporin should be used; none has adequate activity, and meningitis has developed in patients receiving cephalosporins. For this reason, ampicillin is always included in empirical therapy for septicemia or meningitis in infants $\leq$2 months of age.

Vancomycin has been used successfully in a few patients with penicillin allergy, but other patients have developed listerial meningitis while receiving the drug. Rifampin is active in vitro and is known to penetrate phagocytic cells; clinical experience is minimal, however, and in animal models the addition of rifampin to ampicillin was not more effective than ampicillin used alone. Both imipenem and meropenem have been used successfully to treat listeriosis, but caution is advised because both drugs lower the seizure threshold, treatment failures have been reported, and imipenem was less effective than ampicillin in a mouse model.

Initial dosing of antibiotics as for meningitis is prudent for all patients, even in the absence of CNS or CSF abnormalities, because of the high affinity of this organism for the CNS. Patients with meningitis should be treated for no fewer than 3 weeks; bacteremic patients without CSF abnormalities can be treated for 2 weeks.

No data exist concerning antimicrobial efficacy in listerial gastroenteritis; the illness is self-limited, and treatment is not warranted. Clinically significant antimicrobial resistance has not been encountered, but vigilance is warranted because transfer of resistance from enterococci to *L. monocytogenes* has been reported, tetracycline and quinolone resistance has emerged, and minimal inhibitory concentrations for penicillin have risen slightly. Because iron is a virulence factor for *L. monocytogenes*, it seems prudent to withhold iron replacement in patients with iron deficiency until the listerial infection is resolved.

PREVENTION

Food industry regulations were instituted in the United States over 20 years ago to minimize the risk of foodborne listeriosis and cut foodborne infection rates by more than one-half; rates have been relatively stable for several years. In contrast, rates of listerial infection appear to be rising in Europe.

Table 144.3 contains recommendations developed by the CDC for prevention of foodborne listeriosis.

Except from infected mother to fetus, human-to-human transmission of listeriosis does not occur; therefore, patients do not require isolation. Neonatal listerial infection complicating successive pregnancies is virtually unheard of, and intrapartum antibiotics are not recommended for mothers with a history of perinatal listeriosis. There is no vaccine. Listerial infections are effectively prevented by TMP–SMX given as prophylaxis against *P. jirovecii* to recipients of organ transplants or to individuals with the human immunodeficiency virus. The utility, or even the feasibility, of eradicating gastrointestinal colonization as a means to prevent invasive listeriosis is unknown. However, asymptomatic persons at high risk for listeriosis, known to have ingested a food implicated in an outbreak, could reasonably be given several days of oral ampicillin or TMP–SMX.

Table 144.3 Dietary recommendations for preventing foodborne listeriosis

For all persons
1. Cook raw food from animal sources (e.g., beef, pork, and poultry) thoroughly
2. Wash raw vegetables thoroughly before eating
3. Keep uncooked meats separate from vegetables, cooked foods, and ready-to-eat foods
4. Avoid consumption of raw (unpasteurized) milk or foods made from raw milk
5. Wash hands, knives, and cutting boards after handling uncooked foods
Additional recommendations for persons at high risk[a]
1. Avoid soft cheeses (e.g., Mexican-style, feta, Brie, Camembert) and blue-veined cheese; there is no need to avoid hard cheeses, cream cheese, cottage cheese, or yogurt
2. Leftover foods or ready-to-eat foods (e.g., hot dogs) should be reheated until steaming hot before eating
3. Consider avoidance of foods in delicatessen counters[b]

[a] Those immunocompromised by illness or medications, pregnant women, and the elderly.

[b] Although the risk for listeriosis associated with foods from delicatessen counters is relatively low, pregnant women and immunosuppressed persons may choose to avoid these foods or to thoroughly reheat cold cuts before consumption.

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145. *Nocardia*

Lisa Haglund

Nocardia species are soilborne bacteria that are aerobic and slow-growing. In culture, they may require days to weeks before colonies appear. *Nocardia* are filamentous gram-positive rods, and are variably acid-fast, 0.5 to 1.0 μm in diameter, with branching at right angles (Figure 145.1). Taxonomy of the genus has evolved considerably, and by the use of 16S rRNA sequence analysis, there are now 81 named *Nocardia* species, of which more than 30 have been implicated in human infections. The most frequent nocardial species pathogenic for humans are: *Nocardia nova* complex, *Nocardia brasiliensis, Nocardia farcinica, Nocardia cyriageorgica*, and *Nocardia transvalensis* complex. Less common human pathogens include *Nocardia otitidiscaviarum*, *Nocardia brevicatena/paucivorans*, and *Nocardia pseudobrasiliensis*. At this point, *Nocardia asteroides sensu stricto* is not currently defined in molecular terms, having been resolved into several other species. *Nocardia* are opportunistic pathogens; *N. brasiliensis* is more virulent, affecting normal hosts, and has a range geographically restricted to areas with warmer climates.

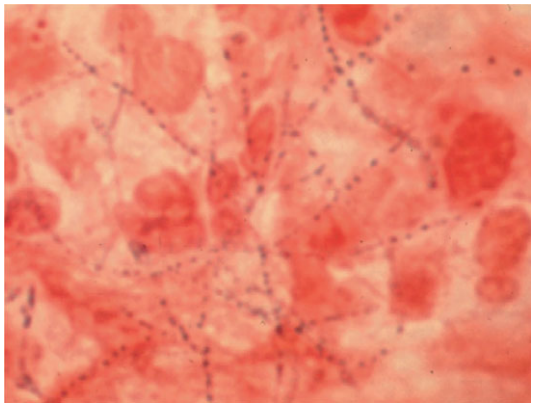

Figure 145.1 *Nocardia*, Gram stain. (Courtesy of David Schlossberg MD.)

Nocardiosis is typically a suppurative infection with multiple abscesses. It is rarely granulomatous and not fibrotic. Acquisition of infection is by inhalation or by traumatic inoculation. Although nocardia are ubiquitous, they rarely colonize the human respiratory tract. Accordingly, treatment should be initiated when nocardia are isolated repeatedly from pulmonary specimens, particularly in an immunocompromised host. Antimicrobial therapy (alone or in combination with surgical drainage) is recommended, and the duration of therapy must be prolonged to prevent relapse.

More than 75% of patients with systemic nocardiosis possess underlying risk factors. Predisposing conditions are listed in Table 145.1. As the number of solid organ and hematopoietic stem cell transplantations has increased, the incidence of nocardiosis has risen. There is a correlation with the level of immunosuppression following transplantation, with most cases of nocardiosis occurring >1 but <12 months after transplantation, and any time following intensified immunosuppression. Among human immunodeficiency virus (HIV)-infected persons,

Table 145.1 Risk factors for systemic nocardiosis

Chronic pulmonary disease	Solid organ transplantation	Systemic lupus erythematosus	Renal failure
Alcoholism	Hematopoietic stem cell transplantation	Systemic vasculitis	Whipple's disease
Cirrhosis	Chronic corticosteroid use	Ulcerative colitis	Hypogammaglobulinemia
Lymphoreticular malignancy	Other drug-induced immunosuppression	Sarcoidosis	Chronic granulomatous disease
Diabetes	Cushing syndrome		Human immunodeficiency virus infection
			Pulmonary alveolar proteinosis

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there is also a correlation with level of immunosuppression, as almost all cases of nocardiosis occur in individuals with CD4 lymphocyte count $\leq$100 cells/mm^3. In both of these severely immunocompromised populations, co-occurrence of other opportunistic infections, particularly aspergillosis, may be found and should be sought if expected clinical improvement fails to occur with therapy.

Nocardiosis remains an uncommon opportunistic complication of HIV infection and transplant recipients. One explanation is that the prophylactic use of trimethoprim–sulfamethoxazole (TMP–SMX), pyrimethamine, or dapsone for *Pneumocystis jirovecii* (*carinii*) may also prevent nocardiosis. A minority of HIV-infected persons and transplant recipients diagnosed with nocardiosis had been receiving these drugs prophylactically. The nocardia isolates causing these infections are seldom resistant to sulfa drugs in vitro.

PATHOGENESIS OF SYSTEMIC NOCARDIOSIS

Neutrophils inhibit the growth of nocardia, but eradication of organisms requires cell-mediated immunity. If cellular immunity is impaired, nocardia can cause indolent abscesses with slow spread to distant sites, such as the brain or cerebrospinal fluid. Illness is usually subacute to chronic but may be fulminant in an immunocompromised host. Weight loss, anorexia, and fatigue are common in systemic nocardiosis. Bacteremia is rare, although central line-associated bloodstream infections (CLABSIs) have been described, which require removal of the implicated catheter for cure.

MYCETOMA, CUTANEOUS NOCARDIOSIS, TRAUMATIC NOCARDIOSIS

Nocardial species can cause mycetoma, which typically manifests as a swollen area with sinuses draining purulent material. Primary cutaneous nocardiosis manifests as nontender, red, irregularly shaped raised lesions which may form sinus tracts and drain purulent material. Regional lymphadenopathy is uncommon. *Nocardia* arthritis usually presents as a monoarthritis, commonly involving the knee. Disease is often inoculated through a puncture wound, and may follow a contaminated intramuscular injection. Other inoculation nocardial infections described include postoperative wound infections, osteomyelitis, and keratitis.

PULMONARY NOCARDIOSIS

Pulmonary disease is apparent in 65% to 85% of systemic nocardial infections. The roentgenographic features include infiltrates that may cavitate, sometimes accompanied by empyema, pericarditis, or mediastinitis. There is no specific radiographic appearance, thus a high degree of suspicion must be maintained to make the diagnosis. Sputum cultures may be overgrown with other organisms before *Nocardia* colonies appear. Therefore, it may be helpful to notify the microbiology lab to use selective media and hold cultures for *Nocardia* if it is a suspected pathogen. Respiratory samples submitted for fungal culture are more likely to grow *Nocardia* than those submitted for mycobacterial (acid-fast bacillus [AFB]) culture.

NOCARDIA MENINGITIS AND BRAIN ABSCESS

Central nervous system (CNS) nocardiosis is detected in 20% to 40% of systemic nocardial infections. Two-thirds have clinical findings such as fever, headache, stiff neck, or altered mental status. Hypoglycorrhachia is found in two-thirds of patients. Mildly elevated cerebrospinal fluid protein and a neutrophilic pleocytosis of approximately 1000 white blood cells are usually found. Nocardial brain abscess can be a complication of nocardial meningitis or can present in the absence of meningitis. Although meningitis without underlying brain abscess has been described, this is quite unusual, and an underlying abscess should always be suspected. Because of the high incidence of CNS infection, an imaging study of the brain should be performed if any personality or neurologic changes are found during workup of systemic nocardiosis.

THERAPY OF NOCARDIOSIS: SULFONAMIDE THERAPY

Sulfonamides remain the first-line agents for nocardiosis, and sulfadiazine, 6 to 8 g intravenously (IV) or orally daily, is a typical adult regimen. Trimethoprim–sulfamethoxazole (TMP–SMX) is an alternative first-line treatment for nocardiosis. Disparity in sulfonamide susceptibility has been reported for nocardia; however several recent studies found overall 2% sulfonamide resistance in *Nocardia* species, with less resistance to TMP–SMX, and it appears that some of the disparate observations were methodologic due to inherent difficulties in performing nocardia

Table 145.2 Sulfonamide dosage and duration of therapy for treatment of nocardia

Type of nocardiosis	Dosage (divided BID-QID)	Duration	Comments
Cutaneous	5–10 mg/kg/d TMP–SMX[a]	2–4 mo	Longer for extensive disease or bony involvement as seen in mycetoma
Pulmonary	10 mg/kg/d TMP–SMX	6–12 mo	12-mo minimum duration for immunocompromised host
Central nervous system	15 mg/kg/d TMP–SMX 50–100 mg/kg/d sulfadiazine	12 mo	

[a] TMP–SMX dosage based on mg/kg of the trimethoprim (TMP) component.

Table 145.3 Other regimens for treatment of nocardia

Drug	Dosage	Duration	Comments
Minocycline	100–200 mg PO BID	3–6 mo	Useful for pulmonary disease; poor CNS penetration
Imipenem–cilastatin	500 mg IV q6h	Until oral agent can be given	Dose must be adjusted for renal failure
Amikacin	5–7.5 mg/kg IV q12h	Until oral agent can be given	Nephrotoxic; dosage must be adjusted for renal failure
Ceftriaxone	2 g IV q12h	Until oral agent can be given	
Linezolid	600 mg PO or IV q12h		Bone marrow suppression and peripheral neuropathy

susceptibilities for some antimicrobial agents. Table 145.2 summarizes typical dosages and durations of therapy for sulfonamide therapy of nocardiosis.

Sulfadiazine is a short-acting sulfonamide with low urinary solubility. TMP–SMX is a well-absorbed combination agent with a long plasma half-life of 11 and 9 hours for TMP and SMX, respectively. It is available orally as single- or double-strength tablets (80 mg TMP plus 400 mg SMX and 160 mg TMP plus 800 mg SMX, respectively) and as a liquid suspension containing 40 mg TMP plus 200 mg SMX per 5 mL. It is also available IV (5 mL = 80 mg TMP plus 400 mg SMX).

The most frequent side effects of TMP–SMX are upper gastrointestinal symptoms and skin rashes (3%–4% each). Leukopenia, thrombocytopenia, and megaloblastic changes can develop rarely. Adverse effects of sulfonamide therapy include acute renal failure as a result of tubular damage from sulfa crystalluria. This effect may be prevented by adequate hydration and by alkalinizing the urine. Organ transplant recipients may be at increased risk of both bone marrow and renal toxicity due to overlapping toxicities with immunosuppressive medications. Hepatitis, intrahepatic cholestasis, pancreatitis, and aseptic meningitis have been reported with TMP–SMX. Serious adverse reactions are rare and include anaphylaxis, Stevens–Johnson syndrome, and hematologic effects, including thrombocytopenia, leukopenia, and hemolytic anemia.

TMP–SMX and other sulfonamides should not be given to patients with a demonstrated deficiency of folic acid or glucose-6-phosphate dehydrogenase. In HIV-infected patients, there is an increased incidence of adverse reactions to TMP–SMX, including reversible hyperkalemia and a severe hypersensitivity reaction with fever, hypotension, and multiorgan involvement on rechallenge with the drug.

OTHER AGENTS WITH ANTINOCARDIAL ACTIVITY

N. farcinica, *N. otitidiscaviarum*, and *N. transvalensis* complex have been reported to have resistance to sulfonamides. The Clinical and Laboratory Standards Institute (CLSI) recommends use of the broth microdilution method for determining nocardial susceptibilities, while acknowledging that consistent interpretation of sulfonamide susceptibilities, in particular, is difficult with this method. Susceptibility results are most reliable from an experienced laboratory. In vitro susceptibility does not uniformly correlate with clinical outcome in humans; therefore, clinical response should also guide selection of definitive antimicrobial therapy. The parenteral agents with greatest in vitro activity include imipenem–cilastatin (500 mg IV every 6 hours), amikacin (5–7.5 mg/kg IV every 12 hours), or ceftriaxone (2 g IV every 12 hours) (Table 145.3). With susceptible organisms, these agents have been as efficacious as sulfonamides in animal models; in

Table 145.4 Antimicrobial susceptibilities of selected *Nocardia species*

	N. brasilensis	*N. cyriageorgica*	*N. farcinica*	*N. nova complex*	*N. transvalensis complex*
Sulfamethoxazole	S	S	S	S	S
Amoxicillin	R	R	R	S	R
Amoxicillin-clavulanate	S	R	V/S	R	R
Ceftriaxone	V	S	R	S	V/S
Imipenem	R	S	V/S	S	S
Amikacin	S	S	S	S	R
Clarithromycin	R	R	R	S	R
Minocycline	S	V	V	S	V
Ciprofloxacin	R	R	S	R	V/S
Linezolid	S	S	S	S	S

Abbreviations: R = resistant; V = variable susceptibility; S = sensitive.

fact, they may be more rapidly bactericidal than sulfonamides. Clinical experience with alternative parenteral regimens is being assimilated, and treatment courses often include sulfonamide therapy. In the immunocompromised patient, or those with disseminated disease or CNS involvement, strong consideration should be given to initial empiric use of amikacin and imipenem–cilastatin, while awaiting results of in vitro susceptibilities. For CNS nocardiosis, meropenem may be a useful alternative to imipenem–cilastatin, which may cause seizures; ertapenem, however, has significantly less in vitro activity.

Tetracyclines have good in vitro activity against some nocardial species. Minocycline has the best in vitro activity among the tetracyclines and is given 100–200 mg orally twice a day for 3 to 6 months (Table 145.3). Its drawbacks include poor cerebrospinal fluid penetration and side effects of vertigo, making it unsuitable for CNS nocardial disease.

Amoxicillin–clavulanate is an alternative to TMP–SMX or minocycline for treatment of cutaneous and lymphocutaneous disease caused by *N. brasiliensis*. Macrolides and the respiratory quinolones show some in vitro activity. Linezolid 400 to 600 mg orally twice daily has been used with success, but the long treatment course needed for nocardiosis may be complicated by drug toxicities. Table 145.4 summarizes antimicrobial susceptibilities of selected *Nocardia* species.

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146. *Pasteurella multocida*

Paulina A. Rebolledo, Naasha J. Talati, and David S. Stephens

Pasteurella multocida ("killer of many species") is a nonmotile, gram-negative, facultative coccobacillus best known for its association with soft-tissue infections after animal bites. However, this organism is also capable of causing invasive and life-threatening infections.

Pasteurella multocida is found worldwide. It commonly colonizes the upper respiratory tract of many animals, most notably cats (70% to 90%) and dogs (50% to 66%). Human infection is usually related to animal exposure. The most common mode of transmission to humans is by direct inoculation by a bite or scratch. Inoculation can also occur by nontraumatic animal contact, such as when a wound is licked by an animal. The second mode of transmission is by colonization of the human respiratory tract occurring with exposure to animals such as nuzzling or grooming of pets. *Pasteurella* has been cultured from the respiratory tract of healthy veterinary workers and animal handlers as well as from ill patients. Infections can occasionally occur in the absence of animal contact.

There are several species and subspecies of *Pasteurella*, with the most common ones causing human disease being *P. multocida* subsp. *multocida, P. multocida* subsp. *septica, Pasteurella dagmatis, Pasteurella canis*, and *Pasteurella stomatis*. These organisms can resemble *Haemophilus* and *Neisseria* species when visualized on Gram stain, grow well on sheep and chocolate agar, and appear as smooth, mucoid blue colonies.

Most of the virulence factors have been studied in animals. Pathogenesis of *Pasteurella* depends on the bacteria's ability to adhere to the host's respiratory epithelium, typically the tonsils, which can be mediated through fimbrae. Some species are capable of producing a leukotoxin that affects leukocytes and inhibits cellular immune responses. Differences between virulent strains of *Pasteurella* are identified according to capsular antigens A to F, which cause different animal diseases. Binding of transferrin is another mechanism by which *Pasteurella* can ensure a continuous supply of iron for its growth.

CLINICAL PRESENTATION

Infections caused by *P. multocida* can be divided into three groups: bite wound infections, infections of the respiratory tract, and invasive disease.

Bite wound infection

Infections of the skin and soft tissue most commonly follow bites or scratches, but can occasionally occur after an animal licks an open wound. Bite wounds account for 60% to 86% of *P. multocida* infections. *Pasteurella multocida* is found as a pathogen in 75% of infected cat bites and in up to 50% of infected dog bites. Most bite wounds grow multiple organisms. Infection with *P. multocida* is characterized by extremely rapid onset. Local pain and inflammation often occur within 4 to 6 hours of the injury and almost always within 24 hours. Purulent drainage and lymphangitis has been noted in 40% of cases, but fever and systemic symptoms are often absent. A rapid inflammatory reaction with no fever should prompt the clinician to suspect *P. multocida* in bite wound infections.

Bite wound infections with *P. multocida* can lead to serious sequelae, even with appropriate antibiotic and aggressive surgical management. Tenosynovitis, abscess formation, and osteomyelitis often result, but bacteremia is rare. Cat bites are more commonly associated with osteomyelitis because of the deep puncture wounds that penetrate the periosteum. Poor functional outcome is common with these infections, especially when involving the extremities. In patients with risk factors for invasive infections, an apparently insignificant and uninfected wound may lead to serious sequelae weeks later.

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Respiratory tract infection

The respiratory tract is the second most common site of infection and colonized patients usually suffer from chronic obstructive pulmonary disease (COPD) and bronchiectasis. *Pasteurella* has been associated with sinusitis, otitis, epiglottitis, bronchitis, pneumonia, lung abscess, and empyema. The mode of acquisition into the lower respiratory tract includes inhalation of contaminated aerosols or direct inoculation of the oral cavity with animal secretions and subsequent aspiration. Bacteremia is seen in 15% to 50% of cases. Most patients are elderly and have underlying respiratory illness, such as COPD, bronchiectasis, chronic sinusitis, or pulmonary neoplasm. The clinical presentation is indistinguishable from other forms of bacterial pneumonia.

Invasive or disseminated infection

Invasive or disseminated infection with *P. multocida* is rare and spreads hematogenously from wounds or from pulmonary colonization. Invasive infections generally occur in children, pregnant women, the elderly, cirrhotic patients, patients on chronic steroids, or amongst HIV-positive individuals or organ transplant recipients. Most cases are associated with animal bites or scratches, some are associated with animal exposure without injury, and a small percentage of cases have no history of exposure to animals.

Infectious arthritis is a rare complication of *Pasteurella* and generally occurs in patients with underlying joint disease or steroid use. The arthritis is usually monoarticular, and primarily affects the knee. Fifteen percent of patients have polyarticular arthritis, usually in association with bacteremia. In a series of 37 cases, 32% had a prosthetic joint infection. Osteomyelitis has usually been seen following animal bites (9 of 13 cases) and usually involves the upper extremity.

Meningitis, a relatively rare manifestation of *P. multocida* infection, is usually seen among infants or adults over the age of 55. The largest series of adult patients in the literature reports 29 cases from 1989 to 1999. There are four mechanisms by which *P. multocida* can cause meningitis: (1) direct inoculation following animal bite, (2) contamination from colonized site after trauma or neurosurgery (29%), (3) bacteremic seeding of meninges (25%), and (4) local spread from an infected site, such as otitis (28%). The clinical presentation and cerebrospinal fluid (CSF) findings are typical of bacterial meningitis. A useful clue to diagnosis is that 89% of patients report animal exposure (with only 15% reporting animal bites). Bacteremia is seen in 60% of patients and CSF Gram stain is positive in 50%. Neurologic complications such as cranial nerve palsies and seizures occur in 22%, and mortality approaches 30%.

Bacteremia is documented in 20% to 30% of invasive infections. The main risk factors for bacteremia are cirrhosis, diabetes, and malignancy. However, up to 38% of patients have no underlying disease, 17% have no animal exposure, and 13% have no localized site of infection. A comprehensive review of 156 cases of *P. multocida* bacteremia found a mortality rate of 23%. Thirty-three cases of endocarditis caused by *Pasteurella* species have been reported, including one case of prosthetic valve disease. The mitral and aortic valves are most commonly affected. Presentation is acute in 64% of cases. Mortality is 40%, but rises to 57% in immunocompromised individuals.

Pasteurella is also known to cause intra-abdominal infections. Twelve cases of spontaneous bacterial peritonitis have been reported, mostly in patients with alcoholic cirrhosis; mortality is around 30%. Cases of peritoneal dialysis-associated infection have been reported in 26 patients, the majority of whom had a cat, and all patients improved with antibiotic therapy. Cases of appendicitis-associated peritonitis have also been reported.

Other serious infections caused by *P. multocida* for which there are case reports in the literature include pyelonephritis, thyroiditis, mycotic aneurysm, vascular graft infection, endophthalmitis, uvulitis, liver abscess, chorioamnionitis, neonatal sepsis, and chronic ulceration of the penis.

THERAPY

Antibiotics

The antibiotic of choice for treatment of *P. multocida* infections is penicillin. Ampicillin and amoxicillin are effective, but antistaphylococcal penicillins such as oxacillin and nafcillin are not recommended. The second- and third-generation cephalosporins have good activity against *P. multocida*, but first-generation cephalosporins and cefaclor are not reliable. Twenty to thirty percent of bovine and porcine species are resistant to penicillin. Thus far there are only five human

Table 146.1 Antibiotic susceptibilities of *Pasteurella multocida*

Usually susceptible	Variable	Usually resistant
Penicillin and derivatives	Semisynthetic penicillins	Vancomycin
Ampicillin (± sulbactam)	Oxacillin	Clindamycin
Amoxicillin (± clavulanate)	Dicloxacillin	Erythromycin (oral)
Ticarcillin (± clavulanate)	Cloxacillin	
Piperacillin (± tazobactam)	Nafcillin	
Second- and third-generation cephalosporins[a]	Cefaclor	
Cefuroxime	First-generation cephalosporins	
Cefotetan	Cephalexin	
Cefoxitin	Cefazolin	
Cefixime[b]	Cephradine	
Cefprozil[b]	Cefadroxil	
Loracarbef[b]	Erythromycin (IV)	
Cefpodoxime[b]	Aminoglycosides	
Ceftriaxone	Gentamicin	
Ceftizoxime	Tobramycin	
Cefotaxime	Amikacin	
Ceftazidime		
Advanced-generation cephalosporins		
Ceftaroline[b]		
Ciprofloxacin[b]		
Chloramphenicol		
Trimethoprim–sulfamethoxazole[b]		
Aztreonam		
Imipenem		
Tetracycline		
Doxycycline		

a Cefaclor, an oral second-generation cephalosporin, is often not effective.
b There are few clinical data on the use of these agents but by in vitro testing they should be effective.

Table 146.2 Doses of the most efficacious agents for treatment of *Pasteurella multocida*

Agent	Oral	Parenteral
Penicillin V	500–750 mg q6h	
Penicillin G		10 million to 20 million units/d divided q4h
Amoxicillin (± clavulanate)	250–500 mg q6h	
Ampicillin	250–500 mg q6h	1–2 g q4–6h
Ampicillin–sulbactam		1.5–3 g q6h
Ticarcillin–clavulanate		3.1 g q4–8h
Piperacillin		3–4 g q4–6h
Cefuroxime	250–500 g q12h	750 mg–1.5 g q8h
Cefoxitin		1–2 g q4–8h
Cefotaxime		1–2 g q4–8h
Ceftriaxone		1–2 g q24h
Ciprofloxacin	500–750 mg q12h	400 mg q12h
TMP–SMX	160 mg TMP (1 DS tab) BID	10 mg/kg/d TMP divided q6–12h
Aztreonam		500 mg–2 g q6–12h
Imipenem		500 mg–1 g q6–8h
Meropenem		2 g q8h
Tetracycline	250–500 mg q6h	500 mg–1 g q12h
Doxycycline	100–200 mg q12h	100–200 mg q12h
Chloramphenicol	12.5–25 mg/kg q6h	12.5–25 mg/kg q6h

Abbreviations: TMP–SMX = trimethoprim–sulfamethoxazole; DS = double strength.

cases of β-lactamase-producing *P. multocida* reported in the literature, all corresponding to respiratory tract infections. This plasmid-mediated resistance to penicillin is thought to have been acquired from oropharyngeal flora present in humans. All patients treated with amoxicillin–clavulanate had favorable outcomes. Antibiotic susceptibility testing should be routinely performed.

Pasteurella is uniformly sensitive to tetracycline and chloramphenicol. Fluoroquinolones, azithromycin, clarithromycin, and trimethoprim–sulfamethoxazole (TMP–SMX) have good in vitro activity. Clinical experience with these agents is limited, but they are an option for patients allergic to penicillin and cephalosporins who cannot tolerate tetracyclines. Tables 146.1 and 146.2 show appropriate antibiotics and doses.

While *Pasteurella* is universally resistant to clindamycin and vancomycin, most strains are resistant to erythromycin, and only moderately sensitive to aminoglycosides.

Prophylactic antibiotic therapy for bite wounds

Although antimicrobial therapy is indicated for infected bite wounds, its value in prophylaxis following bite injury is controversial. This is largely due to the small number of patients enrolled in such studies. The decision to prescribe antibiotics at the time of injury depends on the risk of infection, which can be assessed by the criteria in Table 146.3. In addition, specific risk factors for *P. multocida* are listed in Table 146.4.

Table 146.3 Risk factors for wound infection

	High	Low
Type of wound	Puncture Crush injury Foreign material introduced Extends to bone or joint Requires surgical repair	Laceration No crushing of tissues No contamination Superficial No surgical repair
Site of wound	Extremity, especially hand	Trunk, buttocks, head, minor facial wounds
Species of animal	Cat, pig, bovine	Dog, rodent
Delay before presentation	>8 h	≤6 h, or >48–72 h without signs of infection
Management prior to presentation	Poor cleaning	Good cleaning
Patient characteristics	>55 yr or ≤1 yr of age	No underlying disease

If a wound generally shows no sign of infection after 24 hours, *P. multocida* infection is unlikely to develop. However, for individuals with underlying risk factors and bites at risk for *P. multocida* infection, prophylaxis is reasonable even if they present late. As bite wounds usually contain multiple organisms, including anaerobes, prophylaxis is usually with amoxicillin–clavulanate for 3 to 5 days. Alternatives include TMP–SMX or quinolones, in addition to clindamycin or metronidazole to cover anaerobes. For further discussion of the management of bite wounds, see Chapter 23, Animal and human bites.

Table 146.4 Risk factors for *Pasteurella multocida* infection

Wound	Patient
Deep puncture	≤1 yr or >55 yr of age
Feline, porcine	Liver disease, especially cirrhosis HIV
Deep feline scratch	Solid tumors, leukemias Immune-modulating medications Chronic respiratory disease Collagen vascular disease Pregnancy Artificial heart valve History of cranial trauma or surgery

Treatment of infected wounds

Infected wounds should be thoroughly cleaned and have deep cultures performed before the initiation of antibiotics. Surgical evaluation should be performed especially when joints or extremities are involved or when there is extensive tissue damage. If infection with intense local inflammation develops within 24 hours, *Pasteurella* should be strongly suspected. Because the rate of serious sequelae is high, the clinician should have a low threshold for admission and surgical consultation. If infection develops after 24 to 48 hours, gram-positive organisms are more likely to be the cause, and therapy should be directed toward *Staphylococcus, Streptococcus* species, and anaerobes. However, if the patient has underlying risk factors for *P. multocida* infection, coverage for this organism should be included in the regimen. Table 146.1 shows the antibiotics of choice for *P. multocida*. Uncomplicated cellulitis should be treated for 7 to 10 days, but more complicated wound infections may require longer treatment.

Therapy for other *P. multocida* infections

A key factor in successful treatment of other *P. multocida* infections is suspicion of the organism. A history of animal contact should always be obtained and the patient examined carefully for signs of even minor trauma. Gram stains of wounds or purulent collections are positive in up to 50% of cases. If *P. multocida* infection is a possibility, therapy should include penicillin or a second- or third-generation cephalosporin. Tetracycline, fluoroquinolones, and TMP–SMX are alternatives if β-lactam allergy is present.

In β-lactam-allergic patients presenting with meningitis, chloramphenicol can be used. Cases of successful treatment with aztreonam and meropenem have been reported. The optimal duration of treatment for meningitis and respiratory infections is unknown, but most series suggest 2 weeks and 7 to 10 days, respectively. Joint infections, osteomyelitis, and abscesses require drainage and debridement in addition to antibiotic therapy. In a review of prosthetic joint

infections reported in the last 10 years, 63% resulted in removal of the prosthesis. Patients with endocarditis should be treated with medical and surgical therapy, and duration of antibiotics is generally 6 weeks.

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147. Pneumococcus

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INTRODUCTION

An enduring pathogen since its discovery in 1881, *Streptococcus pneumoniae* (pneumococcus) ranks first among all causes of community-acquired pneumonia (CAP), second as a cause of bacterial meningitis among adults, and is a frequent cause of sepsis and meningitis among children. The high case-fatality rates from invasive (bacteremic) pneumococcal disease (IPD) attest to its importance as a pervasive pathogen. Case-fatality rates in IPD approach about one in six cases of pneumonia among elderly and about one in ten among middle-aged adults, about one in three cases of meningitis among adults and one in 20 cases of meningitis in children, and nearly nil in cases of bacteremia without localization among children 4 years of age or younger. Persistent high case-fatality rates from IPD during the second half of the twentieth century, despite effective antibiotic treatment regimens, drove the development and licensure of polysaccharide vaccines for adults and children.

DIAGNOSTIC PROCEDURES

Pneumonia

The antibiotic treatment of CAP among patients admitted to hospital must be initiated without delay and should be started before the patient leaves the emergency department, based on expert empiric treatment guidelines, even before the causative organism is established by diagnostic laboratory procedures. The diagnosis of *S. pneumoniae* pneumonia initially represents a presumptive clinical judgment taking into account its common occurrence, symptoms and signs, age of the patient, and the results of rapid laboratory tests, when available. Unequivocal evidence of the specific etiologic diagnosis of *S. pneumoniae* pneumonia requires isolation of the organism from blood or another otherwise sterile site, such as pleural fluid, with results not available usually until the next day. Blood cultures should be done to assess the invasive nature of the infection and to test the isolated strain for antibiotic sensitivity, because of the increasing emergence of intermediate and high resistant strains worldwide. A single set of cultures obtained before the start of antibiotic treatment is adequate for recovery of the organism. All *S. pneumoniae* strains recovered from sputum and blood, cerebrospinal fluid (CSF), and pleural fluid must be tested for susceptibility to penicillin and other antibiotics commonly used in the treatment of pneumococcal disease. *S. pneumoniae* can be recovered also from respiratory tract secretions. The finding of pneumococci in sputum or a nasal swab should be interpreted in light of their frequent carriage in the upper respiratory tract. Their recovery from the respiratory secretions adds only modest confidence for establishing a specific etiologic diagnosis. To monitor in a community the occurrence of pneumococcal vaccine serotypes or the emergence of replacement serotypes, specific serotypes can be determined by capsular swelling procedures (quelling reaction) employing serotype-specific antisera (Statens Serum Institut, Copenhagen, Denmark).

Although recovery of *S. pneumoniae* from blood or pleural fluid represents the "gold standard" of etiologic diagnosis in CAP, rapid laboratory procedures can provide early evidence of this infection. Such tests include recognition of the organism on a Gram-stained smear of respiratory secretions by the presence of characteristic gram-positive, lancet-shaped diplococci (Figure 147.1) and detection of pneumococcal antigen in urine. The detection of pneumococcal C-polysaccharide cell wall antigen in a urine specimen by a commercial immunochromatographic membrane assay (BinaxNOW® *Streptococcus pneumoniae* Test) provides a quick (about 15 minutes), reasonably sensitive, and highly specific test for establishing the diagnosis in adults who become blood culture positive. In IPD, the immunochromatographic

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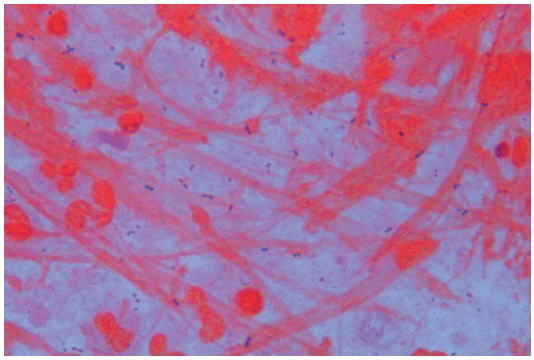

Figure 147.1 Gram-stained sputum specimen positive for *S. pneumoniae* demonstrates lancet-shaped gram-positive diplococci.

membrane assay of urine is about 77% to 87% sensitive and about 97% to 100% specific. In children with IPD, it is somewhat less specific. The immunochromatographic membrane assay applied to pleural fluid also provides a sensitive and highly specific means of identifying pneumococcal antigen.

The BinaxNOW® test involves dipping a special swab into a urine specimen, or a pleural fluid specimen, at room temperature and applying the swab to an immunochromatographic membrane in a booklet-like device that is closed after the swab is set up. A positive test result, which must be read 15 minutes later, appears as a pink-to-purple colored line in a window on the cover of the booklet. Importantly, isolation of the pneumococcal organism is still necessary to assess susceptibility to penicillin and other antibiotics.

Meningitis

A specific diagnosis of pneumococcal meningitis can be confirmed quickly during the initial examination of the patient by identification of the organism on a Gram stain of CSF or by detection of pneumococcal C-polysaccharide cell wall antigen in a CSF specimen using the immunochromatographic membrane assay. The test is performed and read in the same manner as described above for testing a urine specimen. However, in patients with pneumococcal meningitis, the test shows a very high sensitivity (100% or nearly so) and very high specificity (100% or nearly so) in both children and adults. The availability of rapid diagnostic tests for the diagnosis of *S. pneumoniae* meningitis facilitates prompt initiation of appropriate antibiotic therapy while waiting for the results of the culture of CSF.

Antibiotic susceptibility testing

The spectrum of antibiotic minimum inhibitory concentrations (MICs) of *S. pneumoniae* strains is routinely determined employing automated procedures against a panel of antibiotics specified by the Clinical and Laboratory Standards Institute (CLSI, Wayne, PA). The panel of antibiotics includes penicillin, cefaclor, cefuroxime, cefotaxime, ceftriaxone, cefepime, meropenem, levofloxacin, azithromycin, erythromycin, tetracycline, chloramphenicol, clindamycin, amoxicillin-clavulanate, trimethoprim–sulfamethoxazole, and vancomycin. MIC breakpoints for non-meningitis and meningitis isolates to selected antibiotics are included in the footnotes of Tables 147.1 and 147.2, respectively.

Although automated procedures have eclipsed other means of MIC determination, the MIC of an individual isolate of *S. pneumoniae* can be determined employing the E-test (AB Biodisk, Solna, Sweden). In this test, a penicillin-impregnated plastic-coated paper strip is placed on a blood agar plate inoculated with the isolate to produce a semiconfluent growth and incubated for 24 hours in a 5% CO_2 atmosphere. The MIC represents the point of intersection of the strip by the ellipsoid zone of inhibition.

INFECTIONS DUE TO THE PNEUMOCOCCUS

Pneumonia

IMPORTANCE

Pneumonia is the most common clinical presentation of *S. pneumoniae* infection and accounts for about 40% to 60% of CAP. *S. pneumoniae* remains the most common cause of CAP; *Mycoplasma pneumoniae* and *Haemophilus influenzae* are the second and third most common causes, respectively. Only about 20% of pneumococcal pneumonias are invasive infections. The burden of pneumococcal pneumonia represents the number of invasive and noninvasive cases. By one estimate, almost one million cases of pneumococcal pneumonia occur each year in the United States, resulting in between 100 000 and 400 000 hospitalizations. Pneumococcal pneumonia affects every age group, but it is most prevalent in children under 5 and adults greater than 65 years of age. Case-fatality rates vary widely, from about 2% in children to as high as 40% in elderly persons.

Certain underlying morbidities increase the risk of acquiring pneumococcal pneumonia. In

Table 147.1 Recommended empiric antibiotic treatment regimens for *S. pneumoniae* pneumonia when the diagnosis is suspected on clinical findings or confirmed by laboratory procedures or a positive blood culture

Clinical assessment of pneumonia	Recommended antibiotics[a]	Recommended antibiotic dosages[a]
Ambulatory adult without any comorbidity or recent antibiotic treatment	First choice: a macrolide, either azithromycin or clarithromycin or erythromycin Alternate choice: doxycycline	Azithromycin 500 mg on d 1 and then 250 mg PO for 4 d; or clarithromycin 500 mg PO q12h for 7–14 days; or erythromycin 500 mg PO q12h for 7–14 d Doxycycline 100 mg PO q12h for 7–14 d
Ambulatory adult 50 years of age and older with one or more comorbid condition and/or recent antibiotic treatment	First choice: a fluoroquinolone with antipneumococcal activity. Alternate choice: amoxicillin–clavulanate or amoxicillin or cefuroxime plus a macrolide	Levofloxacin, 750 mg PO q24h for 5 d; gatifloxacin, 400 mg PO q24h for 7–14 d; moxifloxacin, 400 mg PO q24h for 7–14 d; or gemifloxacin, 320 mg PO q24h for 7 d Amoxicillin–clavulanate 875 mg/125 mg PO q12h for 7–14 d; amoxicillin 875 mg PO q12h for 7–14 d; or cefuroxime axetil 500 mg PO q12h for 7–14 d, plus azithromycin or clarithromycin as described above
Hospitalized adult with or without either comorbid conditions or recent antibiotic treatment	First choice: a fluoroquinolone with antipneumococcal activity Alternate choice: ceftriaxone or cefotaxime plus a macrolide	Levofloxacin, 750 mg PO q24h for 5 d; gatifloxacin, 400 mg PO q24h for 7–14 d; moxifloxacin, 400 mg PO q24h for 7–14 d; or gemifloxacin, 320 mg PO q24h for 7 d Ceftriaxone, 1–2 g IV/IM q24h for 7–14 d; or cefotaxime, 1–2 g IV q8h for 7–14 d; plus Azithromycin, 500 mg IV, then PO, q24h for 7–10 d; or clarithromycin 500 mg PO q12h for 7–14 d

[a] *Streptococcus pneumoniae* isolated from blood or pleural fluid must be tested for antibiotic susceptibility and choice of antibiotic treatment should be based on these results. For these *S. pneumoniae* isolates (non-meningitis isolates), the MIC breakpoints in μg/mL of penicillin parenterally administered susceptible $\leq$2, intermediate = 4, and resistant $\geq$8; ceftriaxone susceptible $\leq$1, intermediate = 2, and resistant $\geq$4; cefotaxime susceptible $\leq$1, intermediate = 2, and resistant $\geq$4; azithromycin susceptible $\leq$0.5, intermediate = 1, and resistant $\geq$2; levofloxacin susceptible $\leq$2, intermediate = 4, and resistant $\geq$8. The antibiotic regimen selected should exceed these MICs.

Table 147.2 Recommended empiric antibiotic treatment regimens for *S. pneumoniae* meningitis

Penicillin allergy	Age group	Recommendations for antibiotics	Recommendations for dosage of antibiotics[a]
No	Child	Ceftriaxone or cefotaxime plus vancomycin	Ceftriaxone, 50 mg/kg IV q12h, or cefotaxime[a], 50 mg/kg IV q6h plus vancomycin, 10–15 mg/kg IV q6h (or q12h if 12–16 yr), 10–14 d plus dexamethasone 0.15 mg/kg IV q6h for 2–4 d, starting 10–20 minutes before first dose of antibiotics[b]
	Adult	Ceftriaxone or cefotaxime plus vancomycin plus dexamethasone, maybe plus rifampin	Ceftriaxone, 2 g IV q12h, or cefotaxime, 2 g IV q4h plus vancomycin, 1 g IV q12h, 10–14 d plus dexamethasone 0.15 mg/kg IV q6h for 2–4 d, 10–20 minutes before antibiotics, maybe plus rifampin, 300 mg PO q12h for 10–14 d
Yes	Child	Chloramphenicol plus vancomycin plus dexamethasone	Chloramphenicol, 75–100 mg/kg IV q6h plus vancomycin 10–15 mg/kg IV q6h (or q12h if 12–16 yr), 10–14 d plus dexamethasone 0.15 mg/kg IV q6h for 2–4 d, starting 10–20 minutes before first dose of antibiotics[b]
	Adult	Chloramphenicol plus vancomycin plus dexamethasone, maybe plus rifampin	Chloramphenicol, 1500 mg IV q6h plus vancomycin, 1 g IV q12h, 10–14 d plus dexamethasone 0.15 mg/kg IV q6h for 2–4 d, 10–20 minutes before antibiotics, maybe plus rifampin, 300 mg PO q12h for 10–14 d

[a] *Streptococcus pneumoniae* isolates recovered from cerebrospinal fluid (CSF) must be tested for antibiotic susceptibility and an antibiotic treatment regimen should be selected based on these results. For these CSF *S. pneumoniae* isolates, the MIC breakpoints in μg/mL of penicillin parenterally administered susceptible $\leq$0.06 and resistant $\geq$0.12; ceftriaxone susceptible $\leq$1, intermediate = 2, and resistant $\geq$4; cefotaxime susceptible $\leq$1, intermediate = 2, and resistant $\geq$4; vancomycin susceptible $\leq$1; chloramphenicol susceptible $\leq$4 and resistant $\geq$8. The antibiotic regimen selected should exceed these MICs. *S. pneumoniae* CSF isolates respond to ceftriaxone and cefotaxime because these third-generation cephalosporins achieve levels in the CSF above the MIC of most of these strains.
[b] Adjunctive dexamethasone, 0.15 mg/kg, every 6 hours for 2–4 days, in children residing in high-income countries (not low-income countries), preferably started 10–20 minutes before antibiotic therapy is begun, shows a decrease in any hearing loss and short-term neurologic sequelae, modest diminution of severity of illness, and slightly lowered case-fatality rate.

children, these include age less than 5 years, especially less than 2 years, absence of breastfeeding, day-care attendance, exposure to cigarette smoke, and lack of immunization with PCV7 or PCV13. In adults, these include age 55 years or older, immunodeficiencies due to human immunodeficiency virus (HIV), diabetes mellitus, functional or actual asplenia, humoral immunity defects, complement deficiencies, and neutrophil dysfunction. Additional risk factors include asthma; chronic obstructive pulmonary disease; viral infections (especially influenza infection); chronic cardiac, hepatic, or renal conditions; alcoholism; and active and passive exposure to cigarette smoke.

CLINICAL AND LABORATORY FINDINGS

The incubation period of pneumococcal pneumonia is 1 to 3 days. The onset of symptoms may be sudden, starting with rigors or a single shaking chill followed by high fever (102°F to 105°F), cough productive of rusty or blood-streaked sputum, dyspnea, tachypnea, hypoxia, pleuritic chest pain, and malaise. Because of pleuritic pain, patients may be observed to splint the affected lung. Other less specific symptoms include nausea, vomiting, headache, fatigue, and muscle aches. Some of the more serious complications that may develop and contribute to fatality rates are empyema, pericarditis, and respiratory failure.

Physical examination of the lungs may reveal rales over the affected lobe or segment. An increase in tactile fremitus and the presence of egophony indicates consolidation. Larger pleural effusions or empyema are demonstrated by dullness on chest percussion.

Neutrophilic leukocytosis occurs in about 80% of patients at presentation with most other patients developing leukocytosis within a few days. Some elderly and immunocompromised patients may never develop leukocytosis, so the absence of leukocytosis either at presentation or throughout the illness does not rule out pneumonia or invasive disease.

A chest radiograph should be obtained on each adult suspected of CAP. Pneumococcal pneumonia typically shows a lobar pattern of infiltration, but may demonstrate a focal segmental infiltrate. Chest radiographs may be clear early in the disease or in a dehydrated patient so a negative chest radiograph should be repeated after 24 hours. A negative chest radiograph may persist in some elderly or immunocompromised patients even in the presence of pneumonia.

COURSE AND TREATMENT

With appropriate antibiotic treatment the earliest response usually occurs within 12 to 36 hours, but sometimes as late as 96 hours. Fever defervesces first followed by amelioration of the respiratory rate, cough, and chest pain. Radiographic findings should not be used to assess early response to treatment because infiltrates usually clear slowly, over the next 2 to 3 weeks.

As *S. pneumoniae* is the dominant pathogen of CAP, deciding on a treatment regimen for CAP involves two key points: (1) judging the likelihood that *S. pneumoniae* is the pathogen and whether it is resistant to penicillin or other antibiotics, because as many as one-third of the *S. pneumoniae* strains exhibit intermediate or high resistance to penicillin, depending on the individual community, and (2) applying a validated quantitative severity score for assessing the severity of the pneumonia, as an adjunct to clinical judgment.

S. pneumoniae is frequently suspected as the pathogen of CAP on clinical grounds, sometimes aided by the results of rapid diagnostic procedures; however, the physician will not know whether the strain is penicillin susceptible or resistant unless cultures become positive. Consequently, appropriate antibiotic treatment must be started based on guidelines for the empiric antibiotic treatment of CAP (Table 147.1). Importantly, invasive pneumococcal pneumonia caused by intermediate resistant strains (MICs 4 μg/mL) can be successfully treated with antibiotic regimens that are employed to treat penicillin-susceptible strains.

A scoring method commonly used for stratifying risk in patients presenting with pneumonia is the CURB-65 score, which is a straightforward evaluation that divides patients into low- and high-risk categories. The patient receives one point for the presence of each of the following characteristics: *C*onfusion (acute) ($\leq$8 on an abbreviated Mental Test), *U*rea (blood urea nitrogen $>$ 19 mg/dL or 7 mmol/L), *R*espiratory rate $>$ 30/minute, *B*lood pressure: diastolic $<$ 60 or systolic $<$ 90 mm Hg, and age $\geq$65 years. A score of 3, 4, or 5 represents severe pneumonia with a high risk of death that must be managed in the hospital; a score of 2 represents less severe pneumonia, but one that carries an increased risk of death and should also be managed in the hospital; and a score of 0 or 1 represents mild pneumonia that can be managed on an ambulatory basis.

For an ambulatory adult without comorbid conditions or recent antibiotic treatment (within

3 months) and a CURB-65 of 0 or 1, the recommended treatment is a macrolide, either azithromycin, clarithromycin, or erythromycin, or alternatively, doxycycline (Table 147.1). For an adult older than 50 years with a score of 0 or 1, who has one or more comorbid conditions and/or recent antibiotic treatment, the recommendation is for a fluoroquinolone with antipneumococcal activity such as levofloxacin, gatifloxacin, moxifloxacin, or gemifloxacin. If *S. pneumoniae* is recovered from the patient and determined to be penicillin susceptible then amoxicillin-clavulanate or amoxicillin or cefuroxime plus either a macrolide or doxycycline is an alternative treatment.

A hospitalized (non-ICU) adult (CURB-65 score of 2 or greater) with or without comorbid conditions or recent antibiotic therapy should be treated with a fluoroquinolone with antipneumococcal activity or ceftriaxone or cefotaxime plus a macrolide (Table 147.1).

Meningitis

IMPORTANCE AND CLINICAL FINDINGS

Pneumococcal meningitis, the most common bacterial meningitis, affects mainly older adults. Fatalities occur in about 20% to 30% of cases, with adults older than 50 years suffering the highest case-fatality rates. Among children, the case-fatality rate varies between 5% and 15%, substantially higher than the rate in invasive pneumococcal pneumonia. Between one-fourth and one-half of children who survive meningitis develop neurologic sequelae. The disease can develop as a complication of invasive *S. pneumoniae* pneumonia, purulent mastoiditis and sinusitis, endocarditis, asplenia, sickle cell disease, alcoholism, or a skull fracture with communication between the nasopharynx and the subarachnoid space. Patients with meningitis need to be tested for extra-meningeal sources of infection.

The clinical symptoms of meningeal inflammation include fever, headache, and stiff neck and the presence of a Kernig or Brudzinski sign or both; elevated CSF pressure; and CSF findings of frequent neutrophils, glucose level <40 mg/mL, and total protein about 100 mg/mL. Among elderly persons, the symptoms of meningitis may be confounded by changes of age, such as a stiff-feeling neck because of arthritic changes in the cervical vertebrae or the confusion of dementia. Common neurologic complications include seizures and cranial nerve abnormalities.

Pneumococcal meningitis is a medical emergency and patients suspected of having meningitis require immediate diagnosis and treatment. A clinical diagnosis of meningitis almost always seems apparent based on clinical findings alone. A specific etiologic diagnosis of pneumococcal meningitis requires confirmatory laboratory procedures. Initially, this can be accomplished by recognition of the typical morphology of *S. pneumoniae* on a Gram smear of CSF or by testing the CSF using the rapid immunochromatographic membrane assay or both. Ultimately, the infecting strain needs to be isolated so that its MIC to the panel of antibiotics (see above, Antibiotic susceptibility testing) can be determined.

During the years 2000–2010 of routine immunization of children with PCV7, pneumococcal meningitis caused by vaccine serotypes decreased by almost two-thirds in children 2 years of age or younger and by about one-half among adults 65 years and older, but nonvaccine serotypes accounted for almost two-thirds of cases.

TREATMENT (TABLE 147.2).

Both adults and children should be treated with combination therapy, including a third-generation cephalosporin and vancomycin. Adjunctive dexamethasone, in children residing in high-income countries (not low-income countries), preferably started 10 to 20 minutes before antibiotic therapy is begun, shows a decrease in any hearing loss and short-term neurologic sequelae, modest diminution of severity of illness, and slightly lowered case-fatality rate. Adjunctive dexamethasone in adults, given 10 to 20 minutes before antibiotics, can provide some benefit, mainly by reduction of neurologic and auditory sequelae among survivors, although it does not significantly reduce case-fatality rates and questions remain of its ultimate benefit.

Otitis media

IMPORTANCE AND TREATMENT

S. pneumoniae ranks among the three most common pathogens of acute otitis media (AOM) in children (*Haemophilus influenzae* and *Moraxella catarrhalis* are the other two pathogens) and penicillin-resistant *S. pneumoniae* represents a continuing problem in the treatment of this common infection. PCV7 was developed, in part, for prevention of AOM and its routine administration has substantially decreased AOM and long-term recurrent episodes due to vaccine serotypes.

Among children infected with a penicillin-susceptible strain, amoxicillin remains the preferred antibiotic (80–90 mg/kg/day PO, q12h for 5 to 7 days, limited to 1000 mg/dose) or amoxicillin–clavulanate (90 mg/kg/day PO, q12h for 10 days, preparation 600 mg/42.9 mg/5 mL suspension, given with milk or food). Treat children allergic to penicillin with erythromycin–sulfisoxazole (40–50 mg/kg/day PO, divided q6–8h, limited to 2 g/day). When penicillin-resistant strains are suspected, treat with amoxicillin–clavulanate (90 mg/kg/day PO, q12h for 10 days) or ceftriaxone (50 mg/kg IM/IV, once, limited to 1 g/dose).

AOM in adults can be treated with amoxicillin (500 mg q12h PO for 5–7 days or with more serious disease 500 mg q8h PO for 5–7 days), amoxicillin–clavulanate (500 mg/125 mg or 875 mg/125 mg PO, q12h, with food or milk), azithromycin (500 mg PO q24h × 1 day and 250 mg PO q24h × 4 days), erythromycin, clarithromycin, or trimethoprim–sulfamethoxazole. When penicillin-resistant strains are the likely pathogen, treat with azithromycin or clarithromycin.

PNEUMOCOCCAL POLYSACCHARIDE VACCINE

Two pneumococcal vaccines of differing production are licensed (as of June 2013) for immunoprophylaxis of adults and children in the United States (see above, Introduction). The first PPSV23 received approval by the Food and Drug Administration (FDA) in 1983 and the second vaccine PCV13 received approval in February 2010.

PPSV23 is safe, cost-effective, and efficacious, with an overall efficacy rate of about 65% to 70% in immunocompetent adults for the serotypes contained in the vaccine. The 23 serotypes included in PPSV23 represent the most common serotypes that infect children and adults (namely 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F) and cover between 70% and 80% of IPD, depending upon the locality in the United States. Serotype 6A is not included in PPSV23, but is included in PCV13.

PPSV23 is recommended for adults at increased risk of serious IPD, including all adults 65 years and older and adults younger than 65 years of age who suffer certain underlying diseases including chronic heart and lung diseases, diabetes mellitus, CSF leak, cochlear implant, alcoholism, chronic liver disease and cirrhosis, functional and anatomic asplenia, lymphoma, leukemia, Hodgkin's disease, HIV infection, chronic renal failure, nephrotic syndrome, generalized malignancy, solid organ transplant, multiple myeloma, iatrogenic immunosuppression and who smoke cigarettes. However, adults 19 years of age and older who suffer immunocompromising diseases, CSF leaks, cochlear implants, and functional or anatomic asplenia, and who never previously received PPSV23 should, when these underlying diseases are recognized, receive one dose of PCV13 first and then receive one dose of PPSV23 about 8 weeks subsequently. If they previously received one or more doses of PPSV23, they should receive one dose of PCV13 one year after the last dose of PPSV23.

Routine revaccination with PPSV23 is not recommended. Adults who received their first dose of vaccine before 65 years of age should receive a second dose of PPSV23 after 65 years of age and at least 5 years after the first dose. Also a second dose of vaccine is recommended 5 years after the first dose for adults 19 years and older with immunocompromising diseases, CSF leaks, cochlear implants, and functional or anatomic asplenia. Antibodies wane over time in all adults; second doses of vaccine provide satisfactory booster responses. Injection site reactions occur somewhat more frequently after revaccination than after primary vaccination.

Recently, PCV13 was recommended for all adults age 65 years and older. If they have never received a pneumococcal vaccine the recommendation is for a single dose of PCV13 followed in 6 to 12 months by a single dose of PPSV23. However, if they have received a single dose of PPVS23 after age 65, they should receive also a single dose of PCV13 at least 1 year later. If they had received a single dose of PPVS23 before 65 years of age, then after age 65 years they should receive first a single dose of PCV13 and 6 to 12 months later a single dose of PPVS23. The two doses of PPVS23 should be given at least 5 years apart.

Routine immunization of children with PCV7 (which included serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) for prevention of otitis media and IPD cases began in 2000 and ended in 2010. In assessments conducted during the ensuing 10 years, PCV7 proved highly efficacious in children, reducing substantially IPD cases due to vaccine serotypes, as much as 80% to 90%, or near elimination of some vaccine serotypes, and a reduction by at least one-half of total cases of IPD. Unexpectedly, an additional benefit of its usage in children was a substantial decrease among adults of IPD cases

caused by PCV7 serotypes, likely due to diminished shedding of these serotypes by children, and consequently, less spread of these serotypes from children to adults, especially grandparents. As the number of cases of IPD due to vaccine serotypes declined both in children and adults, several other serotypes emerged worldwide to occupy this void, designated replacement serotypes, which were not included in PCV7 vaccine. The need to cover these replacement serotypes led to the development and approval of PCV13.

In 2010, PCV13 (which includes serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) replaced PCV7 for routine childhood immunization against pneumococcal otitis media and IPD. It is recommended for routine immunization of children 6 weeks to 5 years of age, starting at 2 months of age. The dose is 0.5 mL intramuscularly administered at 2, 4, 6, and 12 to 15 months of age. A catch-up schedule for children with an incomplete schedule of PCV13 or only PCV7 is available at the ACIP website (http://www.cdc.gov/vaccines/acip/index.html). A single dose of PCV13 is recommended for children 6 to 18 years of age. Children 2 years of age and older who are immunocompromised or have sickle cell disease or functional or anatomic asplenia should receive one dose of PPSV23 eight weeks or later after their last dose of PCV13 and a second dose of PPSV23 five years later, whereas immunocompetent children 2 years of age and older with chronic illness (chronic heart or lung diseases, cochlear implants, CSF leaks, or diabetes mellitus) should receive only a single dose of PPSV23 eight weeks or later after their last dose of PCV13.

Currently, pneumococcal vaccine coverage among at-risk adults falls short of Healthy People 2020 goals. Wider vaccine usage in children and adults can be expected to alter the prevalence of *S. pneumoniae* as an etiologic agent of AOM, pneumonia, and meningitis.

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148. *Pseudomonas*, *Stenotrophomonas*, and *Burkholderia*

Titus L. Daniels and David W. Gregory

Pseudomonas aeruginosa is an aerobic, gram-negative bacillus with a diversified ecologic niche. *Pseudomonas aeruginosa* is highly pathogenic among immunocompromised patients and is responsible for substantial morbidity and mortality. *Pseudomonas aeruginosa* is principally a healthcare-associated pathogen, although community-onset infection has been described among immunocompetent and immunocompromised patients (i.e., neutropenia, human immunodeficiency virus [HIV], acquired immunodeficiency syndrome [AIDS]). Such patients may be encountered by primary care and subspecialty physicians alike, and diagnosis requires a high index of suspicion. Infections commonly associated with *P. aeruginosa* include pneumonias, bloodstream infections (BSI), urinary tract infections, and surgical site infections (Table 148.1). Two related species, *Stenotrophomonas maltophilia* and *Burkholderia cepacia*, are briefly discussed.

Table 148.1 Risk factors for *P. aeruginosa* infections

Type of infection	Setting
Bacteremia	Neutropenia, pulmonary or urinary tract focus, burns
Pneumonia	Mechanical ventilation, neutropenia, chronic lung disease
Endocarditis	Injection drug use, prosthetic heart valve
Meningitis, brain abscess	Hematogenous or contiguous spread, neurosurgery, penetrating head trauma
Urinary tract infection	Bladder instrumentation
Osteomyelitis, septic arthritis (e.g., sternoclavicular joint)	Contiguous or hematogenous spread, injection drug use
Osteochondritis	Puncture wounds of the feet
Malignant external otitis	Diabetes, advanced age
Green nail syndrome	Water immersion, wet skin

EPIDEMIOLOGY

The epidemiology of *P. aeruginosa* infections reflects its predilection for moist environments. In hospitals, *P. aeruginosa* has been isolated from respiratory devices, disinfectants, distilled and tap water, and sinks. *Pseudomonas aeruginosa* can readily colonize the upper respiratory tract of mechanically ventilated patients, the gastrointestinal tract of patients receiving chemotherapy or broad-spectrum antibiotics, and the wounds of burn patients. Colonization usually precedes invasive infection.

Among healthcare-associated infections occurring in intensive care units, *P. aeruginosa* is the most commonly identified gram-negative pathogen, and the second most commonly identified organism overall. Emergence and spread of antimicrobial resistance, especially multidrug resistance (MDR), among *P. aeruginosa* is frequent. The National Nosocomial Infections Surveillance System 2003 report revealed that 29.5% of intensive care unit isolates are resistant to quinolones and 31.9% are resistant to third-generation cephalosporins. Furthermore, 21.1% of the isolates are resistant to imipenem, an agent once considered universally active against *P. aeruginosa*. The emergence and spread of MDR *P. aeruginosa* challenges the clinician when selecting appropriate antimicrobial therapy and underscores the importance of obtaining cultures with susceptibility testing in patients suspected to have bacterial infections. Knowledge of local antimicrobial resistance trends is essential to ensure optimal patient outcomes.

DIAGNOSIS

The clinical features of *P. aeruginosa* infections are indistinguishable from those of other bacterial organisms, and a definitive diagnosis requires specimen cultures from the suspected site of infection

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Table 148.2 Antimicrobial agents for *P. aeruginosa*

Antimicrobial agent	Dose[a]/route /interval	Comment
β-Lactams		
Ticarcillin–clavulanate	3.1 g IV q4–6h	
Piperacillin	3–4 g IV q4–6h	
Piperacillin– tazobactam	4.5 g IV q6h 3.375 g IV q6h	Recommended pneumonia dose Recommended nonpneumonia dose
Ceftazidime	2 g IV q8h	Preferred agent for CNS infections
Cefepime	2 g IV q12h	
Meropenem	1 g IV q8h	
Imipenem–cilastatin	0.5 g IV q6h	
Aztreonam	2 g IV q8h	Frequently reserved for penicillin-allergic patients
Quinolones		
Ciprofloxacin	400 mg IV q12h 500–750 mg PO q12h	Most active antipseudomonal quinolone in vivo
Levofloxacin	750 mg IV/PO daily	
Aminoglycosides[b,c,d]		
Amikacin	15 mg/kg IV once daily or 7.5 mg/kg IV q12h	
Gentamicin	5 mg/kg IV once daily or 2 mg/kg loading dose, then 1.7 mg/kg IV q8h	
Tobramycin	5 mg/kg IV once daily or 2 mg/kg loading dose, then 1.7 mg/kg IV q8h	
Polymyxins		
Polymyxin E (colistin)	1.5 mg/kg IV q8h	
Polymyxin B	0.75–1.25 mg/kg IV q12h	

[a] Suggested dosing is for adult patients with normal renal and hepatic function.
[b] Aminoglycosides are not recommended for monotherapy against *P. aeruginosa*.
[c] Once-daily aminoglycoside dosing has been shown to be effective, less nephrotoxic, and less ototoxic, and is the preferred dosing method.
[d] Aminoglycoside levels and renal function should also be closely monitored during therapy.
Abbreviation: CNS = central nervous system.

(i.e., blood, sputum, urine) to identify the organism. Other clinically important gram-negative organisms that resemble *P. aeruginosa* come from the genera *Stenotrophomonas*, *Burkholderia*, and *Ralstonia*.

ANTIMICROBIAL THERAPY

Initial selection of an agent should be guided by the site of infection, the patient's allergic history, and the institutional antibiogram. Early, aggressive antimicrobial therapy, with modification when susceptibility results become available, imparts a survival advantage and minimizes the emergence of antimicrobial resistance. Although several antipseudomonal antibiotics exist (Table 148.2), intrinsic or acquired resistance and bacterial persistence at sites of infection complicate management and eradication.

β-lactam antibiotics active against *P. aeruginosa* include the extended-spectrum penicillins, some extended-spectrum cephalosporins, the carbapenems (except ertapenem), and the monobactam aztreonam. These agents form the basis for treatment of most *Pseudomonas* infections due to extensive clinical experience and patient tolerability. The high prevalence of reported penicillin allergy is the primary limitation.

The aminoglycosides tobramycin, amikacin, and gentamicin have excellent in vitro activity against *P. aeruginosa*. The concentration-dependent bactericidal activity and the postantibiotic effect of aminoglycosides provide the rationale for once-daily dosing. Aminoglycoside monotherapy should be avoided due to selection

of resistant mutants and increased risk of clinical failure. Renal function and serum aminoglycoside levels should be monitored closely.

The quinolones have been frequently used for the treatment of *P. aeruginosa* and other bacteria. They possess excellent tissue penetration, good oral bioavailability, and a favorable safety profile. Ciprofloxacin and levofloxacin are the most active quinolones against *P. aeruginosa*, with ciprofloxacin considered the more active of the two. Increasing resistance to the quinolones, however, should temper reliance on their use as the basis for empiric therapy against *P. aeruginosa*, especially among hospitalized patients.

Use of polymyxin antibiotics has re-emerged due to MDR and pandrug-resistant gram-negative infections, including *P. aeruginosa*. The polymyxins possess activity against a variety of gram-negative organisms but have been limited in use due to their adverse effects, namely nephrotoxicity and neurotoxicity. Polymyxins are currently recommended only for isolates resistant to other antibiotics. Susceptibility testing should be performed as resistance to the polymyxins has been reported.

Much controversy exists over the use of combination therapy ("double-coverage") for the treatment of infections due to *P. aeruginosa*. Data from a Cochrane review of sepsis comparing β-lactam and aminoglycoside combination therapy versus β-lactam monotherapy found no advantage to combination therapy for all-cause mortality (RR 1.01; 95% CI 0.75–1.35) or clinical failure (RR 1.11; 95% CI 0.95–1.29). Empiric combination therapy for most serious infections may still be warranted when considering local resistance data and to ensure appropriate treatment of other possible infecting organisms. The guiding principle for selecting combination therapy should be that each agent has a unique mechanism of action to avoid a possible antagonistic effect; β-lactam and aminoglycoside combination therapies are the most studied and continue to be primarily recommended.

INFECTIONS CAUSED BY *P. AERUGINOSA*

Respiratory infections

Pseudomonas aeruginosa pneumonia may follow colonization of patients in the setting of mechanical ventilation, antibiotic administration, neutropenia, AIDS, and chronic pulmonary disease, particularly in patients with cystic fibrosis (Table 148.3). Lower respiratory tract infection may be distinguished from airway colonization by an increase in quantity and purulence of respiratory secretions. Clinical manifestations may be fulminant with fever, chills, dyspnea, productive cough, and systemic toxicity. Diffuse bronchopneumonia with nodular infiltrates is commonly seen on chest radiograph. Cavitary lesions may occasionally be seen. Pneumonia may be accompanied by bacteremia, particularly in neutropenic patients. Empiric antimicrobial treatment in the hospitalized or neutropenic patient with fever and lung infiltrate should include coverage for *P. aeruginosa*. Conventional antimicrobial therapy for *P. aeruginosa* pneumonia includes an antipseudomonal β-lactam combined with an aminoglycoside or a quinolone.

Table 148.3 Management of *P. aeruginosa* infections

Infection	Antibiotics[a]	Adjunctive
Meningitis	Ceftazidime[b] + AG	Intrathecal AG
Bacteremia	AP-BL + AG or FQ	Identify source
Endocarditis	AP-BL + AG or FQ	Valvulectomy for persistent bacteremia
Pneumonia	AP-BL + AG or FQ	Aggressive respiratory care
Malignant external otitis	AP-BL + AG or FQ	Surgical debridement may be necessary
Osteomyelitis	AP-BL + AG or FQ	Surgical debridement
Urinary tract	FQ alone or AP-BL ± AG	Remove catheter

Abbreviations: AP-BL = antipseudomonal β-lactam; AG = aminoglycoside; FQ = fluoroquinolone (i.e., ciprofloxacin or levofloxacin).

[a] Recommended antibiotics for empiric coverage against *P. aeruginosa*. Therapy should be refined once susceptibility data are available.

[b] Aztreonam may be used for patients with penicillin or cephalosporin allergy. Other AP-BL do not achieve reliable cerebrospinal fluid concentrations.

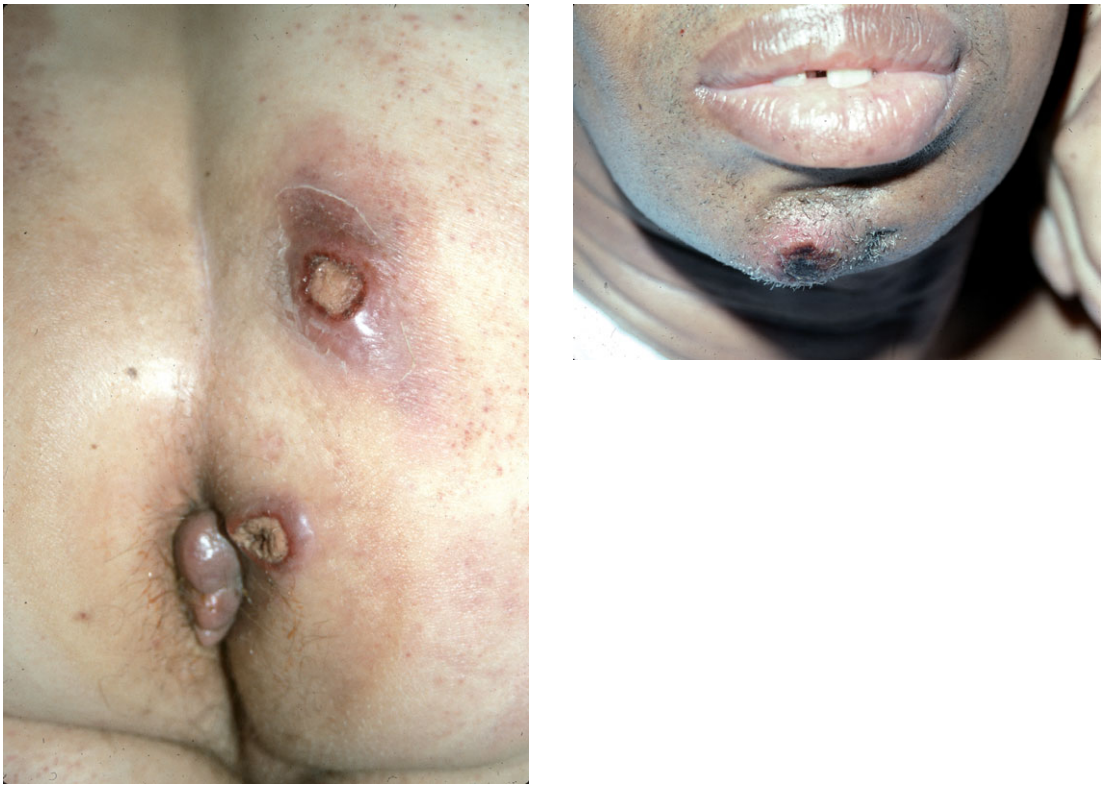

Figure 148.1 Ecthyma gangrenosum. (A) Lesions with ulceration and surrounding erythema. (B) A more classic lesion with necrosis and surrounding erythema.

Inhaled tobramycin (300 mg every 12 hours) may be considered as adjunctive therapy.

Patients with cystic fibrosis are prone to chronic lower respiratory infections with mucoid strains of *P. aeruginosa*. These infections usually persist for a lifetime, with frequent acute exacerbations manifested by decreased exercise tolerance, increased cough and sputum, and weight loss. Therapy consists of an antipseudomonal penicillin containing ticarcillin or piperacillin plus an aminoglycoside. These patients may require large doses because of altered pharmacokinetics. Aggressive physiotherapy, nutrition, and hydration are essential.

Bloodstream infections (BSI)

BSI may complicate *P. aeruginosa* infections at other sites. Predisposing factors include neutropenia, hematologic malignancy, organ transplantation, vascular and urinary tract catheterization, and antibiotic use. The lower respiratory tract is the most common source of *Pseudomonas* bacteremia, followed by skin, soft tissues, and the urinary tract. Evaluation should include an aggressive search for the source of the bacteremia.

No distinct clinical characteristics differentiate *P. aeruginosa* BSI from other gram-negative bacteremias. Most patients have fever, tachycardia, and tachypnea. Many have signs of systemic toxicity with hypotension, shock, disseminated intravascular coagulopathy, and altered mental status. Skin manifestations include papules, bullae, and, rarely, ecthyma gangrenosum (Figure 148.1), a focal skin lesion characterized by hemorrhage, necrosis, and vascular invasion by bacteria. Prompt initiation of combination antimicrobial therapy is crucial because there is a high mortality. Therapy should continue for 2 to 3 weeks in seriously ill patients.

Infective endocarditis

Infective endocarditis caused by *P. aeruginosa* occurs primarily in the setting of injection drug use and occasionally with prosthetic heart valves.

Injection drug users acquire this organism from nonsterile diluents such as tap water or nonsterile paraphernalia. Bacteremia with fever is invariably present. Tricuspid valve infection, which is typical, commonly presents with signs of septic pulmonary embolism. If treatment is early and aggressive with effective antibiotics, cure may be achieved without surgery. Tricuspid valvulectomy may be necessary in the event of bacteriologic failure or recurrence. Involvement of the aortic and mitral valves may manifest as a severe acute illness with sepsis and large arterial emboli necessitating early surgical valve replacement in addition to antimicrobial treatment. Combination therapy with a β-lactam agent and an aminoglycoside in high doses (e.g., tobramycin, 8 mg/kg/day) is recommended. Antibiotic therapy should be continued for at least 6 weeks.

Urinary tract infections

Pseudomonas aeruginosa is the third most common nosocomial urinary pathogen. These infections are most commonly associated with indwelling urinary catheters. Bacteremia, a common complication, may lead to metastatic infection (e.g., vertebral osteomyelitis). Symptomatic urinary tract infections should be treated by removing the catheter when possible and by administering an antibiotic. Monotherapy with an antipseudomonal β-lactam or a quinolone suffices unless there is secondary bacteremia or upper urinary tract infection. Oral quinolones may be used successfully even in complicated urinary tract infections. A 7- to 10-day course of treatment is adequate for uncomplicated cases. Longer courses of 2 to 3 weeks may be necessary for pyelonephritis, renal abscess, or complicating bacteremia. Asymptomatic bacteriuria does not typically require treatment. Eradication of the bacteriuria is often impossible if the patient has an anatomic abnormality or a foreign body, and antibiotics in this setting may select only for resistant organisms.

Meningitis

Pseudomonas aeruginosa is a rare cause of meningitis and brain abscess in the general population, though it is a well-described complication of neurosurgery-related meningitis. Infection may occur by (1) extension from a contiguous structure such as mastoid or sinuses, (2) direct inoculation from penetrating trauma or neurosurgical procedures, or (3) metastatic spread from a distant site. Ceftazidime is the antimicrobial of choice because of its excellent in vitro activity and its ability to penetrate cerebrospinal fluid (CSF). Aztreonam and the carbapenems have good in vitro activity, but experience with these agents is limited. Addition of an aminoglycoside may be justified on the basis of possibly conferring synergy and preventing emergence of antibiotic resistance. Because of poor penetration of aminoglycosides into CSF, intrathecal or intraventricular doses may be required. There are anecdotal reports of successful therapy with parenteral ciprofloxacin, but quinolones should be used only when other antibiotics have failed or when organisms are resistant to β-lactam agents. Cure of *Pseudomonas* central nervous system infections may require surgical drainage of brain abscesses, debridement of infected tissues, and removal of prosthetic materials. A minimum of 2 weeks and as many as 6 weeks of antimicrobial therapy may be necessary.

Ear infections

Otitis externa is most commonly caused by *P. aeruginosa* and is usually associated with immersion (swimmer's ear). Patients complain of pain and pruritus. Examination reveals edema, exudate, and erythema of the pinna and external canal. This infection is treated with topical agents such as antibiotic drops (polymyxin, neomycin, or a quinolone) plus hydrocortisone or dilute acetic acid (see Chapter 6, Otitis media and externa).

A more invasive and necrotizing process involving the bone and soft tissues of the external auditory canal and with potential to extend to the temporal bone and base of the skull is referred to as *malignant otitis externa* (Figure 148.2). This principally affects elderly persons and diabetics. Otalgia and purulent drainage from the external ear canal are present. Neurologic complications such as cranial nerve palsies may become manifest. Computed tomography (CT) or magnetic resonance imaging (MRI) is useful to delineate the extent of bone and soft-tissue destruction and to monitor treatment. Because debridement may be necessary, surgical consultation is advised. Combination antimicrobial treatment is recommended for a minimum of 4 weeks. The course of treatment should be extended to 6 to 8 weeks for more extensive disease.

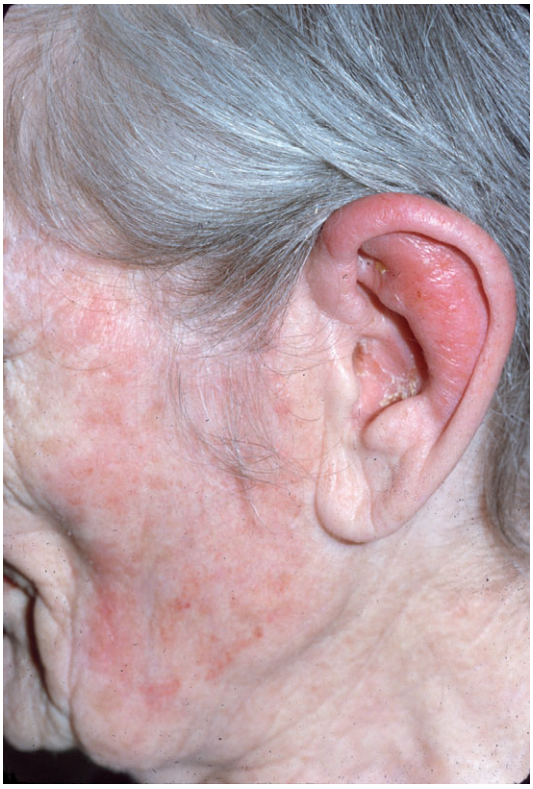

Figure 148.2 Malignant otitis externa. Edema and erythema of the helix, antihelix, and scapha of the ear are seen here. As infection progresses, the tragus often becomes involved. Visualization of the canal is frequently limited due to edema and pain.

Bone and joint infections

Pseudomonas aeruginosa causes osteomyelitis and septic arthritis as a result of hematogenous dissemination or contiguous spread. Vertebral osteomyelitis usually occurs in elderly patients with urinary tract infections associated with bladder instrumentation and in intravenous drug users. Neck or back pain with paraspinal tenderness is a common presentation. CT and MRI are sensitive diagnostic means of defining the extent of disease. The pathogen can be isolated by needle aspiration or biopsy under fluoroscopic or CT guidance. Occasionally, surgical exploration for biopsy, culture, and decompression is necessary. Removal of prosthetic material is usually necessary. Combination antibiotic therapy with an antipseudomonal β-lactam and either an aminoglycoside or quinolone should be used for a minimum of 4 to 6 weeks. Monotherapy has been used successfully, but treatment failures have occurred.

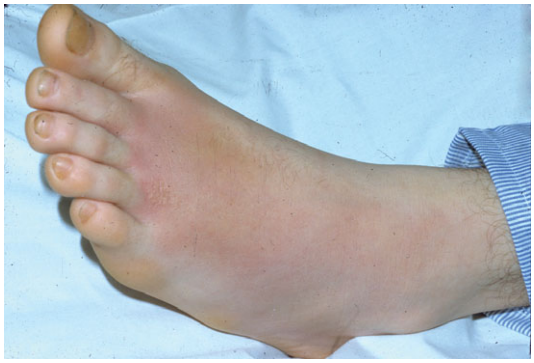

Figure 148.3 Osteochondritis following a nail puncture wound of the sole. Cellulitis is often a prominent feature in patients with acute osteochondritis due to *P. aeruginosa*, as evidenced in this photo. Edema is also a common finding.

Contiguous osteomyelitis arises from direct extension of infected overlying skin and soft tissues or penetrating trauma. *Pseudomonas aeruginosa* may be implicated in this setting in patients with infected diabetic foot ulcers. Vascular insufficiency and the polymicrobial nature of this infection may complicate management. The goal of therapy is to achieve effective levels of antimicrobials in bone and soft tissues. Prolonged antimicrobial treatment (up to 6 weeks), including a β-lactam antipseudomonal agent and an aminoglycoside, has been the current standard, but quinolones used either alone or in combination with a β-lactam have proved efficacious in open-label trials.

Osteochondritis of the foot involving bone and fibrocartilaginous joints is frequently seen following puncture wounds through the soles of footwear colonized by *P. aeruginosa* (Figure 148.3). Treatment consists of surgical debridement combined with an antimicrobial agent such as ceftazidime or ciprofloxacin for a minimum of 4 weeks.

Skin infections

Exposure to contaminated whirlpools, hot tubs, and swimming pools may produce *P. aeruginosa* folliculitis, a diffuse red maculopapular or vesicopustular rash (Figure 148.4). The eruption is self-limited and does not require specific antimicrobial treatment.

Burn wounds may become colonized and subsequently infected with *P. aeruginosa*. Bloodstream invasion may thus occur, resulting in

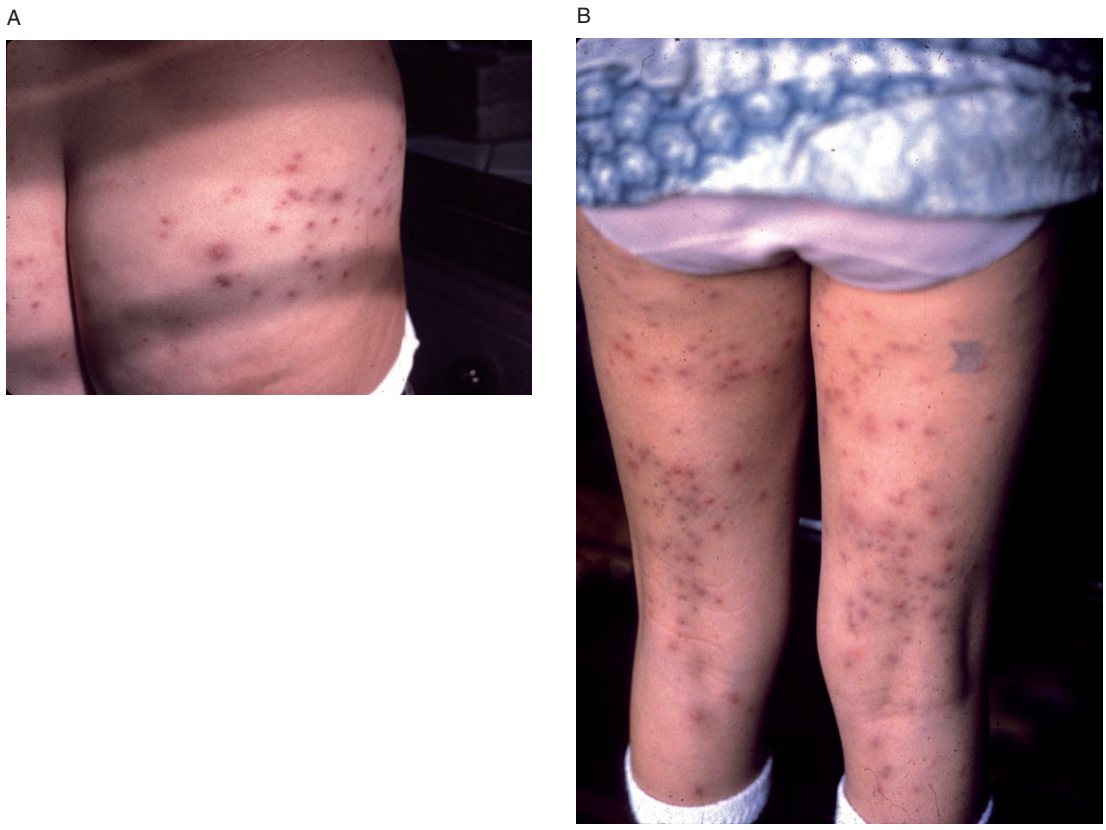

Figure 148.4 Folliculitis. The folliculitis of *P. aeruginosa* may appear similar to other common dermatologic conditions. The appearance of the lesions in **A** raises the possibility of shingles. The patient in **B** has a widespread infection that may be confused with staphylococcal infection or steroid-induced folliculitis. Culturing the contents of the lesions will aid in obtaining an accurate diagnosis.

septicemia. Systemic antibiotic combinations should be administered. A topical agent such as mafenide acetate or silver sulfadiazine may be considered to reduce burn wound colonization. Avoidance of hydrotherapy also reduces the risk of *Pseudomonas* infections in burn patients.

Persons with a history of submersion of the hands may develop greenish discoloration of the nail plates and *Pseudomonas* nail bed infection. This condition has been called *green nail syndrome* (Figure 148.5). Treatment requires elimination of the exposure; orally administered ciprofloxacin is a useful adjunct.

The warm, moist toe webs of the feet may become infected with *P. aeruginosa*. The spaces between the third, fourth, and fifth toes are the most common sites. Toe web infections have been most commonly associated with military recruits, athletes, and laborers. Tinea pedis is a common antecedent. The infected tissue is damp, boggy, macerated, and white. Adjacent skin and subcutaneous tissue may become inflamed. More severe infection can progress to ulceration (Figure 148.6).

Pseudomonas toe web infection may resemble tinea pedis but does not improve with topical antifungal agents. *Pseudomonas* should be suspected when green pigment is visible on the patient's socks, bandages, or on dried exudate. Green toenails strongly suggest the diagnosis, and further evidence is obtained if Wood's light shows green–white fluorescence (Figure 148.7).

Treatment of toe web infections includes an antipseudomonal antimicrobial and soaking with 2% acetic acid solution. Prevention of infection is best achieved by keeping feet and toes clean and dry and by wearing work boots or athletic shoes on alternate days to allow for the lining to fully dry.

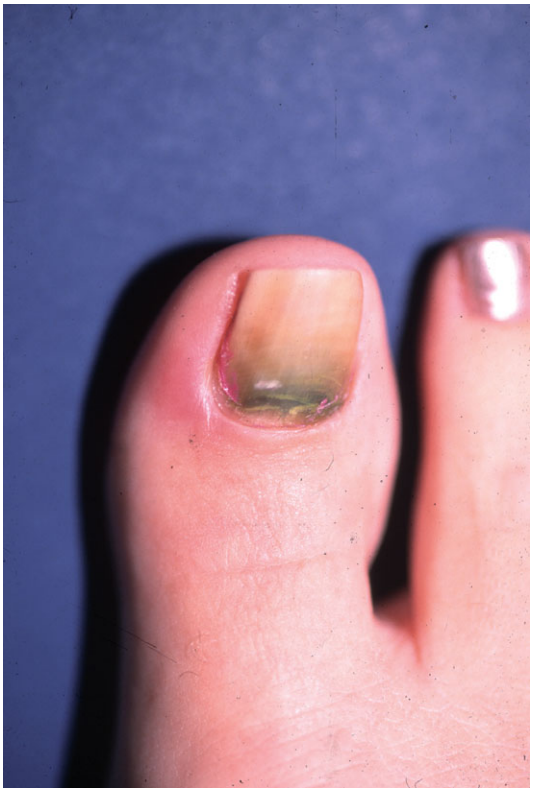

Figure 148.5 Green nail syndrome. Note the characteristic green appearance of the nail.

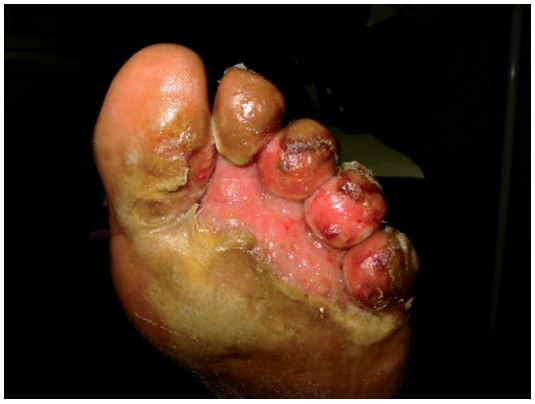

Figure 148.6 Toe web infection. As toe web infections progress, a characteristic macerated appearance is seen.

Figure 148.7 Use of a Wood's light reveals the typical luminescence classically described with *P. aeruginosa*.

INFECTIONS CAUSED BY RELATED SPECIES

Stenotrophomonas maltophilia is a healthcare-associated, gram-negative pathogen that may cause bacteremia, pneumonia, and wound infection. *Stenotrophomonas maltophilia* healthcare-associated pneumonia is associated with mechanical ventilation, tracheostomy, use of nebulizers, and previous exposure to broad-spectrum antibiotics. Patients usually have pre-existing lung conditions such as chronic obstructive pulmonary disease. Isolation of *S. maltophilia* from the respiratory tract in ventilator-associated pneumonia is an important predictor of mortality. Management of *S. maltophilia* pneumonia and other infections is often difficult because the organism is usually resistant to most antipseudomonal β-lactams, carbapenems, and aminoglycosides. Trimethoprim–sulfamethoxazole (TMP–SMX) is the antibiotic of choice for therapy. Ceftazidime, ticarcillin–clavulanate, and the quinolones have variable activity among strains. Combination therapy with TMP–SMX and a β-lactam such as ticarcillin–clavulanate or ceftazidime (if susceptibility is documented) has been proposed based on in vitro synergy and anecdotal reports of clinical efficacy. The polymyxins retain activity against selected highly resistant isolates.

Burkholderia cepacia is an opportunistic pathogen that may colonize the respiratory tract of a patient with cystic fibrosis and lead to persistent disease with progressive respiratory failure. Therapy is thwarted by antibiotic resistance to many β-lactam agents and aminoglycosides. Susceptibility testing is essential as resistance to quinolones, TMP–SMX, and the carbapenems is common and variable. Chloramphenicol may retain activity, whereas the polymyxins are generally ineffective.

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149. Rat-bite fevers

Neil S. Lipman

For 2300 years, illness associated with rat bites has been recognized in India, which is believed to be the country of origin for the disease. The first recorded description of rat-bite fever was in lectures by a physician at Yale in the early nineteenth century. It was not until 1902 that Japanese workers describing the clinical entity in a European journal coined the term "*Rattenbisskrankheit*," or rat-bite fever. Rat-bite fever comprises two clinically similar but distinct bacterial diseases, caused by two unrelated agents, *Streptobacillus moniliformis* and *Spirillum minus*. The organisms are distributed worldwide, with *S. moniliformis* more common in the United States and Europe, and *S. minus* more common in the Far East.

Rat-bite fevers are most frequently associated with the bite or, less frequently, a scratch or direct contact (e.g., child kissing pet rat) with pet, wild, or laboratory rats. A number of reported cases were not associated with rat bites or contact, although all patients had a history of occupational exposure to rat-infested areas or contaminated materials. Disease caused by these agents has also followed contact with a variety of other species, including mice, gerbils, guinea pigs, squirrels, dogs, cats, ferrets, turkeys, and weasels, all of which presumably had contact with rats or contaminated materials. Estimates are that 2 million animal bites occur annually in the United States of which ~1% are caused by rats. Many cases of rat-bite fever occur in individuals of low socioeconomic status in cities or, with increasing frequency, in association with pet rats, whose popularity is increasing. Rats are also often fed to pet snakes and other reptilians with cases of rat-bite fever described in their owners. Asymptomatic rats are the principal reservoirs for the organisms that reside as commensals in the nasopharynx, middle ear, and proximal trachea.

Diagnosis is rare, likely the result of a low incidence of disease despite substantial potential exposure, a low index of suspicion of attending physicians, the routine postexposure use of effective antimicrobials, and the difficulty of isolating the organism in the laboratory. The true incidence in the United States is unknown, since the disease is not reportable. More than 50% of the reported cases in the United States are associated with children under the age of 12. Rat-bite fever is also an occupational disease of laboratory workers; it is the most commonly reported zoonosis associated with laboratory rats.

The rat is the natural reservoir and primary host of both *S. moniliformis* and *S. minus*, neither of which is routinely associated with natural disease in the species. Rarely, otitis media has been described with *S. moniliformis* in the laboratory rat. The organisms are nasopharyngeal commensals and may be found in other tissues including the urine and the blood. It is estimated that 10% to 100% of domestic and 50% to 100% of wild rats are colonized with *S. moniliformis*. Estimates of infection rates in laboratory rats during the first half of the previous century were similar to those reported for wild populations, but modern production techniques and maintenance, in concert with frequent monitoring of commercial suppliers, has reduced this rate dramatically. The actual carrier rate in laboratory rats is unknown but is suspected to be extremely low. Although disease in humans has occasionally been associated with other species, these species are not believed to be commensal carriers.

PRESENTATION

Rat-bite fevers are acute, systemic illnesses with relapsing fever. Streptobacillary rat-bite fever, streptobacillary fever, or streptobacillosis follows infection with *S. moniliformis*. Haverhill fever and epidemic arthritic erythema are diseases caused by streptobacillosis acquired through ingestion of contaminated water, raw milk, or food. Sodoku, which derives from the Japanese word for rat (*so*) and poison (*doku*), spirillary rat-bite fever, and

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Table 149.1 Clinical features of rat-bite fevers

Clinical features	Streptobacillary form	Spirillary form
Incubation period	2–10 days	7–21 days
Fever	+++	+++
Chills	+++	+++
Myalgia	+++	+++
Rash	++ Morbilliform/petechial	++ Maculopapular
Lymphadenitis	+	++
Arthralgia, arthritis	++	–
Indurated bite wound	–	+++
Recurrent fever/ constitutional signs (untreated)	Irregular periodicity	Regular periodicity

spirillosis are diseases resulting from *S. minus* infection. Although similar, these diseases can be differentiated clinically (Table 149.1). Streptobacillary rat-bite fever has a shorter incubation period than the spirillary form and is often accompanied by rash and arthralgia. Haverhill fever is more frequently associated with vomiting, diarrhea, and sore throat. An indurating chancre develops at the site of inoculation and accompanies clinical signs in the spirillary form. Dual infections, albeit extremely rare, may occur. Most cases of streptobacillary disease spontaneously resolve within 2 weeks. If the patient goes untreated, 7% to 10% of cases are fatal. The clinical course of disease in infants may be particularly rapid and fatal. Mortality has been reported in adults following a short (<12 hour) presentation.

The incubation period of streptobacillary rat-bite fever is 2 to 10 days; however, onset usually occurs within 3 days of exposure. Clinical signs develop despite rapid healing of the bite wound, presumably as a result of bacteremia and septicemia. Illness of sudden onset is characterized by remittent chills, fever, headache, and myalgia, and results from direct infectious as well as immune-mediated mechanisms. A morbilliform or petechial rash, which may be a result of leukocytoclastic vasculitis, develops in 75% of patients, frequently within days of onset, on either the lateral or the extensor surfaces of the extremities, occasionally involving the palms and the soles. Infrequently, the rash may be generalized and/or present with pustules, desquamation, and purpura. Simultaneous with rash development, approximately 50% of patients have severe arthralgia or frank arthritis of at least one, but frequently more than one, large joint. The arthritis may be suppurative or nonsuppurative; monoarticular, or migrating and polyarticular; and rarely occurs without other manifestations. Untreated, the course is biphasic, with fever and symptoms diminishing 2 to 5 days after onset and recurring several days later. Arthritis, endocarditis, myocarditis, pericarditis, hepatitis, pancreatitis, parotiditis, prostatitis, pneumonia, nephritis, meningitis, metastatic abscessation, septicemia, and chorioamnionitis are reported complications. Relapsing fever with return of constitutional symptoms of 1 to 6 days' duration is not uncommon. Afebrile cases have been described.

In the United States, the spirillary form is considerably less common than streptobacillary disease and is rarely associated with infection acquired from laboratory rats. Illness follows an incubation period, usually 7 to 21 days but sometimes as short as 2 days or as long as months. There is initial healing of the bite wound. Subsequently, an indurated chancre or eschar develops at the wound site and is accompanied by a regional lymphadenitis and lymphangitis, fever, rigors, myalgia, and, in about 50% of the cases, an erythematous maculopapular rash originating from the wound. Arthritis is uncommon. Untreated, fevers and other symptoms resolve but then recur regularly, and mortality is estimated between 7% and 13%.

DIAGNOSIS

Diagnosis is suggested by a rat bite or rat contact, or exposure to rat-infested areas or contaminated materials, and clinical presentation. Patients may present without a history of rat bite or after a prolonged disease course. For infections caused by *S. moniliformis*, definitive diagnosis depends on isolation of the organism by microbiologic culture and/or identification of the bacterium in culture or blood, fluid, or tissue samples by amplifying part of the 16S RNA gene using a generic primer set, followed by sequencing, using polymerase chain reaction (PCR). A *S. moniliformis*-specific PCR has also been described using primers based on human and rodent strains. Detection by PCR in blood is more difficult than tissues because the copy number is lower, hemoglobin is inhibitory, and clearance of dead organisms is quicker after antibiotic treatment is initiated. There are no reliable serologic tests currently available in humans for either organism. A high index of suspicion in the laboratory is

frequently necessary, as these organisms are extremely difficult to isolate.

S. moniliformis is a fastidious, facultatively anaerobic, highly pleomorphic, asporogenous, gram-negative rod, measuring less than 1 × 1 to 5 μm long. Curved and looping, nonbranching filaments as long as 150 μm may be formed. Characteristic bulbous swellings may be observed in older cultures or in cytologic specimens, resulting in dismissal of the organism as proteinaceous debris. The bacterium has two variants, the bacillary and the cell-wall-deficient, penicillin-resistant, apathogenic L-phase variant. Spontaneous conversion from one form to another, which alters the organism's sensitivity to antimicrobial agents, may be responsible for clinical relapses and resistance to therapy. *S. moniliformis* is difficult to identify in most hospital laboratories because of its fastidious growth requirements and slow growth. The organism may be demonstrated by Giemsa, Gram, Wright, or silver stain in blood, synovial fluid, or other body fluids; samples should be mixed with 2.5% sodium citrate to prevent clotting before examination. Blood and joint fluid should be cultured in media enriched with 15% blood; 20% horse, calf, or rabbit serum; or 10% to 30% ascitic fluid. Media employed successfully include blood agar bases, chocolate agar, Schaedler agar, thioglycollate broth, meat-infusion broth, and tryptose-based media. Nalidixic acid can be added to the media to prevent overgrowth by gram-negative bacteria. Brain–heart infusion cysteine broth supplemented with Panmede, a papain digest of ox liver, has been advocated. The medium should not contain sodium polyanethol sulfonate (SPS), an anticoagulant and bacterial growth promoter used in blood culture media, as it inhibits the growth of the organism. Inoculated media are incubated at 37°C (98.6°F) in humidified 5% to 10% carbon dioxide atmosphere. Characteristic "puffballs" appear after 2 to 6 days in broth; on agar 1- to 2-mm round, gray, smooth, glistening colonies are observed. L-forms produce colonies with a typical fried-egg appearance. Identification is made by biochemical profile. The API ZYM® system and fatty acid profiles may be valuable in rapid identification. In the United States the Center for Disease Control's Meningitis and Special Pathogens Branch or a state public health laboratory can be contacted for assistance with culture and/or diagnosis. The shell vial cell culture technique has been described to isolate *S. moniliformis* when growth in culture media was unsuccessful.

S. minus is a gram-negative aerobic, motile, rigid spiral bacterium. It is 0.2 to 0.5 × 3 to 5 μm long and has two to six wide angular windings and pointed ends with one flagellum at each pole. *S. minus* cannot be grown on any artificial medium. It may be demonstrated in dark-field microscopy in wet mounts of blood, exudate from the bite wound, cutaneous lesions, and lymph nodes or in Giemsa- or Wright-stained specimens from these sites. Isolation requires intraperitoneal inoculation of infected materials into guinea pigs or mice followed by dark-field examination of the animal's blood or peritoneal exudate 1 to 3 weeks later.

Differential diagnosis of rat-bite fevers can be broad, and can include septic arthritides such as Lyme disease, gonococcal arthritis, and brucellosis and noninfectious inflammatory polyarthropathies such as rheumatoid arthritis. Presentation with fever and rash mimic systemic lupus erythematosus, viral exanthems, rickettsial infections, secondary syphilis, and drug reactions. A biologic false positive for syphilis occurs in up to 25% of patients with streptobacillary disease and in up to 50% of cases with the spirillary form.

THERAPY

Both streptobacillary and spirillary forms of rat-bite fever respond well to appropriate antimicrobial therapy. *S. minus* is more sensitive to therapy. Penicillin is the drug of choice for both organisms and a dramatic response to therapy may be expected. Dosage of 600 000 U of procaine penicillin G, administered intramuscularly, twice daily for at least 7 days, is recommended for uncomplicated forms of the disease. Intravenous penicillin therapy should be initiated, until antimicrobial sensitivity is determined, in cases of severe disease. Adults should receive 400 000 to 600 000 U/day, increasing dosage to 1.2 million U/day if no response is observed within 48 hours. Children are treated with 20 000 to 50 000 U/kg/day for 7 days followed by 7 days of oral penicillin V therapy. Endocarditis, if present, should be treated with high-dose penicillin G (susceptible isolates: 4.8 million U/day procaine penicillin intramuscularly; resistant isolates: 20 million U/day intravenously) in combination with gentamicin or streptomycin daily for 4 to 6 weeks. Streptomycin enhances activity against the L forms of *S. moniliformis*. Children with endocarditis should be treated with 160 000 to 240 000 U/day penicillin G up to the maximum adult dose. Tetracycline (500 mg/kg every 6 hours

by mouth) or streptomycin (7.5 mg/kg twice daily intramuscularly) are effective alternatives in penicillin-allergic patients. Amoxicillin-clavulanate, doxycycline, second- and third-generation cephalosporins, ciprofloxacin, chloramphenicol, clindamycin, the macrolides erythromycin and clarithromycin, and vancomycin have been successfully employed. Treatment failures have been reported with erythromycin. Prophylactic administration of penicillin may be considered following a rat bite, although the risk of nascent infection is low. However, prophylaxis should be a high consideration in infants because of the possibility of rapid progression and severe outcomes.

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150. *Salmonella*

Bruce S. Ribner

The salmonellae are gram-negative, non-spore-forming, facultatively anaerobic bacteria in the family Enterobacteriaceae. More than 2500 different serotypes of *Salmonella* have been identified.

Salmonellae are widely distributed in nature. They are generally found in the gastrointestinal (GI) tracts of the hosts with which they are associated. Some salmonellae, such as *Salmonella typhi* and *Salmonella paratyphi*, are found to colonize only the human GI tract. Other *Salmonella* serotypes, such as *Salmonella typhimurium*, have a wide range of hosts, including humans. Finally, some organisms, such as *Salmonella dublin* and *Salmonella arizona*, are rarely found in the GI tracts of humans. The specificity and range of the different serotypes helps to determine the epidemiology of infections caused by these bacteria.

Infections caused by the salmonellae are grouped into three major syndromes: gastroenteritis, typhoid or enteric fever, and localized infection outside of the GI tract. Although there is considerable overlap between these syndromes, their epidemiology and clinical presentations are distinct enough to make discussion by syndrome useful.

GASTROENTERITIS

Gastroenteritis accounts for most *Salmonella* infections in humans. The incidence of *Salmonella* gastroenteritis in the United States doubled during the 1980s and 1990s. Much of this increase was attributed to the widespread contamination of chickens and eggs as the industry became increasingly centralized. While the rate of *Salmonella* gastroenteritis stabilized in the late 1990s, due to increased public awareness and improved sanitation during commercial processing, since then this rate has increased by 44%. It is estimated that there are 1.2 million episodes of *Salmonella* gastroenteritis annually in the United States, resulting in 20 000 hospitalizations and 400 deaths. Most cases of *Salmonella* gastroenteritis are traced to the ingestion of inadequately cooked poultry or eggs, either directly or through the consumption of such foods as Caesar salad, sauces containing raw eggs, and inadequately cooked stuffing contaminated by salmonellae from raw poultry. A recent study detected salmonellae contamination in 14% of the chickens sold in the United States: 68% of these isolates were resistant to at least one antibiotic. Beef, milk, and, rarely, fruits and vegetables have also been responsible for salmonellae infections. Pet reptiles, such as turtles, snakes, and lizards, frogs, and baby ducklings and chicks often have asymptomatic colonization of the GI tract. Young children who play with these animals may forget to wash their hands before eating, resulting in *Salmonella* gastroenteritis. Individuals at greatest risk for acquiring disease are neonates, those with achlorhydria, either naturally or secondary to medication, or who are taking antacids, transplant recipients, individuals with lymphoma, patients with acquired immunodeficiency syndrome, and the elderly. Children under 5 years of age represent 27% of all patients with *Salmonella* gastroenteritis.

Salmonella gastroenteritis

Salmonella gastroenteritis has an incubation period of 12 to 72 hours, with shorter incubation periods being associated with higher amounts of ingested bacteria. The typical illness is accompanied by fever, nausea, vomiting, abdominal cramping, and watery diarrhea; it lasts 4 to 7 days. The stool usually contains neutrophils, but dysentery, with gross blood and pus in the stool, is uncommon. Patients with *Salmonella* gastroenteritis occasionally have headaches and myalgias. Bacteremia, seen in approximately 8% of patients, is most common in those with impaired immunity (children younger than 3 months and adults greater than 65 years of age, those on corticosteroids or other immune suppressants, those with inflammatory bowel disease, and those with

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hemoglobinopathies) or who are on hemodialysis. Bacteremia tends to occur early during the course of the illness. *Salmonella* gastroenteritis is typically a mild disease; it rarely leads to severe dehydration and cardiovascular collapse, although it is estimated that there are 400 fatalities a year in the United States from *Salmonella* gastroenteritis.

Approximately 50% of newborns with *Salmonella* gastroenteritis have GI carriage of the organism for longer than 6 months. This rate decreases with age; fewer than 10% of adults remain colonized at 3 months. The administration of antibiotics during the early phase of illness is felt to increase the likelihood of carriage.

TYPHOID OR ENTERIC FEVER

Typhoid fever is caused by salmonellae serotypes such as *S. typhi* and *S. paratyphi*, which are almost exclusively associated with humans. Transmission is by ingestion of contaminated food and water; although person-to-person transmission is possible, it is uncommon because of the large inoculum size required to cause illness in normal individuals. In contrast to *Salmonella* gastroenteritis, the incidence of typhoid fever in developed countries has markedly decreased over the past few decades as sanitation and the quality of the water supply have improved. Most typhoid fever in the United States is acquired during foreign travel. A high percentage of infections acquired in the United States results from the ingestion of food prepared by chronic carriers, many of whom initially became colonized in another country.

Typhoid fever has an incubation period that is usually 7 to 21 days (range of 3 to 60 days), depending on the size of the inoculum and the health of the host. Symptoms consist of fever, abdominal pain, hepatosplenomegaly, headache, and myalgias. Diarrhea is rare after the first few days. Although typhoid fever has classically been characterized as having a temperature–pulse dissociation with bradycardia in the face of a high fever, this phenomenon is uncommon. Rose spots, which are faint, maculopapular, salmon-colored blanching lesions found predominantly on the trunk, are seen in approximately one-third of patients. Biopsy of these lesions reveals perivascular, mononuclear cell infiltration, and culture frequently yields the organism.

Ninety percent of patients with typhoid fever have bacteremia during the first week of illness. This percentage decreases as the illness progresses. Positive stool cultures do not appear before the second week of illness, and the rate increases until, by the third week, 75% of patients have positive stool cultures. The white blood cell count is usually low in relation to the degree of illness. Occasionally an absolute leukopenia is seen.

The patient with untreated typhoid fever will have 4 to 8 weeks of sustained fever. Mortality of those with untreated disease is estimated to be 15% worldwide but only 1% in the United States. Mortality is highest in the immunocompromised, especially those with hemoglobinopathies, malaria, schistosomiasis, and infection with human immunodeficiency virus (HIV). The major complication of untreated disease is hemorrhage from intestinal perforation secondary to ulceration and necrosis of the Peyer's patches in the ileum. Such hemorrhage may be seen during the third or fourth week of illness, often when the patient seems to be clinically improving. Other complications include pericarditis, endocarditis, splenic and hepatic abscesses, cholangitis, meningitis, and pneumonia. Ten percent of untreated patients relapse. Although one-fourth of patients with typhoid fever will have positive urine cultures, actual infection of the urinary tract with *S. typhi* and *S. paratyphi* is rare.

The differential diagnosis in a patient presenting with enteric fever may include malaria, amebiasis, and viral illnesses such as dengue or Epstein–Barr virus infection, and infection with non-*Salmonella* bacterial pathogens such as *Yersinia, Campylobacter*, and *Pseudomonas*.

LOCALIZED INFECTIONS OUTSIDE OF THE GASTROINTESTINAL TRACT

On rare occasions, *Salmonella* infection may present as a localized infection at a site other than the GI tract. This is most likely in patients with underlying illnesses. Sustained bacteremia with *Salmonella choleraesuis* or *S. dublin* suggests an intravascular focus such as seeding of an atherosclerotic plaque or of the clot within a pre-existing aneurysm, especially if the patient is elderly. If infection is localized to the abdominal aorta, surgery is generally necessary, as medical management alone is associated with a high mortality rate. Rarely, sustained bacteremia may result from endocarditis with a valve ring or septal abscess. Localized infection may also present as a hepatic or splenic abscess, especially if the patient has biliary tract stones, cirrhosis, or cholangitis.

Salmonellae are the second most common cause of gram-negative meningitis in neonates. They are also a common cause of osteomyelitis in children with hemoglobinopathies such as sickle cell disease.

Historically, *Salmonella* infection of the urinary tract was rare in the absence of nephrolithiasis, renal schistosomiasis, or renal tuberculosis. However, recent studies have documented an increase in *Salmonella* cystitis in elderly women, most of whom lacked structural abnormalities. It is felt that *Salmonella* cystitis most likely represents ascending infection of strains with greater pathogenicity for the urinary tract.

Approximately 2% of individuals who have *Salmonella* gastroenteritis will develop Reiter's syndrome. This occurs within 2 weeks of the onset of diarrhea and is associated with human leukocyte antigen (HLA) B27.

CHRONIC CARRIAGE

Because *Salmonella* is excreted in the stool of a high percentage of those recovering from acute infection for several months, the chronic carrier state is not considered to be present unless the organism persists in the stool for more than 1 year. This occurs in approximately 1% to 4% of those with *S. typhi* infection and in fewer than 1% of those infected with other serotypes. Biliary tract carriage is most likely to occur in the elderly and those with chololithiasis. Urinary tract carriage is most likely in those with bladder schistosomiasis and nephrolithiasis. Many chronic carriers have no clear history of a preceding acute *Salmonella* infection.

DIAGNOSIS

Gastroenteritis

Although certain features may suggest *Salmonella* gastroenteritis in a patient, many other pathogens may produce an illness that is clinically indistinguishable. The diagnosis of *Salmonella* gastroenteritis depends on the isolation of the organism from a stool specimen. As many clinical laboratories report that only 1% to 3% of stool specimens submitted for culture yield an enteric pathogen, and as mild gastroenteritis caused by *Salmonella* should not be treated with antibiotics (see Therapy below), many authorities have devised algorithms for selecting patients with gastroenteritis who should have stool cultures. Epidemiologic factors that should be sought as indicators of possible infectious diarrhea include the following: (1) travel to a developing area; (2) day-care center attendance or employment; (3) consumption of unsafe foods (e.g., raw meats, eggs, or shellfish; unpasteurized milk or juices) or swimming in or drinking untreated fresh surface water from, for example, a lake or stream; (4) visiting a farm or petting zoo or having contact with reptiles or with pets with diarrhea; (5) knowledge of other ill persons (such as in a dormitory or office or at a social function); (6) certain recent or regular medications (antibiotics, antacids, antimotility agents); (7) underlying medical conditions predisposing to infectious diarrhea (acquired immunodeficiency syndrome [AIDS], immunosuppressive medications, prior gastrectomy, extremes of age); (8) receptive anal intercourse or oral–anal sexual contact; and (9) occupation as a food handler or caregiver. Signs and symptoms that suggest a bacterial etiology for gastroenteritis include fever, abdominal pain, and bloody stools. Some laboratories have also included a screen for the presence of fecal leukocytes or lactoferrin to select those stools that warrant further culture for enteric pathogens.

As mentioned previously, only 8% of patients with *Salmonella* gastroenteritis will have an accompanying bacteremia. This is most common in those with underlying diseases and tends to occur early during the course of the illness.

Typhoid or enteric fever

The patient with typhoid or enteric fever most commonly will present with symptoms of fever, abdominal pain, hepatosplenomegaly, headache, and myalgias. In endemic areas, the differential diagnosis is frequently between typhoid fever and malaria. Less commonly, rickettsial infection, dengue fever, plague, and tularemia may present with a similar syndrome. Systemic vasculitis may also present with a clinical picture similar to enteric fever. The definitive diagnosis of typhoid requires isolation of *S. typhi* or *S. paratyphi* or demonstration of the presence of antigens of these bacteria in body fluids. The body sites most likely to yield positive assays depend on the stage of illness. During the first week, blood cultures are most likely to be positive, whereas during the second and third week of illness stool cultures are usually positive. Cultures of rose spots, if present, and of a bone marrow aspirate are also frequently positive.

Serology for antibody to *S. typhi* antigens has been used widely in the past for the diagnosis of

typhoid fever. Such assays must be used with caution, as the antibodies persist for years after infection and may be elevated from vaccination. Although a 4-fold rise in antibody titers in the context of an appropriate clinical illness is strong support for the diagnosis of enteric fever, a very elevated single assay can also be highly suggestive.

Localized infections outside of the gastrointestinal tract

The diagnosis of localized *Salmonella* infection outside of the GI tract depends on the isolation of the organism. This is especially true of localized infections such as visceral abscesses or endothelial infections, as there are no features that distinguish localized infection by the salmonellae as compared with the more common bacterial pathogens.

Chronic carriage

As mentioned previously, the chronic carrier state is not considered to be present unless the organism persists in the stool for more than 1 year. Although colonic colonization in the absence of biliary involvement has been reported, the overwhelming majority of patients with GI colonization have the gallbladder as the focus. To determine the site of colonization, a colonoscopy to detect colonic mucosal abnormalities and a culture of the common bile duct drainage have been used. Imaging of the gallbladder can also be useful in determining underlying causes for colonization of the gallbladder.

Patients with urinary tract chronic colonization can be evaluated with imaging studies to determine whether anatomic abnormalities, such as strictures or stones, are present. Such abnormalities make medical management alone less likely to be successful.

THERAPY

Gastroenteritis

Salmonella gastroenteritis is usually a self-limited disease, and therapy should be primarily directed to the replacement of fluid and electrolyte losses. Widespread resistance to chloramphenicol, ampicillin, and trimethoprim–sulfamethoxazole (TMP–SMX) now exists among the salmonellae, and multidrug-resistant salmonellae have been reported. Antimicrobial therapy for uncomplicated nontyphoidal *Salmonella* gastroenteritis, including short-course or single-dose regimens with oral fluoroquinolones, amoxicillin, or TMP–SMX, does not significantly decrease the length of illness, including duration of fever or diarrhea, and is associated with an increased risk of relapse, positive cultures after 3 weeks, and adverse drug reactions. However, certain patients are at increased risk for invasive infection and may benefit from pre-emptive antimicrobial therapy. Such patients would include neonates, those older than 65 years of age, those on corticosteroids, and persons with immunosuppression, inflammatory bowel disease, or hemoglobinopathies. It has also been suggested that those with prosthetic heart valves or endovascular abnormalities receive antibiotics to prevent localized infection. Antibiotic therapy is also appropriate in those with severe disease (e.g., those with severe diarrhea, high fever, bloodstream infection, or who need hospitalization). Treatment in these patients should consist of an oral or intravenous antimicrobial administered for 7 days if immunocompetent and 14 days if immune compromised. Specific recommendations are listed in Table 150.1.

Typhoid fever

Fluoroquinolones are the agents of choice for treatment of typhoid fever. They are more rapidly effective and are associated with lower rates of relapse and stool carriage than chloramphenicol, ampicillin, and TMP–SMX. They are also felt to be more effective than ceftriaxone. Strains sensitive to nalidixic acid can be treated with ciprofloxacin for 5 to 7 days. For uncomplicated disease, oral therapy is as effective as parenteral therapy. Patients infected by strains with intermediate resistance minimum inhibitory concentration (MIC) to ciprofloxacin of 0.125 to 1 μg/mL should be treated with higher doses of ciprofloxacin for 10 to 14 days. Patients with *S. typhi* strains with MIC values for ciprofloxacin of 2 μg/mL or greater should be treated with a third-generation cephalosporin or azithromycin.

Although the use of fluoroquinolones in children and pregnant women has been limited by concerns over toxicity, some studies have suggested that they may be superior to other agents in these populations as well. As additional studies document their safety in these populations, they may become first-line therapy. However, due to their toxicity in animal models, further studies are needed.

Table 150.1 Therapy of *Salmonella* infections

Syndrome	Suggested therapy
Gastroenteritis	
Normal host	Rehydration
Normal host with severe disease or risk factors	Levofloxacin, 500 mg (or other fluoroquinolone) once a day for 7–10 d; or azithromycin, 500 mg once a day for 7 d
Immunocompromised adult	Levofloxacin, 500 mg (or other fluoroquinolone) once a day for 14 days; or azithromycin, 500 mg once a day for 14 d
Neonate or immunocompromised child	None or ceftriaxone, 100 mg/kg/d in two equally divided daily doses for 7–10 d; or azithromycin, 20 mg/kg/d once a day for 7 d
Typhoid fever	
Adult, sensitive strain	Ciprofloxacin, 500 mg PO or IV BID for 5–7 d
Adult, intermediate strains[a]	Ciprofloxacin, 750 mg PO or IV BID for 5–7 d
Adult, resistant strains[b]	Ceftriaxone, 2 g IV qd for 10–14 d; or azithromycin, 500 mg PO or IV qd for 7 d
Children, pregnant women	Ceftriaxone, 100 mg/kg/d in two equally divided daily doses for 10–14 d; or azithromycin, 20 mg/kg/d once a day for 7 d
All patients with severe typhoid fever (delirium, obtundation, stupor, coma, or shock) should receive dexamethasone, 3 mg/kg initially, followed by 1 mg/kg q6h for 48 h	
Chronic carrier	
Adult	Ciprofloxacin, 750 mg PO BID for 4 wk; or amoxicillin, 1 g PO TID for 3 mo; or TMP–SMX, 160/800 mg PO BID for 3 mo
Children	Amoxicillin, 40 mg/kg PO up to 1 g TID for 3 mo; or TMP–SMX, 5 mg/kg TMP BID for 3 mo

Abbreviations: TMP–SMX = trimethoprim–sulfamethoxazole; MIC = minimum inhibitory concentration.

[a] MIC to ciprofloxacin of 0.125 to 1 μg/mL.

[b] MIC values to ciprofloxacin of 2 μg/mL or greater.

Most authorities recommend a short course of dexamethasone for severe disease with altered mental status or shock (see Table 150.1).

Chronic carrier

Patients with positive stool or urine cultures for salmonellae >12 months after resolving their acute infection are considered carriers. Over 80% of these patients can have the carrier state eradicated with the administration of ciprofloxacin for 1 month, oral amoxicillin for 3 months, or TMP–SMX for 3 months. The presence of anatomic abnormalities, such as biliary or kidney stones, makes eradication much more difficult and should be evaluated prior to initiating long-term therapy. In the presence of such abnormalities, surgery combined with antimicrobial therapy is often required for eradication. Patients with urinary carriage associated with *Schistosoma haematobium* should be treated with praziquantel before attempting eradication of *S. typhi*.

PREVENTION

The prevention of *Salmonella* infection relies on proper food handling and sanitation. In developed countries, this involves careful attention to the separation of raw and cooked foods and an awareness of the multiple ways in which cross-contamination can occur in food preparation areas. Parents should also monitor their children to insure careful hand hygiene after contact with reptiles and fowl.

For travel to developing countries, there are currently two commercially available vaccines for the prevention of *S. typhi* infection. One is an oral live attenuated vaccine, while the second is a parenteral capsular polysaccharide vaccine. These vaccines achieve approximately 50% to 80% efficacy, starting roughly 2 weeks after vaccination, and confer protection that lasts for several years. They are recommended for travelers to parts of the world where typhoid fever is endemic. However, as none of the available vaccines are completely protective, the first line of prevention for travelers to areas where typhoid is endemic is care in consumption of food and water. Travelers should avoid tap water, ice produced from local tap water, salads, uncooked vegetables, and unpasteurized milk and milk products such as cheese, and should eat only food that has been cooked and is still hot or fruit that has been washed in clean water and then peeled by the traveler personally.

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151. *Staphylococcus*

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Treatment of staphylococcal infection is dependent on the site involved, the severity of infection, and the antibiotic susceptibility pattern of the organism causing the infection. Although most serious staphylococcal infections are due to coagulase-positive staphylococci (*Staphylococcus aureus*), infections due to coagulase-negative staphylococci (e.g., *Staphylococcus epidermidis*) are increasing and may also be life threatening. *S. aureus* is a highly invasive pathogen, able to spread hematogenously to many organs, leading to metastatic foci of infection. Coagulase-negative staphylococci are generally healthcare-associated infections that require the presence of prosthetic material to gain a foothold and cause infection.

SUSCEPTIBILITY TO ANTIBIOTICS

Staphylococci have a propensity to develop resistance to antibiotics relatively quickly. Most staphylococci are no longer susceptible to the effects of penicillins alone because the bacteria produce enzymes or penicillinases that inactivate many of those drugs. One approach to the problem of antibiotic resistance in staphylococci has been the use of penicillinase-resistant penicillins, e.g., nafcillin, oxacillin, and methicillin. Alternatively, penicillins have been combined with inhibitors of penicillinase. Examples of penicillin–penicillinase-inhibitor combinations include: amoxicillin-clavulanate (Augmentin), ampicillin–sulbactam (Unasyn), piperacillin–tazobactam (Zosyn), and ticarcillin–clavulanate (Timentin). The penicillinase-resistant penicillins and penicillin–penicillinase-inhibitor combinations are effective for the treatment of penicillin-resistant, but methicillin-susceptible, staphylococci.

Other β-lactam antibiotics are also useful for the treatment of methicillin-susceptible staphylococci. First-generation cephalosporins (cefazolin, cephalexin) are the most active, followed by second-generation agents (cefuroxime, cefotetan, cefoxitin). Third-generation (ceftriaxone, cefotaxime) and fourth-generation (cefipime) cephalosporins have less activity. First-generation cephalosporins are still considered the first-line agents in this class for most serious methicillin-susceptible staphylococcal infections.

Since the 1970s, both *S. aureus* and coagulase-negative staphylococci have become increasingly resistant to β-lactam antibiotics including penicillinase-resistant penicillins, penicillin–penicillinase-inhibitor combinations, cephalosporins, and carbapenems. These so-called "methicillin-resistant" strains bind most β-lactam antibiotics poorly due to the alterations in penicillin-binding proteins (PBP2a) present on their cell walls. Methicillin-resistant *S. aureus* (MRSA) and methicillin-resistant *S. epidermidis* (MRSE) are common in healthcare settings worldwide. MRSA and MRSE account for more than 50% and 90% of all staphylococcal isolates causing nosocomial infection in some medical centers. These healthcare-associated (HA) strains are usually resistant to many other classes of antibiotics, including macrolides, lincosamines (clindamycin), quinolones, and aminoglycosides, but some remain susceptible to sulfonamides and tetracyclines.

Newer community-associated MRSA (CA-MRSA) strains have emerged that are not related to HA-MRSA strains. These CA-MRSA strains are resistant to β-lactam antibiotics, but, in contrast with HA-MRSA strains, are more frequently susceptible to many classes of antibiotics including clindamycin and sulfonamides. Strains of CA-MRSA that are resistant to erythromycin but appear to be susceptible to clindamycin on initial screening should be further tested for inducible cross-resistance to clindamycin using a double disk diffusion test (D test). If inducible resistance is shown, the laboratory will report resistance to both erythromycin and clindamycin.

Until recently, the glycopeptide vancomycin has been the primary treatment for serious MRSA infections. However, vancomycin treatment can

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be slow or ineffective in clearing MRSA infection, and vancomycin-resistant *S. aureus* (VRSA) has emerged with prolonged use. Minimum inhibitory concentrations (MICs) of vancomycin appear to be increasing for MRSA. Some experts now recommend using higher dosages of vancomycin to achieve a trough serum concentration of 15 to 20 μg/mL when treating serious MRSA infections. These higher serum vancomycin concentrations may be associated with more toxicity, however. A new glycopeptide, telavancin, has been approved for treatment of skin and soft-tissue infection (SSTI); its toxicity profile is similar to vancomycin.

Other antibiotics with activity against MRSA, linezolid, quinupristin–dalfopristin, daptomycin, and tigecycline, have been developed. These drugs have been used primarily when patients have side effects from vancomycin or when treatment with vancomycin fails. Currently, the greatest experience in the treatment of serious MRSA infections in patients intolerant or refractory to vancomycin has been with linezolid and daptomycin. Side effects have limited the use of quinupristin–dalfopristin. Tigecycline is bacteriostatic, and increases in all-cause mortality have been described during treatment of serious infection with this drug. The cephalosporin ceftaroline has potent activity against *S. aureus* and MRSA due to its increased ability to bind to PBP2a, but this drug is currently approved only for the treatment of MRSA SSTI.

Although it may be tempting to treat both methicillin-susceptible *S. aureus* (MSSA) and MRSA infections with vancomycin or one of the newer agents, there are several reasons why this practice should be discouraged. One is that MSSA infections clear more slowly when treated with vancomycin than with a β-lactam antibiotic. The second is that the overuse of vancomycin has contributed to the increase in vancomycin resistance among enterococci (VRE) as well as *S. aureus*. Finally, resistance to newer agents has already been reported in *S. aureus*. Thus, organisms that are identified as MSSA should be treated with a penicillinase-resistant β-lactam antibiotic; only if the infecting organism is MRSA should vancomycin or newer agents be used.

The situation with coagulase-negative staphylococci is more difficult, because the routine assays used by most laboratories to determine methicillin resistance are not as well established for coagulase-negative staphylococci as for *S. aureus*. Thus, some authorities recommend the use of vancomycin for serious coagulase-negative staphylococcal infections in spite of routine antimicrobial susceptibility testing that suggests methicillin susceptibility. A polymerase chain reaction test for methicillin resistance that detects the presence of the *mec*A gene that encodes for PBP2a is used in some laboratories for both *S. aureus* and coagulase-negative staphylococci; however, this test is costly, labor intensive, and not readily available at most hospitals. Detection of methicillin resistance by latex agglutination testing for the presence of PBP2a is also available.

For patients allergic to β-lactam antibiotics, other antimicrobial agents for staphylococcal infections include (depending on susceptibility results) trimethoprim–sulfamethoxazole (TMP–SMX), quinolones, such as levofloxacin or moxifloxacin, clindamycin, and erythromycin. The use of these antistaphylococcal agents should generally be restricted to the treatment of localized, uncomplicated infections. Vancomycin, daptomycin, linezolid, quinupristin–dalfopristin, and tigecycline are alternatives for serious staphylococcal infections in allergic patients.

INFECTION CONTROL ISSUES

Because of the difficulty in treating MRSA infections and the propensity for *S. aureus* to spread among patients from the hands of healthcare providers, guidelines for the control of MRSA within acute care hospitals have been issued. Patients who have MRSA isolated should be placed in a private room in Contact Precautions, ensuring that healthcare providers wear gloves for general care of the patient, don gowns when performing tasks likely to result in contamination of clothing by secretions, and assiduously wash their hands before and after patient care. Special care should be taken with wounds from which MRSA has been isolated and with sputum in a patient with pneumonia due to MRSA.

Routine decolonization of patients who are infected or colonized with MRSA is generally not done, in part because the effect is transient and recolonization within 90 days is common. However, for some acutely ill patients, colonization with *S. aureus* can increase the risk of infection. Recent randomized trials suggest that transient decolonization of skin with daily chlorhexidine baths and a brief course of mupirocin ointment applied to the nares can decrease the risk of MRSA infection in intensive care unit patients and *S. aureus* surgical site infections in patients undergoing cardiothoracic and

orthopedic procedures. Treatment of all patients should be discouraged as resistance to mupirocin may develop rapidly when use is chronic and widespread. Chlorhexidine resistance may also be emerging with increasing use.

INFECTIONS DUE TO *S. AUREUS* (TABLE 151.1)

Skin and soft-tissue infections

S. aureus is the most common cause of SSTI, and many SSTIs are now caused by CA-MRSA strains. Cellulitis associated with purulent drainage or exudate is most commonly due to *S. aureus*. Folliculitis, furuncles, abscesses, and wound infections are also common.

Superficial infections such as impetigo may be treated with topical agents such as mupirocin. Incision and drainage alone is generally reserved for small localized abscesses in healthy patients; it is not clear that antibiotic use improves the outcome from infection. Initial empiric treatment with systemic antibiotics is recommended when infection is extensive, involves multiple sites, is in an area that is difficult to drain, or is rapidly progressive. Antibiotic therapy should be considered in older adults, diabetics, patients with human immunodeficiency virus (HIV) or neoplasms, or in patients with symptoms and signs of systemic illness or septic phlebitis.

In most instances where antibiotic therapy is warranted, empiric treatment should be directed against MRSA. Culture of abscess or purulent exudate should be performed in patients with severe infection or signs and symptoms of systemic illness, those who do not respond to initial treatment, and in suspected outbreak settings.

For patients with less severe infection who can take and tolerate oral medications, empiric therapy with TMP–SMX, doxycycline or minocycline, clindamycin, and linezolid can be considered. In patients with systemic toxicity and rapidly progressive or worsening infection, empiric IV vancomycin, daptomycin, telavancin, ceftaroline, and linezolid can be given.

Once culture results are known, then antibiotic therapy can be modified appropriately. Many patients will require intravenous administration of antibiotics until the acute illness has improved, then therapy can be switched to oral agents. If MSSA is identified, nafcillin or cefazolin followed by dicloxacillin or cephalexin is preferred.

Osteoarticular infections

Staphylococcus aureus is the leading cause of osteoarticular infections. These infections are difficult to treat and frequently require long-term therapy with intravenous antibiotics.

In general, intravenous therapy directed against MRSA should be used until results of culture and antibiotic susceptibilities are available from deep tissue or joint aspirates. In the case of native joint septic arthritis, drainage of infected synovial fluid is essential to preserve joint function and eradicate infection. Intravenous therapy should continue for at least 3 to 4 weeks.

For treatment of osteomyelitis, intravenous antibiotics should be given for a minimum of 6 to 8 weeks. Patients with vertebral osteomyelitis, paraspinous abscess, and/or epidural abscess often require treatment for months beyond 6 to 8 weeks to assure healing and to prevent relapse. Prolonged treatment can usually be accomplished by giving an oral agent for MRSA (TMP–SMX, doxycycline, or clindamycin) or MSSA (cephalexin, dicloxacillin, clindamycin, or amoxicillin–clavulanate) based on antimicrobial susceptibility patterns.

Treatment of staphylococcal infections in patients with prosthetic joints or spinal hardware in place can be particularly difficult without removal of the device. For prostheses present less than 30 days or when symptoms have been present less than 3 weeks, a strategy to debride and retain the prosthesis may be tried. Two weeks of therapy consisting of oral rifampin in combination with vancomycin or daptomycin for methicillin-resistant staphylococci and rifampin plus nafcillin or cefazolin for methicillin-susceptible staphylococci is given followed by 3 months of rifampin in combination with a susceptible oral agent.

For late prosthetic infections and those with more prolonged symptoms, resection of the device is generally advised followed by 4 to 6 weeks of intravenous therapy with the goal of reimplantation. For patients who cannot tolerate surgical resection, intravenous antibiotics may be followed by chronic suppression of the infection with a susceptible and single oral agent. In no instance may rifampin be given as treatment alone due to the prompt emergence of resistance.

Pulmonary infections

In the past, *S. aureus* pneumonia was seen primarily in elderly patients with underlying illnesses. Recently, severe CA-MRSA pneumonia has been

Table 151.1 Treatment of noncardiac infections due to *Staphylococcus aureus*

Infection	First-line drugs[a]	Second-line drugs[a,b]	Comments
Folliculitis, impetigo	Mupirocin		Community-acquired MRSA (CA-MRSA) causes >50% outpatient SSTI
Simple abscesses	Incision and drainage		
Cellulitis Outpatient Rx			Treat for 5–10 d
Nonpurulent	Dicloxacillin, 250 mg, or Cephalexin, 250 mg PO q6h	Clindamycin, 300 mg q6h	
Purulent	TMP–SMX,160/800 mg PO q12h Clindamycin, 300 mg q6h	Linezolid, 600 mg PO q12h Doxycycline 100 mg PO q 12	Suspect CA-MRSA if cellulitis has pus present
Inpatient Rx	See moderate to severe wound infections		Treat IV until patient afebrile and nontoxic, then switch to oral agent
Moderate to severe wound infections Inpatients			
MSSA	Nafcillin, 2 g q4h, or Cefazolin, 2 g IV q8h	Vancomycin, 1 g IV q12h	Drainage and culture of abscesses essential for resolution
MRSA	Vancomycin, 1 g IV q12h	Linezolid, 600 mg PO q12h Daptomycin, 4 mg/kg IV q24h	Treat minimum 7–14 d based on extent of infection and response Monitor vancomycin troughs Aim for 10–15 μg/mL
Osteomyelitis			
MSSA	Nafcillin, 2 g IV q4h, or Cefazolin, 2 g IV q8h	Vancomycin, 1 g IV q12h	Vertebral osteomyelitis, with or without paraspinous or epidural abscess, often requires longer duration of therapy
MRSA	Vancomycin, 1 g IV q12h	Daptomycin, 4 mg/kg IV q24h Linezolid, 600 mg PO q12h	Treat IV 6–8 wk followed by an oral regimen Monitor vancomycin troughs Aim for 15–20 μg/mL
Septic arthritis			
MSSA	Nafcillin, 2 g q4h, or Cefazolin, 2 g IV q8h	Vancomycin, 1 g IV q12h	Repeated needle aspiration, arthroscopic drainage, or operative drainage of joint fluid essential for resolution of infection
MRSA	Vancomycin, 1 g IV q12h	Daptomycin, 4 mg/kg IV q24h Linezolid, 600 mg PO q12h	Treat 3–4 wk
Pneumonia			
MSSA MRSA	Nafcillin, 2 g IV q4h Vancomycin 1 g IV q12h	Vancomycin, 1 g IV q12h Linezolid, 600 mg IV/PO q12h	Empyema, when present, must be drained Treat 7–21 d Daptomycin not effective
Bacteremia			
MSSA	Nafcillin 2 g IV q4h (see text for discussion regarding length of therapy)	Vancomycin, 1 g IV q12h (see text for discussion regarding length of therapy)	Length of therapy depends on source of bacteremia and whether visceral foci of infection, including endocarditis, are present.
MRSA	Vancomycin 1 g IV q12h (see text for discussion)	Daptomycin, 6 mg/kg IV q24h (see text)	Careful diagnostic workup and clinical assessment of the patient is essential regarding length of therapy

Abbreviations: MSSA = methicillin-susceptible *Staphylococcus aureus*; MRSA = methicillin-resistant *Staphylococcus aureus*; SSTI = skin and soft-tissue infection; TMP–SMX = trimethoprim–sulfamethoxazole.

[a] Usual adult doses. Doses of cefazolin and vancomycin dependent on renal function. Linezolid, monitor complete blood count weekly. Daptomycin, monitor creatine phosphokinase 1×–2× weekly.

[b] Second-line drugs used mostly for patients allergic or intolerant to β-lactam antibiotics.

seen in children and young adults, sometimes following influenza infection or in the setting of HIV infection. Patients with severe community-acquired pneumonia requiring admission to the intensive care unit or who have necrotizing pneumonia, cavitating infiltrates, or empyema should be treated empirically for MRSA until sputum and blood culture results are known. Vancomycin or linezolid may be given empirically until culture and susceptibility results are known. Vancomycin, linezolid, or clindamycin may be given for 7 to 21 days depending upon the extent of the infection and the patient response. Daptomycin should not be used because the drug does not achieve adequate lung tissue levels. Drainage of loculated fluid in the pleural space is essential for resolution of infection.

Bacteremia

S. aureus bacteremia may reflect an uncomplicated or transient event, often associated with a removable focus, most often an intravascular catheter, or it may be the first indication of deep-seated visceral infection, including endocarditis. *S. aureus* bacteremia is considered uncomplicated if there is no evidence for endocarditis, there are no implanted prosthetic devices, and catheters have been removed and foci promptly drained. In addition, the patient must have resolution of fever within 72 hours of treatment and documented clearance of blood cultures drawn within 2 to 4 days of the initial positive culture, and no evidence for metastatic sites of infection.

Recent guidelines recommend that all patients with *S. aureus* bacteremia have echocardiography, and preferably a transesophageal echocardiogram (TEE). However, some studies have questioned that recommendation for uncomplicated bacteremia. Others have found that if none of the following risk factors (bacteremia greater than 4 days' duration, presence of a permanent intracardiac device, hemodialysis dependency, spinal infection, and presence of non-vertebral osteomyelitis) are present, then the likelihood of *S. aureus* endocarditis is less than 1% and echocardiography is not warranted. One suggested approach is to perform a transthoracic echocardiogram (TTE) only in patients with *S. aureus* bacteremia that have one or more risk factors, complicated bacteremia, or clinical suspicion for endocarditis. If a good quality TTE cannot exclude endocarditis, then a TEE should be performed in those patients.

For patients who have uncomplicated *S. aureus* bacteremia or complicated bacteremia without echocardiographic or deep visceral evidence of infection, 14 days of treatment with nafcillin or cefazolin for MSSA and vancomycin or daptomycin for MRSA is recommended. For patients in whom deep-seated infections are documented and for those in whom the clinical suspicion of endocarditis remains high, longer courses of therapy (4–6 weeks) are required. Relapse of infection is common following *S. aureus* bacteremia, so patients should be carefully watched for recurrence of symptoms and signs following the discontinuation of treatment.

In contrast with *S. aureus*, metastatic complications from coagulase-negative bacteremia are uncommon. Temporary intravenous devices, such as central venous catheters, peripherally inserted central catheters, and midline catheters, should be removed, and 7 to 10 days of antimicrobial therapy given. For semi-permanent intravenous devices, such as Hickman or Groshong catheters and subcutaneous ports, which are more difficult to remove, a 2-week trial of vancomycin or nafcillin with or without rifampin may be adequate to cure the infection. However, if bacteremia relapses, or if tunnel infection or septic phlebitis is present, then the catheter or port should be removed (see Chapter 107, Intravascular catheter-related infections).

Endocarditis

S. aureus is the most common cause of native valve endocarditis; the presentation can be acute with frequent complications and high mortality. Patients with left-sided cardiac lesions may have metastatic abscesses in spleen, brain, kidney, and myocardium. Right-sided *S. aureus* endocarditis is frequently found in intravenous drug users. In that population, pulmonary emboli is a common presenting symptom, the mortality rate is significantly lower, and shorter courses of therapy may be indicated.

Coagulase-negative staphylococci are the most common cause of endocarditis in patients with prosthetic valves and intracardiac devices, and the presentation may be more subacute. TEE is particularly useful for detection of prosthetic valvular dehiscence and paravalvular abscesses that typically require surgical intervention. For details of specific antibiotic regimens for endocarditis, see Chapter 37, Endocarditis of natural and prosthetic valves: treatment and prophylaxis.

Toxic shock syndrome

Under certain conditions, such as those brought about by the use of tampons during menstruation and by the packing of surgical wounds, *S. aureus* elaborates toxins that lead to multiorgan system disease in the absence of bacteremia. Treatment of shock and the removal of tampons or surgical packing are the primary goals of therapy. Antistaphylococcal therapy is secondary, initiated primarily to eradicate the carriage of toxin-producing *S. aureus* strains (see Chapter 18, Staphylococcal and streptococcal toxic shock and Kawasaki syndromes).

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152. *Streptococcus* groups A, B, C, D, and G

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CLASSIFICATION

In the early 1950s, Lancefield divided streptococci into groups based on carbohydrates present in the cell wall and designated the groups A through H and K through T. In addition, streptococci may be classified by their characteristics on culture on sheep blood agar. β-Hemolytic streptococci produce zones of clear hemolysis around each colony; α-hemolytic streptococci (*Streptococcus viridans*) produce a green discoloration characteristic of incomplete hemolysis; absence of hemolysis is characteristic of γ-streptococci.

GROUP A

Pharyngitis

The sole member of Lancefield group A is *Streptococcus pyogenes*. Group A streptococcus is ubiquitous in the environment but with rare exceptions is exclusively found in or on the human host. About 5% to 20% of the population harbor group A streptococcus in their pharynx, and some are colonized on their skin. This organism produces a variety of suppurative infections; however, streptococcal pharyngitis, the most common, is characterized by the onset of sore throat, fever, painful swallowing, and chilliness. These symptoms combined with submandibular adenopathy, pharyngeal erythema, and exudates correlate with positive throat cultures in 85% to 90% of cases. Sore throat without fever or any of the other signs and symptoms has a low predictive value for pharyngitis caused by group A streptococcus. Rapid strep tests correlate with positive cultures in 68% to 99% of cases, but results depend greatly on the individual performing the test as well as the bacterial colony count. Colony counts greater than 100 per plate correlated with positive rapid strep tests in 95% of patients, and counts less than 100 per plate correlated with positive rapid strep tests for only 68% of patients.

Therapy

Penicillin remains the drug of choice for group A streptococcal pharyngitis and tonsillitis (Table 152.1). In the past, the purpose of treatment of streptococcal pharyngitis was largely to prevent postinfectious immunologic sequelae. However, because some patients with pharyngitis have subsequently developed streptococcal toxic shock syndrome with or without necrotizing fasciitis, it seems prudent to diagnose and treat streptococcal pharyngitis aggressively in an attempt to prevent this complication as well. Antibiotic treatment of streptococcal pharyngitis reduces pharyngeal pain and fever by approximately 24 hours in children. Penicillin treatment within 10 days of the onset of pharyngitis is extremely effective in the prevention of rheumatic fever, although it is unclear whether it prevents poststreptococcal glomerulonephritis. Penicillin fails to eradicate group A streptococcus from the pharynx in 5% to 25% of patients with pharyngitis or tonsillitis, although penicillin resistance has never been documented. The most likely explanation for such failure, particularly in patients with tonsillitis, is the inactivation of penicillin by β-lactamases produced by co-colonizing organisms such as *Staphylococcus aureus, Haemophilus influenzae, Moraxella catarrhalis*, and *Bacteroides fragilis*. A second course of penicillin fails in >50% of patients, and treatment with dicloxacillin, a cephalosporin, amoxicillin/clavulanate, erythromycin, or clindamycin will subsequently cure 90% to 95% of patients. Recent studies demonstrate that outer-membrane vesicles from *M. catarrhalis* and *H. influenzae* that are β-lactamase positive hydrolyze penicillin. Preparations containing procaine penicillin G plus benzathine penicillin are no more effective than benzathine alone but are less painful on injection. Ceftriaxone is under study for this indication. Resistance to erythromycin is about 5% in the United States, but in 1970, it reached a prevalence of 70% in Japan during a period of extensive erythromycin use in

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Table 152.1 Streptococcal infections

Organism	Lancefield group	Type of infection	Therapy
Streptococcus pyogenes	A	Pharyngitis and impetigo	Benzathine penicillin IM, 1.2 million U for adults; 600 000 U for children ≤27 kg Penicillin G or V, 400 000 U PO QID for 10 d for adults; 200 000 U QID for children ≤27 kg Erythromycin ethyl succinate, PO 40 mg/kg/d
		Recurrent streptococcal pharyngitis, tonsillitis	Same as above or ampicillin + clavulanic acid, PO 20–40 mg/kg/d Oral cephalosporin Dicloxacillin, 500 mg PO QID for 10 d for adults Clindamycin, 10 mg/kg/d PO in 4 doses for 10 d
		Cellulitis and erysipelas Necrotizing fasciitis, myositis, and streptococcal toxic shock syndrome	Nafcillin, 8–12 g/d IV for 7–10 d or penicillin or ceftriaxone in appropriate doses Clindamycin, 900 mg IV q8h and penicillin G, 4 million U IV q4h for adults. Duration until resolution of infection
		Prophylaxis of rheumatic fever	Benzathine penicillin, 1.2 million U IM q28d Penicillin G, 200 000 U PO BID for children ≤27 kg Sulfadiazine, 1 g/d for patients >27 kg; 500 mg/d for patients ≤27 kg Erythromycin, 250 mg PO BID
Streptococcus agalactiae	B	Neonatal sepsis	Penicillin, IV 100 000–150 000 U/kg/d in 2–3 divided doses for infants ≤7 d of age
		Postpartum sepsis Septic arthritis Soft-tissue infection Osteomyelitis Intrapartum prophylaxis	Penicillin, 200 000–250 000 U/kg/d IV in 4 divided doses for infants >7 d of age Ampicillin, 100 mg/kg/d IV in 2–3 divided doses for infants ≤7 d of age Ampicillin, 150–200 mg/kg/d IV in 4 divided doses for infants >7 d of age Ampicillin, 8–12 g IV in 4–6 divided doses or penicillin 12–24 million U/d for adults Penicillin or ampicillin as for neonatal sepsis or postpartum sepsis above Penicillin or ampicillin as for postpartum sepsis above 1. Aqueous penicillin G 5 million U IV loading dose followed by 2.5 million U q4h for 4 doses 2. Ampicillin 2 g IV loading dose followed by 1 g q4h for 4 doses
Streptococcus equi	C	Bacteremia Cellulitis	Penicillin as for streptococcal toxic shock syndrome above
Enterococcus faecalis[a]	D	Endocarditis Bacteremia Urinary tract infection Gastrointestinal abscess	Ampicillin + gentamicin
Streptococcus bovis	D	Bacteremia Abscesses	Penicillin as for *Streptococcus equi* above
Streptococcus canis	G	Bacteremia Cellulitis Pharyngitis	Penicillin as for *Streptococcus equi* above

[a] Linezolid has activity against vancomycin-resistant enterococci (VRE). See Chapter 135, *Enterococcus*, for more details.

that country. In Finland and Sweden, emergence of erythromycin resistance has also paralleled erythromycin use. Recent studies from China document erythromycin and clindamycin resistance in a recent epidemic of scarlet fever following streptococcal pharyngitis. This could be a game changer if this strain spreads to other parts of the world.

Prophylactic treatment for populations at risk (e.g., schools, military) is indicated during

epidemics of streptococcal pharyngitis when rheumatic fever is prevalent. The incidence of rheumatic fever has declined in developed nations but flourishes in developing countries. Antistreptococcal prophylaxis should be continuous in individuals with a history of rheumatic fever. Benzathine penicillin given intramuscularly once each month has the greatest efficacy, although oral agents such as phenoxymethyl penicillin are also effective. In recent years, the US military has demonstrated that such prophylaxis, particularly benzathine penicillin, prevents epidemics of streptococcal infections among young soldiers living in crowded conditions. Routine follow-up culture to verify eradication is not recommended except in patients with a history of rheumatic fever. Following appropriate treatment for symptomatic pharyngitis, treatment is not needed for continued positive cultures unless symptoms recur.

Scarlet fever

Severe cases of scarlet fever were prevalent in the United States, western Europe, and Scandinavia during the nineteenth century, and mortality rates of 25% to 35% were not uncommon. In contrast, scarlet fever today is rare and, when it occurs, is very mild. The primary site of infection is usually the pharynx, although surgical site infections have also been described. Classically, a diffuse, erythematous rash with sandpaper consistency appears 2 days after the onset of pharyngitis. Circumoral pallor and "strawberry" tongue are common findings, and desquamation occurs approximately 6 to 10 days later. The cause of the rash is uncertain, although most agree that extracellular toxins, likely the pyrogenic exotoxins formerly called "scarlatina toxins," are responsible. Treatment of the underlying infection with penicillin (see "Pharyngitis") and general supportive measures are indicated. Specifically, severe hyperpyrexia (fevers to 107°F to 110°F [41.7°C to 43.3°C]) has been described, and antipyretics may be necessary to prevent febrile seizures, particularly in children.

Pyoderma (impetigo contagiosa)

Impetigo is a superficial vesiculopustular skin infection. Although *S. aureus* is the most common organism isolated in modern times, group A streptococcus is likely the most significant pathogen. Impetigo is most common in patients with poor hygiene or malnutrition. Colonization of the unbroken skin occurs first; then minor abrasions, insect bites, and so on initiate intradermal inoculation. Single or multiple thick, crusted, golden-yellow lesions develop within 10 to 14 days. Penicillin orally or parenterally, or bacitracin or mupirocin topically, is effective treatment and will reduce transmission of streptococci to susceptible individuals. None of these treatments, including penicillin, prevent poststreptococcal glomerulonephritis. Although *S. aureus* may cause impetigo, it has never been implicated as a cause of glomerulonephritis.

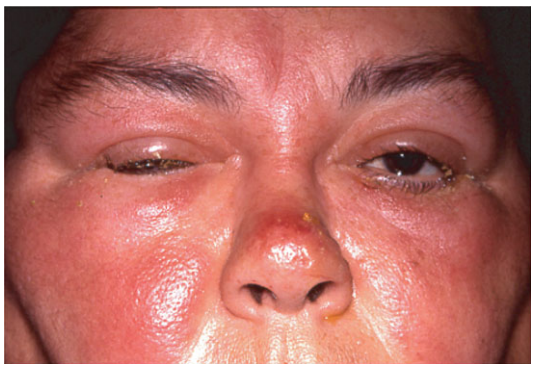

Figure 152.1 Erysipelas in a middle-aged woman. Note the brilliant red (salmon color) and the distinct demarcation along the nasolabial fold. The patient had a temperature of 39°C, tachycardia, normal blood pressure, and negative blood cultures. She responded well to intravenous penicillin G but developed superficial desquamation over the cheeks 10 days after admission.

Erysipelas

Erysipelas occurs most commonly in the elderly and very young. It is caused almost exclusively by group A streptococcus and is characterized by an abrupt onset of fiery red skin localized on the face or extremities (Figure 152.1). Distinctive features are well-defined margins, particularly along the nasolabial fold, scarlet or salmon red rash, rapid progression, and intense pain. Flaccid bullae may develop during the second to third day of illness, and desquamation of the involved skin occurs 5 to 10 days into the illness. In contrast, the rash of scarlet fever is generalized, has a diffuse pink or red hue that blanches on pressure, and has a sandpaper consistency. The organism is present in the lesion, although it is difficult to culture. Treatment with penicillin, a cephalosporin, or nafcillin is effective. Swelling may progress despite treatment, although fever, pain, and the intense redness usually diminish with 24 hours of treatment.

Cellulitis

Streptococcus pyogenes (group A streptococcus) is the most common cause of cellulitis, and although group A is the most common, β-hemolytic streptococci of groups B, C, and G also cause cellulitis in specific clinical settings. Patients with chronic venous stasis or lymphedema are predisposed to recurrent cellulitis caused by groups A, C, and G streptococci. Cellulitis in diabetic and elderly patients, particularly those with peripheral vascular disease, may also be caused by group B streptococci. Clinical clues to the category of cellulitis such as dog bite (*Capnocytophaga*), cat bite (*Pasteurella multocida*), human bite (mouth anaerobes and *Eikenella corrodens*), freshwater injury (*Aeromonas hydrophila*), seawater (*Vibrio vulnificus*), and furuncles (*S. aureus*) are extremely important. Definitive diagnosis in the absence of such factors rests on aspiration of the leading edge of the cellulitic lesion. At best, a bacterial cause is established in only 15% of cases. Cellulitis caused by groups A, B, C, and G streptococci responds to penicillin, nafcillin, erythromycin, clindamycin, and a variety of cephalosporins. Ceftriaxone, cefpodoxime proxetil, and cefuroxime axetil have the greatest in vitro activity, and all have US Food and Drug Administration (FDA)-approved indications for the treatment of streptococcal cellulitis. Although most quinolones have efficacy in the treatment of cellulitis, older quinolones such as ciprofloxacin should be avoided because of their poor in vitro activity against streptococci. Newer quinolones may be considered as second-line therapy.

Invasive group A

In the past 20 years, there has been an increase in the number of severe group A streptococcal soft-tissue infections and bacteremia associated with shock and death in 30% to 70% of cases. Shock and organ failure early in the course of infection define streptococcal toxic shock syndrome, and the inciting infection may be necrotizing fasciitis, myositis, pneumonia, peritonitis, septic arthritis, uterine infection, and others. Predisposing factors include varicella virus infections, penetrating or blunt trauma, and nonsteroidal anti-inflammatory agents.

Therapy

When large numbers of streptococci accumulate, more organisms are in the stationary phase and are less affected by β-lactam antibiotics (the Eagle phenomenon). The decreased expression of critical penicillin-binding proteins in such slow-growing bacteria presumably explains the lack of efficacy of penicillin. In vitro, clindamycin – but not penicillin – prevents synthesis of toxins. Interestingly, in experimental necrotizing fasciitis and myositis, clindamycin has markedly better efficacy than penicillin. Thus some authorities recommend treatment with both penicillin and clindamycin (and debridement when appropriate). Uncontrolled observations suggest that intravenous immunoglobulin may be helpful as well.

GROUP B

Streptococcus agalactiae (the only species in Lancefield group B) colonizes the vagina, gastrointestinal tract, and occasionally the upper respiratory tract of normal humans. Group B streptococci are the most common cause of neonatal pneumonia, sepsis, and meningitis in the United States and western Europe, with an incidence of 1.8 to 3.2 cases per 1000 live births. Preterm infants born to mothers who are colonized with group B streptococci in the third trimester and have premature rupture of the membranes are at highest risk for early-onset pneumonia and sepsis. The mean time of onset is 20 hours postpartum, and symptoms are respiratory distress, apnea, and fever or hypothermia. Ascent of the streptococcus from the vagina to the amniotic cavity causes amnionitis. Infants may aspirate streptococci either from the birth canal during parturition or from amniotic fluid in utero. Radiographic evidence of pneumonia and/or hyaline membrane disease is present in 40% of cases. Type III strains account for most cases of group B streptococcal meningitis in neonates.

Late-onset neonatal sepsis occurs 7 to 90 days postpartum. Symptoms are fever, poor feeding, lethargy, and irritability. Bacteremia is common, and meningitis occurs in 80% of cases.

The standards of modern-day prenatal care include swab culture of the lower vagina and anorectum for these organisms at 35 to 37 weeks of pregnancy. Women presenting in labor without such cultures can be screened with a rapid antigen-detecting kit, although the false-negative rate may be 10% to 30%. Both passive immunization with intravenous immunoglobulin and active immunization with multivalent polysaccharide vaccine show promise and in the future may become the best approach to prevention of neonatal sepsis as well as postpartum infection in the mother. Women colonized with group

B streptococcus in the third trimester should receive penicillin or ampicillin during delivery (see below).

Adults with group B infections include postpartum women and patients with peripheral vascular disease, diabetes, or malignancy. Soft-tissue infection, septic arthritis, and osteomyelitis are the most common presentations.

Therapy

Penicillin is the treatment of choice, although in practice many neonates are empirically treated with ampicillin, 100 to 200 mg/kg/day, plus gentamicin. Once the diagnosis is established, penicillin or ampicillin should be given (Table 152.1). Adults should receive 12 million to 24 million units of penicillin per day for bacteremia, soft-tissue infection, or osteomyelitis; the dosage should be 8 to 12 g of ampicillin or 24 million units per day of penicillin for meningitis. Vancomycin or a first-generation cephalosporin is the alternative for patients allergic to penicillin. Intrapartum administration of ampicillin or aqueous penicillin G to women colonized with group B streptococcus during the third trimester, who had group B strep bacteriuria during the pregnancy, or who have premature labor or prolonged rupture of the membranes prevents group B neonatal sepsis. Infants should continue to receive ampicillin for 36 hours postpartum.

GROUPS C AND G

Groups C and G streptococci may be isolated from the throats of both humans and dogs, produce streptolysin O, and resemble group A in colony morphology and spectrum of clinical disease. Before rapid identification tests were developed, many infections caused by groups C and G, such as pharyngitis, cellulitis, skin and wound infections, endocarditis, meningitis, osteomyelitis, and arthritis, were mistakenly attributed to group A. Rheumatic fever following group C or G streptococcal infection has not been described. These strains also cause recurrent cellulitis at the saphenous vein donor site in patients who have undergone coronary artery bypass surgery. Both organisms are susceptible to penicillin, erythromycin, vancomycin, and clindamycin, though recent studies document clindamycin resistance in 17% of strains of group G.

GROUP D

Group D consists of gram-positive, facultatively anaerobic bacteria that are usually nonhemolytic but may demonstrate α- or β-hemolysis. *Streptococcus faecalis*, renamed *Enterococcus faecalis*, was previously classified as group D because it hydrolyzes bile esculin and possesses the group D antigen. *Streptococcus bovis* is also a cause of subacute bacterial endocarditis and bacteremia often in patients with underlying gastrointestinal malignancy. Enterococci are commonly isolated from stool, urine, and sites of intra-abdominal and lower-extremity infection. Enterococci cause subacute bacterial endocarditis and have become an important cause of nosocomial infection, not because of increased virulence, but because of antibiotic resistance. First, person-to-person transfer of multidrug-resistant enterococci is a major concern to hospital epidemiologists. Second, superinfections and spontaneous bacteremia from endogenous sites of enterococcal colonization are described in patients receiving quinolone or moxalactam antibiotics. Last, conjugational transfer of plasmids and transposons between enterococci in the face of intense antibiotic pressure within the hospital milieu have created multidrug-resistant strains, including some with vancomycin and teicoplanin resistance.

Therapy

Serious infections with enterococci, such as endocarditis or bacteremia, require a synergistic combination of antimicrobials, that is, ampicillin or vancomycin together with an aminoglycoside (see Chapter 135, Enterococcus). Unlike enterococci, *S. bovis* remains highly sensitive to penicillin. Vancomycin-resistant enterococci (VRE) are being described with increasing frequency. Linezolid, an oxyzolidinone antibiotic, has excellent activity against VRE, although antibiotic resistance can develop during therapy.

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153. Viridans streptococci

Caroline C. Johnson

Viridans streptococci are a heterogeneous group of microorganisms that produce (partial) α-hemolysis or no hemolysis when grown on sheep blood agar. They are subdivided into six major groups, *Streptococcus mutans*, *Streptococcus salivarius*, *Streptococcus anginosus*, *Streptococcus sanguinis*, *Streptococcus mitis*, and *Streptococcus bovis*, the last of which is also characterized as nonenterococcal group D streptococci. Various species can be distinguished according to their physiologic and biochemical characteristics; more than 20 of which have been associated with human infections. Typically, however, clinical laboratories speciate isolates only if they are recovered from blood or other usually sterile sites. Isolates recovered in mixed culture or from mucosal surfaces are normally reported only as nonhemolytic or α-hemolytic streptococci. Table 153.1 lists the most common species of viridans streptococci isolated from blood cultures.

Viridans streptococci are an important part of the normal microbial flora in humans. They are indigenous to the oral cavity, the upper respiratory tract, the female genital tract, and the gastrointestinal tract. Because these microorganisms lack traditional virulence factors, such as endo- and exotoxins, they are considered low virulence. However, a propensity to adhere to endovascular tissues accounts for their ability to produce endocarditis; extracellular dextran plays an important role in adherence and propagation of viridans streptococci on cardiac valves. Furthermore, some viridans streptococci are known to cause abscess formation, particularly the *S. anginosus* group (formerly known nonspecifically as *Streptococcus milleri*), composed of *Streptococcus intermedius*, *Streptococcus constellatus*, and *S. anginosus*.

Table 153.1 Most common species of viridans streptococci isolated from blood cultures

Streptococcus sanguis
Streptococcus mitis
Streptococcus salivarius
Streptococcus intermedius
Streptococcus uberis
Streptococcus mutans
Streptococcus constellatus
Streptococcus (Gemella) morbillorum

INFECTIONS

Viridans streptococci are important causes of infective endocarditis. In addition, they are increasingly identified as causes of septicemia in immunocompromised hosts. With infection at other body sites, such as the central nervous system or lower respiratory tract, viridans streptococci may occur as sole pathogens but are more typically found as part of a mixed aerobic-anaerobic infection.

Infective endocarditis

Viridans streptococci account for approximately 20% to 40% of cases of infective endocarditis. The incidence of viridans streptococcal endocarditis has not changed appreciably since the American Heart Association recommended in 2007 the cessation of routine antibiotic prophylaxis before dental procedures for all but those at greatest risk. Typically, patients with infective endocarditis have underlying cardiac valve abnormalities, such as degenerative valve disease or rheumatic heart disease. Viridans streptococcal endocarditis develops insidiously and follows an indolent course. Fever, fatigue, and malaise are characteristic early clinical manifestations. In later stages of infection, cardiac murmurs may be detected in more than 90% of cases. Congestive heart failure and major embolic episodes are the most common complications of infective endocarditis, occurring in nearly one-third of cases. The critical element for diagnosis of infective endocarditis is demonstration of continuous bacteremia. In the absence

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of recent antimicrobial therapy, two blood cultures will yield viridans streptococci in 95% of cases. Echocardiography, either transthoracic or transesophageal, may provide additional diagnostic and prognostic information in cases of endocarditis.

Bacteremia and septicemia

Transient bacteremia due to viridans streptococci may occur in association with dental procedures but also with routine daily activities. It is rarely of clinical significance. In contrast, prolonged bacteremia has emerged as a genuine problem among patients undergoing cancer chemotherapy, especially among children. Viridans streptococci are now a leading cause of bacteremia in febrile, neutropenic patients in many cancer centers. Infection occurs in association with aggressive cytoreductive therapy for acute leukemia or bone marrow transplantation, typically after high-dose cytosine arabinoside treatment. Other predisposing factors include oral mucositis, prophylactic administration of trimethoprim–sulfamethoxazole (TMP–SMX) or quinolone, presence of an indwelling central venous catheter, and use of antacids or histamine type 2 (H2) antagonists. A fulminant shock syndrome characterized by hypotension, rash with palmar desquamation, acute renal failure, adult respiratory distress syndrome, and death has also been described. The viridans streptococcal shock syndrome occurs in up to 25% of pediatric patients with bacteremia, with mortality rates of 40% to 100%.

Meningitis and brain abscess

Viridans streptococci are an uncommon cause of meningitis, accounting for fewer than 5% of culture-proven cases. Infections occur in patients of all ages, including neonates. The source of infection for most cases is underlying ear, nose, or throat pathology, endocarditis, extracranial infection, or head trauma. Clinical manifestations are typical of acute pyogenic meningitis with signs of meningeal irritation, neurologic deficits, seizures, and altered sensorium. Although cerebrospinal fluid (CSF) pleocytosis is characteristically present with viridans streptococcal meningitis, the Gram stain of CSF is positive less than half of the time.

Viridans streptococci are also a cause of primary brain abscess, typically in association with anaerobic bacteria. Predisposing conditions include head and neck infection, lung abscess, and endocarditis. Clinical manifestations of brain abscess are primarily related to the size and location of the intracranial lesion, with headache being the most common presenting complaint. Fever is present in less than half of cases. Computed tomography or magnetic resonance imaging is useful both for diagnosis and to follow the course of antimicrobial therapy. Definitive microbiologic diagnosis can be established from culture of brain abscess material obtained by excision or through stereotactic aspiration.

Pneumonia

Viridans streptococci are frequently identified in cultures of respiratory tract secretions. When recovered from expectorated sputum, viridans streptococci should rarely be considered significant, because of their presence as normal oral flora. However, they may also be found in lower respiratory tract specimens obtained from patients with pneumonia by transtracheal aspiration or protected bronchial brush. Typically, viridans streptococci cause lower respiratory tract infection in association with other oral organisms, especially anaerobes, following aspiration of oropharyngeal material. Predisposing conditions include periodontal disease, gingivitis, depressed cough and gag reflexes, dysphagia from esophageal disease, depressed consciousness, seizures, and ethanol abuse. Pneumonia usually develops in dependent lung segments and may lead to necrosis with abscess formation and/or empyema. The diagnosis of aspiration pneumonia should be suspected by the presence of purulent sputum and an abnormal radiograph in a patient at high risk of aspiration. Viridans streptococci are also occasionally identified as sole pathogens in patients with lower respiratory tract infection.

THERAPY

Penicillin and related β-lactam antibiotics have long been considered the drugs of choice for therapy for infections due to viridans streptococci because of previously uniform susceptibility to these agents. However, resistance has now emerged as a significant problem. Resistance rates vary widely between species and under different clinical situations. The greatest risk appears to occur in pediatric and immunocompromised populations. Using a minimum inhibitory concentration (MIC) breakpoint criterion of $\leq$0.125 μg/mL for determining susceptibility, penicillin resistance has been reported in 25% to 50% of

Table 153.2 Antibiotic treatment of specified infection due to viridans streptococci

Infection type	Antibiotic regimen[a]	Duration
Septicemia	Penicillin G, 12–18 million units IV qd, in divided doses, and/or vancomycin,[b] 15 mg/kg (not to exceed 1 g) IV q12h	2 wk
Meningitis	Ceftriaxone, 2–4 g IV qd, in divided doses, and/or vancomycin,[b] 15 mg/kg (not to exceed 1 g) IV q12h	2 wk
Brain abscess	Ceftriaxone, 2–4 g IV qd, in divided doses, and/or vancomycin,[b] 15 mg/kg (not to exceed 1 g) IV q12h, plus metronidazole, 500 mg IV or PO q6h	≥6 wk
Pneumonia[c] (aspiration)	Clindamycin, 600 mg IV or PO q8h or penicillin G, 8–12 million units IV qd, in divided doses, plus metronidazole, 500 mg IV or PO q6h or β-lactam/β-lactamase inhibitor combination	2–3 wk
Endocarditis	See Chapter 37, Endocarditis of natural and prosthetic valves: treatment and prophylaxis, Table 37.3	

[a] Doses should be adjusted according to age, weight, and renal function.

[b] For suspected or confirmed infections due to β-lactam–resistant viridans streptococci. Selection of empiric treatment for viridans streptococcal infections should take into account local patterns of antimicrobial susceptibility.

[c] Presence of enteric gram-negative bacilli might require additional antimicrobial agents.

isolates recovered in some centers, with 5% to 10% of isolates resistant to high concentrations of penicillin (MIC ≥4 μg/mL). In contrast, most community isolates of viridans group streptococci, including those associated with infective endocarditis, remain susceptible to penicillin. Other β-lactam antibiotics have in vitro activity similar to that of penicillin. Vancomycin, daptomycin, and linezolid have consistently excellent activity against viridans streptococci, whereas tetracycline, clindamycin, and erythromycin have variable activity, often with 25% to 50% of isolates reported resistant. Most strains of viridans streptococci are resistant to TMP–SMX.

Because of the unpredictable antibiotic susceptibility of viridans streptococci, in vitro testing should be performed on all clinically significant isolates recovered from normally sterile body sites, such as blood or CSF. Antibiotic regimens that are currently recommended for treatment of infective endocarditis are summarized in Chapter 37, Endocarditis of natural and prosthetic valves: treatment and prophylaxis, Table 37.3. For streptococcal isolates that are moderately or highly resistant to β-lactam agents, penicillin should be given in combination with low doses of aminoglycoside. Table 153.2 lists recommended antibiotic regimens for the treatment of septicemia, central nervous system infections, and lower respiratory tract infections due to viridans streptococci.

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154. Poststreptococcal immunologic complications

Barbara W. Stechenberg

Infections caused by group A β-hemolytic *Streptococcus (Streptococcus pyogenes)* are unusual in that they have been associated with nonsuppurative complications, acute rheumatic fever (ARF), and acute glomerulonephritis. These distinct clinical entities are not related to toxic effects of the organism and follow the infections by an interval during which immunologic mechanisms are triggered. Table 154.1 compares some features of two clinical syndromes.

Table 154.1 Comparison of acute rheumatic fever (ARF) and acute poststreptococcal glomerulonephritis (AGN)

Feature	ARF	AGN
Prior infection	Pharyngitis	Pharyngitis or pyoderma
M-types	3, 5, 6, 14, 18, 19, 24	Pharynx: 1, 2, 3, 4, 12, 15 Skin: 4, 9, 52, 55, 59, 60, 61
Latency	2–4 wk	Throat: 10 d Skin: 3 wk
Recurrences	Common	Rare
Antibiotic prophylaxis	Useful	Not useful
Sequelae	Common (heart)	Rare

ACUTE RHEUMATIC FEVER

ARF is a multisystem collagen vascular disease that follows untreated or undetected group A streptococcal pharyngitis in <1% of persons. It is seen most commonly in children ages 5 to 15 and is associated with a genetic predisposition. It is more common in developing countries. There also appear to be strains of *S. pyogenes* more likely to be implicated in this condition (see Table 154.1).

The diagnosis of ARF is made clinically and is based on the modified Jones criteria (Table 154.2). The presence of two major or one major and at least two minor criteria suggests the diagnosis. Recent infection with *S. pyogenes* also must be suggested by either isolation of the organism from the throat or serologic evidence in the form of elevation of antistreptolysin O, antihyaluronidase, or antideoxyribonuclease B titers. The exception to this rule is chorea, which becomes manifest 2 to 6 months after infection, by which time evidence of a recent streptococcal infection may be lacking.

Table 154.2 Modified Jones criteria for acute rheumatic fever[a]

Major criteria	Minor criteria
Carditis	Previous rheumatic fever
Arthritis	Clinical
Chorea	Fever
Erythema marginatum	Arthralgia
Subcutaneous nodules	Laboratory
	Prolonged PR interval
	Elevated acute-phase reactants: erythrocyte sedimentation rate, C-reactive protein, white blood cell count

[a] Requirements: (1) evidence of antecedent group A streptococcal infection and (2) two major criteria or one major and at least two minor criteria.

The most common clinical manifestations of ARF are carditis and arthritis. The former usually presents as a significant murmur, most commonly mitral insufficiency. Both myocarditis and pericarditis may accompany this valvulitis. It is the only manifestation that may result in residual disease. The arthritis is a migratory polyarthritis that generally involves the medium-size joints (elbows, wrists, ankles, and knees). Pain is often striking. Another characteristic finding is the dramatic response of the arthritis to salicylate therapy. Chorea known as Sydenham chorea or St. Vitus' dance usually occurs as an isolated, often subtle, neurologic disorder with behavioral aspects, particularly emotional lability. Erythema marginatum and subcutaneous nodules are rarely seen. The strongest diagnoses of ARF are based on carditis or chorea. The weakest is based on arthritis as a single major manifestation with two minor criteria.

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The term *PANDAS* (pediatric autoimmune neuropsychiatric disorder associated with group *A Streptococcus*) has been used to refer to a group of neuropsychiatric or behavioral disorders, particularly obsessive-compulsive disorder (OCD), Tourette's syndrome, and tic disorder, with a possible relationship to group A streptococcal infections, and, perhaps, related pathologically to Sydenham chorea. Swedo and colleagues have proposed an autoimmune pathogenesis for these disorders, although this is controversial. Suggested diagnostic criteria include the presence of OCD or a tic disorder; pediatric onset; abrupt onset of symptoms or a course characterized by dramatic exacerbations of symptoms; a temporal association with group A streptococcal infection; and abnormal results of neurologic examination, such as choreiform movements, motor hyperactivity, and tics. Extensive investigation of its epidemiology, diagnosis, and treatment as well as its relationship to ARF are still underway.

Prevention

Primary prevention of ARF requires the proper diagnosis and treatment of *S. pyogenes* pharyngitis. The accepted standard of care is the performance of a throat culture or rapid streptococcal antigen detection test. If the latter is negative in a child, a throat culture should be done because of the variable sensitivity of that test. Treatment of streptococcal pharyngitis should be undertaken, generally with oral phenoxymethyl penicillin (penicillin V) at 250 to 500 mg two or three times a day for 10 days; if compliance is an issue, benzathine penicillin G, 1.2 million units intramuscularly (IM) (if $\geq$27 kg or 600 000 U if $\leq$27 kg), is acceptable. For patients allergic to penicillin (without anaphylaxis), a first-generation cephalosporin (e.g., cephalexin 20 mg/kg/dose twice daily, max dose = 500 mg) for 10 days is the antibiotic of choice. Alternatives are clindamycin (7 mg/kg/dose three times daily, max dose = 300 mg) or clarithromycin (7.5 mg/kg/dose twice daily, max dose = 250 mg) for 10 days or azithromycin (12 mg/kg once daily, max dose = 500 mg) for 5 days, although resistance to the latter two agents is well known. Prompt treatment should prevent most cases of ARF after symptomatic pharyngitis. Initiation of therapy up to 8 days after infection begins is probably beneficial.

Therapy

Treatment of ARF involves three important areas: eradication of *S. pyogenes*, treatment of the acute manifestations, and prevention of both recurrences and infective endocarditis in those with residual carditis. The first is accomplished with the regimens for primary prevention. These regimens should be used even if the throat culture is negative at the time of diagnosis of ARF. The mainstay of treatment of ARF is salicylates, both for arthritis and mild to moderate carditis. A dosage of 70 to 80 mg/kg/day should be initiated to produce a therapeutic blood level of 20 to 25 mg/dL. This is continued for at least 2 weeks, until acute inflammation has subsided, and then decreased gradually over the next 2 to 4 weeks. Patients with arthritis should be repeatedly evaluated for carditis during the initial 2 weeks. Persons with severe carditis and/or congestive heart failure may be treated with steroids, usually prednisone, at 2 mg/kg/day acutely for at least 2 weeks, with a gradual withdrawal over 4 to 6 weeks, with the introduction of salicylates to prevent rebound. Supportive care of carditis is important; digitalization should be done slowly starting with one-quarter of the usual initial dose.

Sydenham chorea is usually self-limited over several weeks. If symptoms are debilitating, phenobarbital may be started at 15 to 30 mg every 6 to 8 hours. Haloperidol is an alternative. A short course of corticosteroids over 2 weeks with a 2- to 3-week taper may be beneficial.

Secondary prevention

Secondary prevention of infection with *S. pyogenes* is based on the fact that persons with ARF have at least 10% to 30% chance of recurrence of ARF when reinfected with this organism. Because of concerns about compliance, benzathine penicillin G, 1.2 million units IM every 4 weeks, is recommended, particularly in the first 5 years after clinical presentation and in persons with carditis. In areas of high prevalence of ARF, this regimen should be given every 3 weeks. Oral penicillin, 250 mg twice a day, is an acceptable alternative. Patients allergic to penicillin are treated with sulfadiazine, 500 mg twice a day. Erythromycin, 250 mg twice daily, should be reserved for persons allergic to both penicillin and sulfa. The duration of secondary prevention is controversial; many believe it should be lifelong, but there is evidence for discontinuing at age 21 or after 5 years (whichever is longer).

Persons with residual carditis should be educated about the importance of oral hygiene. They should receive antibiotics for prophylaxis against infective endocarditis (see Chapter 37, Endocarditis of natural and prosthetic valves: treatment and prophylaxis).

For patients with PANDAS, prompt recognition and treatment of group A streptococcal infections is important. The role of prophylactic antibiotics to prevent recurrences is unknown.

ACUTE POSTSTREPTOCOCCAL GLOMERULONEPHRITIS

Poststreptococcal acute glomerulonephritis (AGN) is an inflammatory disorder of the glomeruli. It occurs when soluble immunoglobulin G immune complexes are deposited at the glomerular basement membrane, causing complement activation and release of cytokines. This leads to infiltration of inflammatory cells. The streptococcal antigen involved has not been completely elucidated. It can follow either throat or skin infection with *S. pyogenes*. Table 154.1 lists the major strains associated with AGN and designated nephritogenic; since the early 1980s, the incidence of AGN has decreased remarkably, perhaps with a decrease in these M-types. AGN has rarely been associated with infection with group C streptococci.

The epidemiology of AGN reflects that of streptococcal pharyngitis (age 5 to 15 years; winter to spring) and pyoderma (younger age; summer months). Prompt therapy does not prevent AGN. The incubation period is about 10 days with pharyngeal strains and about 3 weeks following pyoderma.

Clinical manifestations include edema (85%), gross hematuria (25%), and hypertension (60% to 80%). A consequence of volume overload, the hypertension may lead to encephalopathic changes in a small number of patients. Symptoms referable to the cardiovascular system (cardiomegaly, congestive heart failure, pulmonary edema) are sometimes present. Fever is uncommon. Some patients have a mixed acute nephritis/nephrotic syndrome with ascites and anasarca. AGN is typically self-limited, with spontaneous diuresis and improvement in hypertension within 1 week. In fact, up to 50% have been asymptomatic during outbreaks. In children, fewer than 2% of cases are complicated by acute renal failure. This number may be higher in adults. Progression to chronic renal failure is also very unlikely.

Freshly voided urine typically demonstrates mild proteinuria, red and white blood cells, and red and white blood cell casts. Gross hematuria (usually brown) disappears rapidly, although microscopic hematuria persists for months as does the proteinuria. Striking hypocomplementemia is seen in 90% of patients, primarily C3 and CH50 with a normal C4. Diagnosis is supported by the latter finding in association with evidence of preceding *S. pyogenes* infection. Following pharyngeal infection, antistreptolysin O elevations are common. However, it is less useful following skin infections, after which anti-DNAase B or antihyaluronidase are more likely to be high. Attempts to culture the organism also should be undertaken.

Therapy

Therapy is supportive. Antibiotics should be given to eradicate any streptococcal carriage, using the same agents as described for ARF. Oral therapy should be continued for 10 days However, no data have demonstrated that this therapy either prevents AGN or alters its natural history. Patients with obvious edema, hypertension, or azotemia may require hospitalization, although most patients respond to careful restriction of fluid and salt intake. Diuretic therapy is usually successful in controlling hypertension. Prognosis is generally excellent. Relapses are rare.

There is no need for antibiotic prophylaxis to prevent future attacks because repeated episodes are rare.

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155. *Shigella*

David W. K. Acheson

Shigella are a family of enteric pathogens consisting of four different species that are a common cause of diarrheal disease. *Shigella* are usually transmitted person to person but may also be transmitted via food, often from an infected food worker. The majority of illness from *Shigella* is short lived and does not require specific antibiotic therapy; however, some forms can be life threatening.

MICROBIOLOGY

Shigella belongs to the family Enterobacteriaceae and closely resembles *Escherichia coli* at the genetic level. Four species of *Shigella* – *Shigella dysenteriae, Shigella flexneri, Shigella boydii*, and *Shigella sonnei* – are differentiated by group-specific polysaccharide antigens of lipopolysaccharide, designated A, B, C, and D, respectively. *Shigella dysenteriae* consists of 10 antigenic types, of which type 1 produces a potent cytotoxin known as Shiga toxin. *Shigella flexneri* is divided into 6 types and 14 subtypes, and *S. boydii* into 18 serologic types. Although there is only 1 S. *sonnei* serotype, there are at least 20 colicin types. Shigellae are biochemically very similar, and differentiation among species is based primarily on serologic methods using group- and type-specific antisera.

EPIDEMIOLOGY

Shigellosis occurs throughout the world with varying species distribution. *Shigella dysenteriae* and *S. flexneri* are the predominant species in developing countries, whereas *S. sonnei* is the major isolate in developed countries, accounting for more than three-quarters of the isolates in the United States. *Shigella flexneri* is being seen more frequently in the United States in homosexual men and is thought to be transmitted sexually in this group. *Shigella boydii* is uncommon except in the Indian subcontinent. Fecal–oral transmission is the typical way for these bacteria to spread. They will colonize only in humans and some nonhuman primates, so when one sees a case of *Shigella* it is likely transmitted from another human. The spread is often person to person directly or via contaminated food (often salads) or water, and the disease is often associated with poor personal hygiene. Flies are also known to transmit *Shigella*. One of the most striking features of shigellosis is the exceedingly small inoculum of organisms required to cause disease. As few as 10 to 100 *S. dysenteriae* have been shown to cause dysentery in adults. The other species may require 1000 to 10 000 bacteria, but this is still a small enough dose to be readily transmitted by fecal contamination of hands, water supply, or food.

CLINICAL FEATURES

Shigellosis characteristically begins with constitutional symptoms, including fever, fatigue, anorexia, and malaise with an incubation period of 1 to 4 days typically but may be as long as 8 days. Watery diarrhea usually develops and may become bloody and progress to dysentery within a few hours or days. The latter classically consists of a small amount of blood and mucus but may be grossly purulent. Progression to clinical dysentery is uncommon in *S. sonnei* infection, occurs more often in *S. boydii* infection, is common in *S. flexneri*, and occurs in most patients when *S. dysenteriae* is the cause. Although fluid loss is usually not a major problem in shigellosis (usually no more than 30 mL/kg/day), hyponatremia can be severe because of inappropriate secretion of antidiuretic hormone, especially in infants infected with *S. dysenteriae* type 1 or *S. flexneri*.

Shigellosis may cause both local and systemic complications. Intestinal obstruction and toxic megacolon during shigellosis are uncommon in the United States but occur regularly in developing countries and are associated with high mortality. *Shigella* bacteremia is considered to be

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uncommon; however, when routinely looked for, it is not rare and has been documented in 4% of a series of patients in Bangladesh. Bacteremic patients were more likely to die, and mortality in *Shigella* sepsis was 21% compared with 10% in the absence of bacteremia. Systemic complications are especially frequent during infection with *S. dysenteriae*, including toxic megacolon and leukemoid reactions with leukocyte counts in excess of 50 000/dL. Hemolytic-uremic syndrome (HUS) and neurologic complications, especially seizures, may occur. HUS is associated with the Shiga toxins produced by *S. dysenteriae* and may result in significant morbidity and mortality. Other complications include reactive arthritis, especially after infection with *S. flexneri* and may occur alone or as part of Reiter's syndrome. The pathogenesis of shigellosis is highly complex, involving multiple genes in both chromosomal and plasmid locations. Several reviews have been published on this topic (see the suggested reading at the end of this chapter).

DIAGNOSIS

Shigellosis may be diagnosed clinically, microbiologically, or serologically. Patients with the classical picture of dysentery, with frequent small-volume bloody stools, abdominal cramps, tenesmus, and large numbers of leukocytes in the stool, especially if febrile, can be given a presumptive diagnosis of shigellosis. However, in the early stages of shigellosis it may be difficult to differentiate clinically from other enteric infections. Studies in Bangladesh indicate that 85% of patients with shigellosis had >50 fecal leukocytes per high-power field. This level is higher than usual in other enteric infections. *Shigella* are especially fastidious and rapidly die off if stool samples are not properly handled. The best way to isolate *Shigella* is to obtain stool as opposed to rectal swabs, rapidly inoculate specimens onto selective culture plates, and quickly incubate them at 37°C (98.6°F). To optimize isolation, a variety of media such as MacConkey, deoxycholate, and eosinmethylene blue, and highly selective media such as Hektoen-enteric, salmonella-shigella, and xylose-lysinedeoxycholate should be used. Detection of antibodies to *Shigella* lipopolysaccharide is an alternative but is generally used for epidemiologic studies and not for routine diagnosis in the clinical microbiology laboratory. Molecular techniques, including DNA probes and polymerase chain reaction techniques, have also been described for the detection of *Shigella* but are not routinely used except in research.

THERAPY

Diarrhea from *Shigella* is generally not severely dehydrating; however, replacement of lost fluids and electrolytes is the most important therapy and can often be done orally and may be all that is required (Table 155.1). Most infections in developed countries are caused by *S. sonnei* and are self-limiting within a few days. In more severe infections, usually those caused by *S. flexneri* or *S. dysenteriae*, hyponatremia with serum sodium below 120 mmol/L may be a significant problem requiring infusion of 3% hypertonic saline 12 mL/kg over 2 hours to raise the serum sodium by around 10 mmol/L. This therapy must be combined with restricted access to drinking water. Hypoglycemia, also a common problem in children with shigellosis in developing countries, may require intravenous replacement therapy. One way to do this is rapid infusion of glucose 1 g/kg body weight over 5 to 10 minutes, and then a continuous infusion of glucose, 50 g/L, until the infection is under control. Shigellosis involves major catabolic stress, and nutritional replacement is an important part of therapy.

Specific antimicrobial therapy in shigellosis requires the administration of agents that shorten the illness and reduce the mortality. Sometimes antibiotics are used in order to reduce transmission and risk to others. Empiric antibiotic therapy may be wise in some patients, e.g., those who are severely ill, or the elderly, in malnourished individuals, and patients with human immunodeficiency virus (HIV) infection, food handlers, healthcare workers, and individuals in day-care centers

Table 155.1 Antimicrobial therapy for shigellosis in adults

Drug	Dose
Ciprofloxacin	500 mg PO 2× daily for 3 d or 750 mg once daily
Levofloxacin	500 mg once daily
Trimethoprim–sulfamethoxazole (TMP–SMX)	160 mg TMP/800 mg SMX PO 2× daily for 5 d
Azithromycin	500 mg PO daily for 1 day, then 250 mg PO daily for 4 d
Ceftriaxone	1–2 g intravenously once daily

Table 155.2 Antimicrobial therapy for shigellosis in children

Drug	Dose
Azithromycin	12 mg/kg for the first day (maximum 500 mg) and then 6 mg/kg/dose (maximum 250 mg) for an additional 4 d
Cefixime	8 mg/kg/d, single dose (maximum 400 mg/d) for 5 d
Ceftibuten	9 mg/kg orally once daily for 5 d (maximum 400 mg/d)
Ceftriaxone	50 mg/kg IV per day (maximum 1.5 g) in a single daily dose, for 5 d
Ciprofloxacin	10 mg/kg (maximum 400 mg/dose) every 12 h for 5 d
Trimethoprim–sulfamethoxazole	10 mg/kg (based upon TMP component) orally in two divided doses for 5 d

The antibiotic of choice for adults with *Shigella* infection is an oral fluoroquinolone. The duration of therapy is 3 days; or 5 to 7 days in patients with infection due to *S. dysenteriae* type 1 or with HIV coinfection. If the patient has a history of travel in the Indian subcontinent, empiric antibiotic therapy may require a third-generation cephalosporin, due to widespread resistance to ciprofloxacin, trimethoprim–sulfamethoxazole, and azithromycin. Once susceptibilities are known treatment can be adjusted as necessary.

In children adequate hydration is critical and as with adults the decision to introduce antibiotics has to be a clinical decision based on the clinical severity, underlying risk (e.g., immunocompromise) and likelihood of spread to others. Empiric therapy may be appropriate in patients with suspected shigellosis if they are also immunocompromised and have symptoms suggestive of bacteremia (Table 155.2).

Children who are stool culture positive may warrant treatment to reduce the likelihood of spread to others especially if they attend institutions since antibiotic treatment will reduce the time of fecal shedding. For children less than 18 years of age azithromycin is suggested as a first-line treatment.

If the clinical situation indicates the need for parentral antibiotic the drug of choice is ceftriazone (50 mg/kg/day IV in single daily doses, maximum 1.5 g for 5 days). Ciprofloxacin is an alternative (10 mg/kg, maximum 400 mg/dose) every 12 hours for 5 days. Obviously the treatment may need to be changed based on microbial antibiotic sensitivity results.

ANTIBIOTIC RESISTANCE

Plasmid-mediated antibiotic resistance is a common problem with *Shigella* and often strains are resistant to ampicillin, chloramphenicol, tetracycline, sulfonamides, and trimethoprim. This is especially a problem in Asia and Africa. Today some strains in the United States are resistant to ciprofloxacin and ceftriaxone and nalidixic acid. In May 2012 an outbreak of *S. sonnei* occurred in the United States in which the organism was resistant to azithromycin – so it is important to be aware of the growing resistance to *Shigella* when using empiric therapy.

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156. Tularemia

Kari A. Neemann and Jessica N. Snowden

Tularemia is an acute febrile zoonosis caused by highly infectious gram-negative coccobacilli. It can present with multiple possible clinical syndromes, depending on the route of infection, and requires a high index of clinical suspicion for diagnosis.

MICROBIOLOGY AND EPIDEMIOLOGY

Francisella tularensis is a small, aerobic, catalase-positive, pleomorphic, gram-negative intra- and extracellular coccobacillus. It is highly infectious, requiring as few as 1 to 10 organisms to cause infection. There are four recognized subspecies of *F. tularensis* (*tularensis* [type A], *holarctica* [type B], *mediasiatica*, and *novicida*). *F. tularensis* type A, which has been described as the more virulent of the subspecies, is found predominantly in North America. *F. tularensis* type B exists throughout the northern hemisphere.

Francisella tularensis can infect a wide variety of invertebrates, including the dog tick (*Dermacentor variabilis*), the wood tick (*Dermacentor andersoni*), the Lone Star tick (*Amblyomma americanum*), deer flies (*Chrysops* spp.), and vertebrates (rabbits, muskrats, prairie dogs, other rodents, and occasionally cats). Transmission to humans is typically via bites of the arthropod vectors or contact with infected animal tissues. It can also be acquired by contact with, or ingestion of, contaminated material, including food and water, and by inhalation of infectious particles.

Tularemia occurs in all age groups with the highest incidence in children. Males have a higher incidence in all age categories, thought to be secondary to their occupational and leisure activities. In areas where tularemia is endemic, predominantly the South Central region of the United States, the disease is seasonal with the highest incidence in late spring extending throughout the summer months into early autumn. In the United States approximately 120 cases of tularemia are reported each year, although this may be underestimated as reporting is not mandatory.

CLINICAL MANIFESTATIONS

The clinical presentation, with severity ranging from mild to fatal disease, depends on patient characteristics, bacterial subspecies, inoculum dose, and route of transmission. The mean incubation period of tularemia is 3 to 5 days, but may range from 1 to 21 days. With all of the clinical syndromes, symptom onset is typically abrupt with fever, chills, myalgia, vomiting, fatigue, and headache. Fever may be continuous or biphasic, with an intermittent period of defervescence. Pulse–temperature dissociation is also a classic finding. Ulceroglandular and glandular tularemia are by far the most frequent forms of the disease, usually acquired by vector-borne transmission, or direct or indirect contact with an infected animal. Ulceroglandular tularemia presents as a skin ulceration at the inoculation site (Figure 156.1) with associated regional lymphadenopathy. The site of inoculation may become evident within the first 24 hours with a swollen papule that ruptures, leaving a punched-out ulcer with raised edges.

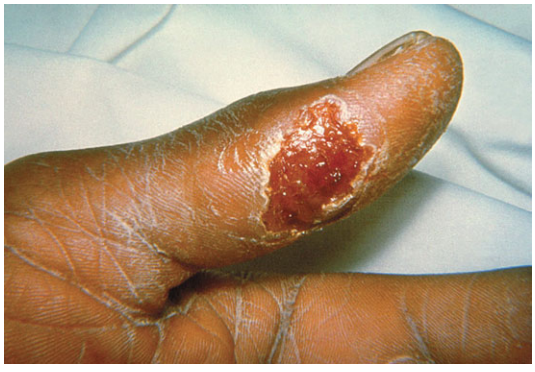

Figure 156.1 Thumb with skin ulcer of tularemia (Public Health Image Library, Centers for Disease Control and Prevention [CDC]).

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The skin overlying the regional lymph nodes may be inflamed and if untreated approximately 50% of the lymph nodes suppurate and drain. The glandular form lacks the more peripheral ulceration but otherwise presents similarly, with tender lymphadenopathy in the region of initial inoculation. Oculoglandular tularemia (1% of cases) occurs after the organism is introduced via touching the eye or infected particles blowing into the eye and presents with irritation and inflammation of the eye and preauricular lymphadenopathy. Oropharyngeal tularemia occurs rarely following the ingestion of contaminated food or water and presents with acute pharyngitis, tonsillitis, pharyngeal ulcers, and cervical lymphadenopathy. Typhoidal tularemia can occur following any initial route of infection and presents as fever of unknown origin, frequently without the classic skin and lymph node involvement. The hallmark clinical findings are high fever, splenomegaly, and hepatomegaly. Pneumonic tularemia occurs either after exposure to aerosolized particles of *F. tularensis* or from hematogenous spread from a distal site that can occur secondary to any other untreated form of tularemia but is more commonly seen with the typhoidal form. Pulmonary infection remains the most lethal form of tularemia with a case-fatality rate of 30% to 60% of those untreated. In pneumonic tularemia, the course of disease differs markedly between type A and type B, with type A resulting in a more fulminant presentation. Other rare presentations include gastroenteritis, endocarditis, and meningitis.

DIAGNOSIS

Diagnosis of tularemia is based on positive tissue culture or, more commonly, serology. Growth of *F. tularensis* in culture, from lymphatic tissue, blood, surface swabs, or other infected tissue, is the definitive means of confirming the diagnosis of tularemia. Because *F. tularensis* has been associated with laboratory-acquired infections laboratory personnel should be notified of the diagnostic possibility to enhance the diagnostic yield and to ensure that safety procedures are followed. Since the organism grows poorly on standard media, it must be grown on media enriched with cysteine (e.g., modified Thayer–Martin media, chocolate agar) and may take upwards of 10 days of incubation for growth.

The diagnosis of tularemia is usually established by serologic testing; a $\geq$4-fold change in *F. tularensis* agglutinin titer between acute and convalescent sera confirms the diagnosis, whereas a single convalescent titer of $\geq$160 is consistent with recent or past infection. In patients with tularemia, antibodies appear approximately 2 to 3 weeks after infection and may be detected several years after recovery.

MANAGEMENT

To date there have been no randomized controlled trials to determine the optimal antimicrobial therapy for tularemia treatment. In the past streptomycin has been the drug of choice in treating this infection. In one meta-analysis the use of streptomycin was associated with a 97% clinical cure rate compared to only 86% with gentamicin. In one series, involving only children, gentamicin was associated with a 93% success rate. Given streptomycin's known vestibular toxicity and reports of hypersensitivity reactions among personnel involved in its administration, gentamicin has now primarily replaced streptomycin (Table 156.1). Of note, in tularemic meningitis streptomycin or chloramphenicol still may be the drug of choice. Chloramphenicol and tetracyclines have been second-line therapy in the past but with their bacteriostatic activity are associated with higher relapse rates, especially with *F. tularensis* type A. Fluoroquinolones, which have intracellular bactericidal activity, have had good in vitro activity against *F. tularensis*. The use

Table 156.1 Treatment of tularemia

	Adults	Children
First-line therapy	Gentamicin 5 mg/kg IM or IV once daily × 10 days *Drug of choice in pregnancy*	Gentamicin 2.5 mg/kg IM or IV three times daily × 10 days
Second-line therapy	Doxycycline 100 mg PO/IV BID × 14 days *Not in pregnancy* Chloramphenicol 15 mg/kg IV q6h × 14 days *Not in pregnancy* Ciprofloxacin 500 mg PO BID × 10 days	Doxycycline (*Children ≥ 8 years old*) Weight <45 kg: 2.2 mg/kg PO/IV BID × 14 days Weight ≥45 kg: 100 mg PO/IV BID × 14 days Chloramphenicol 15 mg/kg IV q6h × 14 days Ciprofloxacin 15 mg/kg PO/IV BID × 10 days

of ciprofloxacin for the treatment of *F. tularenis* type B has shown low relapse rates in both adult and pediatric series. Limited observational studies in the United States, where *F. tularenis* type A is more prevalent, have shown success when fluoroquinolones (ciprofloxacin, levofloxacin) were started earlier in the disease course and used for at least 10 days or in combination with aminoglycoside initially. However, as data are limited on the use of fluoroquinolones for treatment of tularemia in the United States, these are not recommended as first-line therapy.

Prevention of human tularemia relies on avoidance of known vectors and careful handling of potentially contaminated animal tissue. Children in endemic areas should have hair and skin checked regularly for ticks. Hunters handling animal carcasses, especially rabbits, should utilize gloves and cook meat thoroughly. Previously in the United States, a live attenuated vaccine *F. tularenesis* LVS was used to vaccinate at-risk laboratory workers, but currently this is under review by the US Food and Drug Administration (FDA) and is not available.

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157. Tuberculosis

Jay B. Mehta and Asim K. Dutt

In the United States, the epidemiology of tuberculosis (TB) has changed in recent years and since 1992 the incidence of TB has resumed a downward trend; from 10.4 in 1992 to 3.0 in 2013. However, infection by human immunodeficiency virus (HIV) and the increase in homelessness, poverty, and drug abuse continue to remain the major risk factors for active TB. Tuberculosis occurs most commonly among ethnic minorities, African Americans, and Hispanics 25 to 44 years of age. Immigrants from developing countries with a high prevalence of TB and drug resistance and other foreign born have contributed more than one-half of the total new cases in last few years. Drug-resistant disease is a major concern.

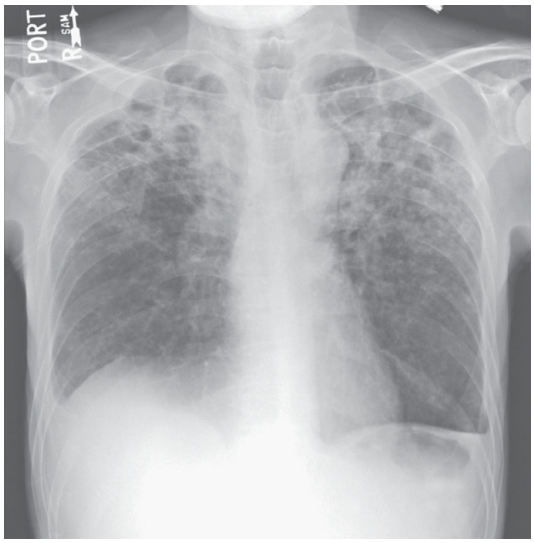

Figure 157.1 Pulmonary tuberculosis. Characteristic findings on chest x-ray (CXR) include upper lobe infiltrates, involvement of apical or posterior segments, and cavities with thick walls, smooth inner contours, and no air–fluid levels. Pleural reaction and distal infiltrates from endobronchial spread may be seen. Disease activity cannot be determined from the CXR alone and must be proven or excluded by sputum smear and culture. (Courtesy of David Schlossberg, MD.)

DIAGNOSIS

After history and physical examination, the chest x-ray is required to support the diagnosis of TB (Figure 157.1). Whenever there is a suspicion of pulmonary TB, three spontaneously produced sputum specimens should be examined by microscopy and culture. If necessary, sputum production may be induced by inhalation of aerosol of warm saline (Figure 157.2). When suspicion of TB is high and microscopy is negative, a bronchial washing, transbronchial biopsy, or postbronchoscopy sputum may be productive. On rare occasions diagnosis must be made by open lung biopsy. Positive sputum microscopy suggests TB, but the only positive identification of *Mycobacterium tuberculosis* is by culture or DNA probe to distinguish it from less virulent nontuberculous mycobacteria (NTB). Drug susceptibility testing should be performed. For early detection of drug resistance DNA analysis might be very useful but this technology is still under investigation.

Latent TB infection

The goal of testing for latent TB infection is to identify the individuals who are at a higher risk for developing TB, and hence who would benefit from preventive therapy. Tuberculosis skin test (TST) has been in use for many decades, but the results are flawed and unreliable in detecting TB infection. With advancement in immunology and genomics, T-cell–based in vitro assays of interferon (IFN) released by T cells after stimulation with *M. tuberculosis* antigens are developed to identify TB infection. Two interferon-gamma release assays (IGRAs) are available as commercial kits: the Quanti FERON-TB gold assay (QFT-GIT) and the T-SPOT.TB (Oxford Immunotec).

Studies indicate that IFN-γ detection has higher specificity for *M. tuberculosis* and less

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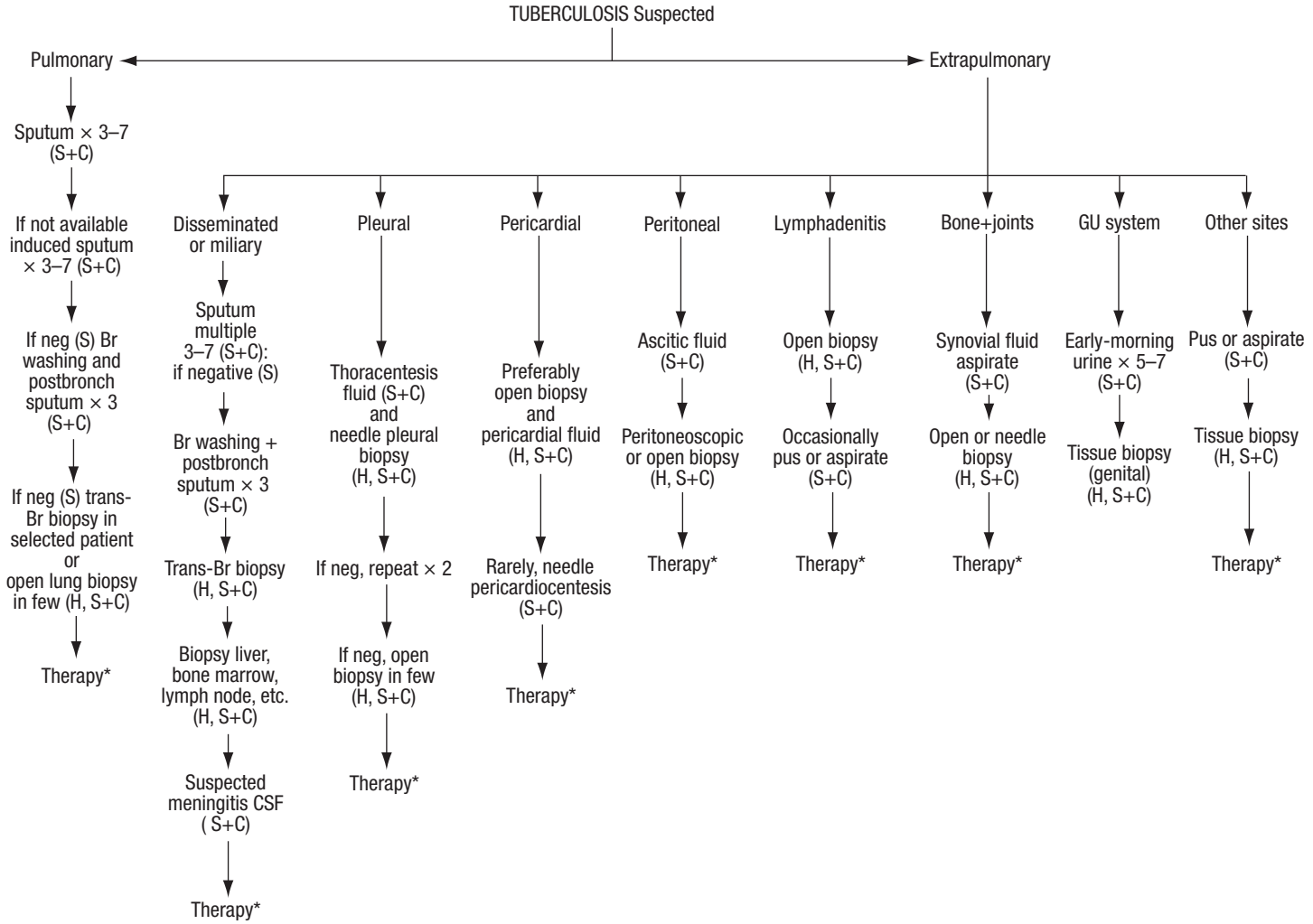

Figure 157.2 Diagnosis of suspected tuberculosis. S = smear; C = culture for mycobacteria; H = histology; Br = bronchial; Bronch = bronchoscopy; CSF = cerebrospinal fluid; neg = negative; GU = genitourinary. * Therapy started in suspected cases, awaiting culture results and/or clinical response.

cross-reactivity with bacille Calmette–Guérin (BCG) vaccination than TST. The sensitivity of T-SPOT.TB appears to be higher than for QFT-GIT or TST, likely because the testing platform ensures that an adequate number of mononuclear cells are available even if the lymphocyte count is low. The Centers for Disease Control and Prevention (CDC) recommends the QFT-GIT test for detection of latent infection, which has the advantage of a single test for patients. IGRAs should not be used for diagnosis of active TB. The guidelines suggest that this test can be used in place of, but not in addition to TST in situations in which CDC recommends use of TST. Although the evidence is limited, IGRAs appear to be unaffected by NTB infection. *Mycobacterium marinum* and *Mycobacterium kansasii* infection are exceptions.

Diagnosis of tuberculosis

Nucleic acid amplification (NAA) tests amplify nucleic acid regions and identify the *M. tuberculosis* complex. The NAA test can be directly used in clinical specimens (such as sputum) as "direct amplification tests." The Amplicor MTB test (Roche Diagnostic System), the Amplified Mycobacterium Direct test (MTD) (Gene-Probe, Inc.), and the BD Probe-Tec ET assay (Becton Dickinson Biosciences) are commercially available. However, NAA tests cannot replace conventional tests (microscopy and culture) and should be interpreted along with conventional tests and clinical data.

Rapid detection drug resistance

Line probe assays are novel DNA strip tests that use the polymerase chain reaction (PCR). Commercially available kits include the INNO-LiPA RIF TB kit (Immunogenetics) and Geno Type MTBDR assays (Hain Lifescience). These kits are not US Food and Drug Administration (FDA) approved. Although sensitivity on culture isolates may be over 95% in detecting rifampin resistance, the tests are expensive and require sophisticated laboratory support.

Also, phage-based assays are available as commercial kits but are not approved by the FDA. The test is performed in culture isolates and has high sensitivity but low specificity. This may be used for rifampin resistance in culture isolates, which increases turnaround time. The tests show promise but are not routinely used.

Extrapulmonary tuberculosis

Extrapulmonary TB cases represent 15% to 20% of the total cases but this percentage could be higher in those with HIV coinfection. TB can involve any organ of the body but the lymphatic system and bone are common sites. Miliary and central nervous system TB are rare but carry high morbidity and mortality. In most extrapulmonary TB cases plain radiograph is frequently not adequate to prove the diagnosis. CT scan or MRI is required.

Signs and symptoms of extrapulmonary TB depend upon the site involved. Atypical presentation such as chronic pain, fatigue, and failure to thrive are not uncommon in elderly patients. Clinical presentation of miliary TB can be acute or subacute. Multiorgan failure including acute respiratory distress syndrome can be life threatening. Tissue diagnosis by microscopy and culture or DNA probe confirmation is required if secretions are negative for acid-fast bacilli smear and culture. Frequently treatment has to be started while the final bacteriologic confirmation is pending.

Patients with lymphatic TB generally present with pain and swelling in the area of involvement. In children cervical lymph nodes are frequently involved.

Bone and joint disease may present with joint pain or back ache (Pott's disease). With chronic disease, destruction of bone with local sclerosis and spinal deformity is noted. Disease is most common in the lower thoracic and lumbar vertebrae. Involvement of the surrounding soft tissue may lead to cold abscess.

For the diagnosis of extrapulmonary TB, secretions and/or biopsy material must be obtained from the site (Figure 157.2). In the case of tuberculous meningitis it may be necessary to initiate therapy empirically because the disease may become irreversible before the diagnosis can be made. Low glucose, high protein, and lymphocytosis is frequently noted in cerebrospinal examination.

THERAPY

Principles of chemotherapy

Initial treatment of TB should include four drugs: generally isoniazid (INH), rifampin (RIF), ethambutol (EMB), and pyrazinamide (PZA). Directly observed therapy (DOT) is the preferred strategy. After daily treatment for the first 4 to 6 weeks, a twice or three time weekly regimen can be selected. Table 157.1 lists drugs, dosages, and

Table 157.1 Antituberculosis drugs

Drug	Daily dosage	Twice-weekly dosage	Side effects	Mode of action
FIRST-LINE DRUGS				
Isoniazid (INH)	5 mg/kg (usually 300 mg) PO or IM	15 mg/kg (usually 900 mg) PO	Peripheral neuritis, hepatotoxicity, allergic fever and rash, lupus erythematosus phenomenon	Acts strongly on rapidly dividing extracellular bacilli; acts weakly on slowly multiplying intracellular bacilli
Rifampin (RIF)	10 mg/kg (usually 450–600 mg) PO	10 mg/kg (usually 450–600 mg) PO	Hepatotoxicity, nausea, vomiting, allergic fever and rash, flu-like syndrome, petechiae with thrombocytopenia or acute renal failure during intermittent therapy	Acts on both rapidly and slowly multiplying extracellular and intracellular bacilli, particularly on slowly multiplying persisters
Rifabutin (Ansamycin)	300 mg PO daily, twice or thrice weekly	Used as RIF substitute	Same as rifampin; uveitis, arthralgia, leukopenia	Same as above
Rifapentine	300–600 mg PO once weekly in continuation phase	Seronegative HIV, noncavitary TB	Same as rifampin; not used in HIV	
Rifamate (INH 150 mg plus RIF 300 mg)	2 capsules PO qd	2 capsules plus 2 tablets of INH (300 mg)	Same as INH/RIF	Same as INH/RIF
Rifater (INH 50 mg plus RIF 120 mg plus PZA 300 mg)	5–6 capsules PO qd		Same as INH/RIF/PZA	Same as INH/RIF/PZA
Pyrazinamide (PZA)	25–30 mg/kg PO (usually 1.5–2 g)	45–50 mg/kg PO (usually 3–3.5 mg)	Hyperuricemia, hepatotoxicity, allergic fever and rash	Active in acid pH (2.5 g) on intracellular bacilli
Ethambutol (EMB)	15–25 mg/kg/d initially, followed after 2 months with 15 mg/kg/d	50 mg/kg PO	Optic neuritis, skin rash, hyperuricemia	Weakly active against both extracellular and intracellular bacilli to inhibit the development of resistance
SECOND-LINE DRUGS				
Streptomycin	10–15 mg/kg (usually 0.5–1 g) 5 days/week; IM or IV	20–25 mg/kg (usually 1–1.5 g)	Cranial nerve VIII damage (vestibular and auditory), nephrotoxicity, allergic fever, rash	Active against rapidly multiplying bacilli in neutral or slightly alkaline extracellular medium
Kanamycin	15–30 mg/kg qd IM or IV	15–30 mg/kg	Same as streptomycin	Same as streptomycin
Amikacin	15–30 mg/kg qd IM or IV	15–30 mg/kg	Same as streptomycin	Same as streptomycin
Capreomycin	15–30 mg/kg/d IM or IV	15–30 mg/kg	Same as streptomycin	Same as streptomycin
Ethionamide	10–15 mg/kg (usually 500–750 mg) in divided doses PO with 100 mg pyridoxine	Not used	Nausea, vomiting, anorexia, allergic fever and rash, hepatotoxicity, neurotoxicity, hypothyroidism	Same as streptomycin
Cycloserine	15–20 mg/kg (usually 0.75–1 g) in divided doses with 200 mg pyridoxine PO	Not used	Personality changes, psychosis, convulsions, rash	Same as ethambutol
Para-aminosalicylic acid	150 mg/kg (usually 12 g) in divided doses PO	Not used	Nausea, vomiting, diarrhea, hepatotoxicity, allergic rash and fever, hypothyroidism	Weak action on extracellular bacilli; inhibits development of drug-resistant organisms
Thiocetazone[a]	150 mg PO	Used rarely	Allergic rash and fever, Stevens–Johnson syndrome, blood disorders, nausea, vomiting	Same as para-aminosalicylic acid
Clofazimine	200–300 mg PO qd	Not used	Pigmentation of skin, abdominal pain	Not fully known

Table 157.1 *(continued)*

Drug	Daily dosage	Twice-weekly dosage	Side effects	Mode of action
NEWER AGENTS				
Ofloxacin	400 mg q12h	Not used	Gastrointestinal: diarrhea, nausea, abdominal pain, anorexia; central nervous system: dizziness, restlessness, nightmares, ataxia, seizures	Rapidly multiplying bacilli at neutral or alkaline pH
Gatifloxacin	400 mg PO qd	Not used	Same as ofloxacin	Same as ofloxacin
Levofloxacin	500 mg PO qd	Not used	Same as ofloxacin	Same as ofloxacin
Moxifloxacin	400 mg PO qd	Not used	Same as ofloxacin	Same as ofloxacin
Azithromycin	500 mg/d	Not used	Diarrhea, nausea, abdominal pain, elevation of liver enzymes	Rapidly multiplying bacilli in macrophages
Clarithromycin	1 g q12h	Not used	Same as azithromycin	Same as azithromycin

[a] Not available in the United States.

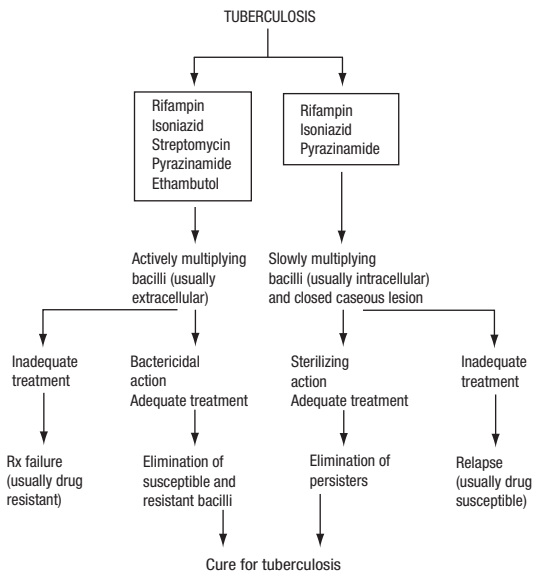

Figure 157.3 Principles of chemotherapy of tuberculosis.

major side effects. Several first-line bactericidal drugs are commonly combined initially because they reduce the bacterial population rapidly without the risk of resistance. Second-line drugs are most useful when resistance to two or more first-line drugs is found or they cannot be used because of life-threatening side effects or intolerance (Figure 157.3). Currently 11 drugs are approved by the FDA. Of the approved drugs, INH, RIF, EMB, and PZA are considered first-line drugs. While fluoroquinolones are not FDA approved for TB, they are commonly used for drug-resistant TB cases. Rifabutin (RBT) and rifapentine (RPT) can be considered as important drugs in certain circumstances. Streptomycin (SM) is no longer included in the list of first-line drugs.

The bactericidal drugs in suitable combinations actually kill actively multiplying extracellular bacilli in TB lesions. Rapid elimination of these bacilli renders the sputum bacteriologically negative, leading to cure. No bactericidal drug should be used alone to treat active TB because this inevitably leads to resistance to that drug. When initial therapy fails at this stage, the sputum bacteriology does not become negative, as shown by persistence of positive sputum smears beyond 2 months. Failure of therapy is usually due to emergence of drug-resistant organisms, most often due to poor compliance, prescription of an inadequate regimen, or inadequate dosage of individual drugs.

In the continuation phase of therapy, the drugs slowly eliminate small populations of intermittently metabolizing bacteria in the closed caseous lesion or within macrophages. Incomplete therapy may lead to relapse after discontinuation of treatment, often with drug-sensitive organisms.

Drug-resistant organisms

The inclusion of a number of drugs in a regimen should be based on the awareness of the circumstances under which drug-resistant bacilli are likely to be present (Table 157.2).

Table 157.2 Conditions and patients with increased risk of drug-resistant TB

History of treatment with anti-TB drugs, including preventive therapy
Patients from areas with high prevalence of initial or primary drug resistance (>4%), e.g., urban population in the northeastern United States, Florida, California, US–Mexican border
Foreign-born persons from areas with high prevalence of drug-resistant TB, e.g., Southeast Asia, Mexico, South America, Africa
Contacts of persons with drug-resistant disease
Disease in persons who are homeless, drug abusers, and HIV infected
Persons with positive sputum smears and cultures after 2 months of chemotherapy

At the minimum, a four-drug regimen should be initiated when drug resistance is likely, until susceptibility results are available. The number of drugs in the initial regimen may have to be increased to five to seven if the organisms are resistant to three or more drugs and HIV infection is present, as often occurs in large cities in the United States and in many developing countries.

Management of tuberculosis

Newer approaches are advocated for a better outcome. For the care of patients with TB, responsibility for completion and success now lies with the healthcare providers and not the patients. The duration of treatment in the continuation phase should be extended in specific situations. New anti-TB medications show promise; these are used when necessary. DOT is strongly recommended; the patient is observed ingesting each dose of medication, for improving completion of therapy with a good outcome.

Drug regimens

There are four basic regimens recommended by the CDC for treatment of adult TB disease caused by susceptible organisms (Table 157.3). Each treatment regimen consists of an initial 2-month therapy of INH, RIF, EMB, and PZA followed by a continuation phase of 4 to 7 months.

It is recommended that the duration of treatment of any of the regimens should be extended in drug-susceptible pulmonary TB patients who show cavitations in the initial chest x-ray or whose sputum culture had not converted to negative during the intensive phase of therapy (2 months). These clinical indicators may predict adverse outcome with regard to failure and relapse. The continuation phase of therapy should be extended for another 3 months. Sputum smears and cultures must be obtained at the end of the intensive phase of treatment.

SIX-MONTH REGIMEN

The addition of PZA to INH, RIF, and EMB daily for the initial 2 months, followed by INH and RIF daily or twice weekly for another 4 months (a total of 6 months), has proved to be highly successful. Addition of PZA accelerates reduction of the bacterial population and shortens the regimen to 6 months, although its cost is greater.

After drug susceptibility results are available, usually in 2 months, the regimen is modified accordingly. If the organisms are found to be susceptible to both drugs, therapy is completed with INH–RIF daily or twice weekly for another 4 months. In cases of INH resistance, therapy may consist of RIF, PZA, and EMB for a total of 6 or 9 months; INH may be included in the regimen because of its action on persisters, which generally remain INH sensitive. In RIF-resistant cases other bactericidal drugs should be continued for at least 10 to 12 months to prevent relapse. If the isolate is resistant to PZA, INH and RIF should be continued for a total of 9 months.

TREATMENT OF MULTIDRUG-RESISTANT DISEASE

Where the prevalence of multidrug resistance (MDR) and HIV infection is very high, it is necessary to initiate a five- to seven-drug regimen, including second-line drugs. This is applicable to large urban populations such as in New York City, Miami, parts of New Jersey, and San Francisco, as well as for persons from developing countries.

In the treatment of MDR disease, i.e., resistance to INH and RIF, some basic principles must be followed: (1) a single drug must not be added to a failing regimen, (2) at least three new drugs that the patient has not yet taken should replace the existing drug regimen until the susceptibility results are available, (3) the total duration of therapy must be prolonged to 24 months or more, (4) the regimen should include an injectable drug for at least 4 months after the culture is converted to negative, and (5) DOT should be used to ensure compliance, because it is the patient's last chance at a cure.

Extensively drug-resistant TB (XDR-TB) has been reported recently from different parts of the world, first from South Africa. XDR-TB is defined as resistance to at least RIF and INH

Table 157.3 Drug regimens for pulmonary TB in adults caused by drug-susceptible organisms

Initial phase			Continuation phase			
Regimen	**Drugs**	**Interval and doses±§**	**Regimen**	**Drugs**	**Interval and doses±§**	**Range of total doses**
1	**INH** **RIF** **PZA** **EMB**	7 days/week for 56 doses (8 weeks) **or** 5 days/week for 40 doses (8 weeks)	**1a**	**INH** **RIF**	7 days/week for 126 doses (18 weeks) **or** 5 days/week for 90 doses (18 weeks)	182–130 (26 weeks)
			1b#	**INH** **RIF**	2 days/week for 36 doses (18 weeks)	92–76 (26 weeks)
			1c	**INH** **RPT**	1 day/week for 18 doses (18 weeks)	74–58 (26 weeks)
2	**INH** **RIF** **PZA** **EMB**	7 days/week for 14 doses (2 weeks), then 2 days/week for 12 doses (6 weeks) **or** 5 days/week for 10 doses (2 weeks), then 2 days/week for 12 doses (6 weeks)	**2a** **2b**	**INH** **RIF** **INH** **RPT**	2 days/week for 36 doses (18 weeks) 1 day/week for 18 doses (18 weeks)	62–58 (26 weeks) 44–40 (26 weeks)
3	**INH** **RIF** **PZA** **EMB**	3 times weekly for 24 doses (8 weeks)	**3a**	**INH** **RIF**	3 times weekly for 54 doses (18 weeks)	78 (26 weeks)
4	**INH** **RIF** **EMB**	7 days/week for 56 doses (8 weeks) **or** 5 days/week for 40 doses (8 weeks)	**4a** **4b**	**INH** **RPT** **INH** **RIF**	7 days/week for 217 doses (31 weeks) **or** 5 days/week for 155 doses (31 weeks) Twice weekly for 62 doses (31 weeks)	273–195 (39 weeks) 118–102 (39 weeks)

Abbreviations: INH = isoniazid; RIF = rifampin; PZA = pyrazinamide; EMB = ethambutol; RPT = rifapentine.

± When DOT is used, drugs may be given 5 days/week and the necessary doses adjusted accordingly.

§ Patients with cavitation in initial chest x-ray and positive cultures at completion of 2 months of therapy should receive a 7-month continuation phase.

Adapted from CDC: Core Curriculum for Tuberculosis Fifth Edition 2011.

among the first line of anti-TB drugs (MDR-TB), in addition to resistance to any fluoroquinolone and to at least one of three injectable second-line anti-TB drugs used in TB treatment (capreomycin, kanamycin, amikacin). This development is a serious concern globally.

Most drugs used for MDR disease are second-line drugs (see Table 157.l): ethionamide, cycloserine, para-aminosalicylic acid (PAS), capreomycin, and kanamycin. Newer drugs, fluoroquinolones (gatifloxacin and moxifloxacin) and amikacin, are available but unproven. Finally, clofazimine and thiocetazone (not available in the United States) may be used but also are unproven. FDA has recently approved bedaquiline for MDR-TB but cardiac toxicity remains a concern. These second-line drugs are often rather toxic, and close monitoring is necessary. Monthly bacteriologic studies are necessary to monitor response to treatment.

Because of high failure and relapse rates in MDR-TB, surgical resection of the major diseased area of the lung is again becoming necessary after reasonable medical treatment has been given to reduce the bacterial load.

Preventive therapy for recent contacts with MDR-TB is controversial. However, possible regimens are PZA plus EMB, and PZA plus a fluoroquinolone, or EMB plus a fluoroquinolone for 12 to 24 months, during which periodic clinical, bacteriologic, and radiologic monitoring must be maintained.

The combination of RIF and PZA or rifabutin and PZA were suggested for shorter periods of time, but the regimens are highly toxic. Experts should be consulted prior to the use of the regimen.

TREATMENT REGIMENS FOR HIV-INFECTED PERSONS

In the United States the current 6-month treatment consisting of INH, RIF, PZA, and EMB or SM daily for 2 months, followed by INH and RIF daily or twice weekly for another 4 months, is not adequate in HIV-infected patients. However treatment of TB in HIV-infected patients is complex and requires due attention to the patient's need for antiretroviral therapy (ART), potential drug reactions, and complication secondary to the immune reconstitution inflammatory syndrome (IRIS). Rifamycins are known to induce liver CYP3A4 enzymes that can increase metabolism of protease inhibitor (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Rifampin is more potent an inducer than rifabutin hence rifabutin is preferred over rifampin if certain antiviral drugs are used to treat HIV infection; however, adjustment of the rifabutin dosage is still necessary with some of the antiretroviral medications. Clinically significant interactions between rifampin and nucleoside analogs are rare. Therefore, nucleoside analogs can be used within ART regimens along with a third antiretroviral agent (e.g., efavirenz).

The CDC recommends that therapy for patients with HIV infection be prolonged to 9 months or for at least 6 months following conversion of sputum cultures to negative (Table 157.3). Treatment-limiting side effects are frequent in HIV-infected patients, and they require innovative measures. Rifabutin has fewer drug–drug interactions due to its decreased induction of the cytochrome P450 system. It works better with those HIV-positive patients who are on certain PI and NNRTI antiviral drugs. Therefore, rifabutin may be used in place of RIF. The current recommendation is that HIV-infected patients with CD4 cell counts $<100/mm^3$ should receive therapy daily during the intensive phase and daily or thrice weekly during the continuation phase. If adverse affects such as uveitis and cytopenia occur, medication must be discontinued at once and appropriate consultation should be obtained.

SMEAR-NEGATIVE TUBERCULOSIS

Positive sputum smears indicate a large bacterial population and advanced disease, whereas negative smears generally suggest less advanced disease. Occasionally a patient who is smear negative is also culture negative but is treated for TB on the basis of clinical and x-ray findings and response to therapy. A suggested regimen for such patients is INH, RIF, PZA, and EMB for 2 months, followed by INH and RIF for an additional 2 months (4 months total). However, HIV-infected patients should be treated for a minimum of 6 months.

EXTRAPULMONARY TUBERCULOSIS

The bacterial load in extrapulmonary TB usually is much smaller than in cavitary pulmonary TB. Thus, 6- to 9-month regimens (see Table 157.3) are adequate for treatment of extrapulmonary TB. Figure 157.2 indicates the steps in the diagnosis of pulmonary and extrapulmonary TB. It is generally recommended that the duration of therapy be prolonged in TB spondylitis (Pott's disease) and meningitis to 9 to 12 months, respectively. Corticosteroids may be added for patients with tuberculous pericarditis and tuberculous meningitis.

DIRECTLY OBSERVED THERAPY

The fact that most of the 6-month regimens may be given intermittently two or three times per week has led to the development of some innovative regimens. The Denver regimen consists of DOT administration of daily INH, RIF, PZA, and SM or EMB for 2 weeks, followed by twice-weekly doses for 6 weeks and then twice-weekly administration of INH or RIF for another 16 weeks. Another DOT regimen is INH, RIF, PZA, and EMB or SM three times a week for 6 months (Table 157.3, options 2 and 3).

To ensure completion of therapy, DOT is the preferred initial strategy and deserves special emphasis. DOT can be provided daily or intermittently in the office, clinic, or in the field by trained personnel. Using DOT can only improve the outcome. Aggressive interventions may be initiated when the patient misses doses.

Therapy in special situations

PREGNANCY

Treatment with INH, RIF, and EMB is safe in pregnancy. SM should not be used because of toxicity to the eighth nerve of the fetus. Experience with PZA is limited in pregnancy, and at present it should be avoided if possible. If PZA is not included in the treatment regimen, the minimum duration of therapy is 9 months. Pregnancy alters the distribution and metabolism of several

drugs, particularly the serum concentration of PIs are decreased. Therefore, treatment of TB in an HIV-infected pregnant woman requires special attention.

RENAL FAILURE

INH and RIF dosages need not be altered in renal failure because these drugs are excreted by the liver. Renal dialysis patients should receive the drugs after dialysis. EMB dosage must be reduced to 8 to 10 mg/kg in advanced renal failure, and the serum level should be assayed. Aminoglycoside dosage must also be adjusted, and the level should be monitored if they must be used in very unusual circumstances. PZA dosage should be reduced to 15 to 20 mg/kg.

LIVER DISEASE

Alcoholic liver disease does not preclude use of anti-TB drugs. However, monitoring for side effects must be careful and regular. In overt liver failure, one suggested regimen is amikacin plus EMB plus a fluoroquinolone.

Combined preparations

In the United States, two commercial preparations of combination drugs are available. It is advantageous to use combination preparations because they preclude the taking of only one bactericidal drug, which encourages drug resistance. Rifamate is a combination capsule of INH, 150 mg, and RIF, 300 mg, and two capsules are the recommended daily dose. Another preparation, Rifater, contains INH, 50 mg, RIF, 120 mg, and PZA, 300 mg, in each tablet; the recommended dose is five tablets daily. We strongly recommend the use of combination preparations for therapy as a safeguard against development of drug resistance and medication errors, particularly for patients not on DOT.

Corticosteroid therapy

Corticosteroids are not routinely used in the treatment of TB. Prednisone, 20 to 30 mg/day, may improve the general sense of well-being, reduce fever, increase appetite, and improve nutrition of markedly toxic or severely debilitated patients. The drug should be tapered off gradually after 4 to 8 weeks. In disseminated TB associated with hypoxemia and respiratory failure, prednisone, 40 to 60 mg/day, may improve oxygenation. Steroids have been successfully used in AIDS patients with TB, but they may promote opportunistic infections. Most authorities believe that complicated tuberculous meningitis should be treated with prednisone, 60 to 80 mg/day, slowly tapered after 8 to 12 weeks. Some advise corticosteroid therapy for all cases of tuberculous pericarditis to prevent constrictive pericarditis.

MONITORING AND FOLLOW-UP OF PATIENTS

Intense bacteriologic monitoring is necessary during therapy of pulmonary TB. We recommend that three to five specimens of bronchial secretions (sputum) be examined initially by smear and culture, followed by drug susceptibility testing. During therapy, at least one specimen of sputum should be examined every 2 weeks until conversion to negative occurs. This permits early detection of noncompliance and impending failure. After completion of treatment, to detect early relapse, one specimen every 3 months three times should be examined before discharging the patient from the clinic.

Monitoring for side effects should be done monthly after explaining to the patient the symptoms of side effects for which to be alert (e.g., nausea, vomiting, anorexia, dark urine, jaundice). Blood should be collected for baseline complete blood count and renal and hepatic function tests. We do not recommend routine monthly blood studies. Rather, the patients are advised to discontinue medication when symptomatic and to report for repeat hepatic function studies at that time. The drugs are then adjusted to the laboratory findings. Some clinicians, however, do recommend routine blood studies, either of all patients or only of those at risk for hepatotoxicity due to underlying liver disease or with other risks for hepatotoxicity. For EMB, vision and color studies are performed monthly, and for SM or other aminoglycosides or capreomycin monthly examination for balance and hearing loss are performed.

PROPHYLAXIS

For prophylaxis, see Chapter 113, Nonsurgical antimicrobial prophylaxis.

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158. Nontuberculous mycobacteria

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INTRODUCTION

The nontuberculous mycobacteria (NTM) are ubiquitous in the environment; so much so that some experts feel they should be referred to as "environmental mycobacteria." While there are almost 150 identified NTM species, the most common NTM associated with human disease in the United States are *Mycobacterium avium* complex (MAC), *Mycobacterium kansasii*, *Mycobacterium fortuitum* and *Mycobacterium abscessus*. Many other NTM species can cause human disease but are generally rarely encountered clinically, while a few NTM species, most notably *Mycobacterium gordonae*, are frequently isolated as specimen contaminants and almost never cause disease.

Infection is thought to occur from environmental exposure to the NTM with three potential portals of entry; the respiratory tract, the gastrointestinal tract, and direct inoculation of the skin and soft tissues. There had been no documented occurrences of either human-to-human or animal-to-human transmission until recent reports of the transmissibility between patients in several cystic fibrosis (CF) clinics.

The most common clinical manifestation of NTM infection in the immunocompetent host is chronic pulmonary disease. Symptoms are usually insidious in onset and variably include cough, sputum production, fatigue, weight loss, weakness, hemoptysis, and night sweats. MAC is the most common respiratory pathogen. Patients with MAC lung disease are divided between two groups. The first are primarily female patients without a history of smoking or pre-existing lung disease who have noncavitary disease characterized by nodular densities and bronchiectasis, usually in the right middle lobe and lingula. The second group are primarily male patients with pre-existing lung disease, most often chronic obstructive lung disease, and cavitary abnormalities radiographically, similar to tuberculosis.

Lymphadenitis is the most common NTM disease manifestation in children and is usually due to MAC or less commonly *Mycobacterium scrofulaceum*. The most important differential diagnosis is tuberculosis lymphadenitis, although NTM account for approximately 90% of mycobacterial lymphadenitis in children (but only 10% in adults). Symptoms are usually minimal with unilateral involvement of submandibular, submaxillary, preauricular, or cervical lymph nodes most common. Skin and soft-tissue infections are usually due to *Mycobacterium marinum* or the "rapidly growing mycobacteria" (RGM), *M. abscessus*, *M. fortuitum*, *Mycobacterium chelonae*, and are the result of direct inoculation either after trauma or surgery. Dissemination of NTM pathogens is most often associated with the severe immunosuppression of advanced acquired immunodeficiency syndrome (AIDS) and caused by MAC. Disseminated NTM infections can also occur in other immunocompromised states, sometimes associated with indwelling foreign bodies such as venous catheters, dialysis catheters, or other prosthetic devices.

DIAGNOSTIC CRITERIA OF NONTUBERCULOUS MYCOBACTERIAL (NTM) LUNG DISEASE

The diagnostic criteria for NTM lung disease include a compilation of clinical, radiographic, and microbiologic criteria. Although a diagnosis of NTM lung disease may be suspected by one or more of these three criteria, all must be present to establish a diagnosis. Clinical, radiographic, and microbiologic criteria are equally important. The minimum evaluation of a patient suspected of NTM lung disease should include (1) chest radiograph or, in the absence of cavitation, chest high-resolution computed tomography (HRCT) scan, (2) three or more sputum specimens for acid-fast bacilli (AFB) analysis, and (3) exclusion of other disorders such as tuberculosis and lung malignancy.

The following criteria apply to symptomatic patients with radiographic infiltrates, nodular or

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cavitary, or an HRCT scan that shows multifocal bronchiectasis with multiple small nodules. These criteria fit best with MAC, *M. kansasii*, and *M. abscessus*. There is not enough known about most other NTM to be certain that these diagnostic criteria are universally applicable for all NTM respiratory pathogens. Expert consultation should be obtained when NTM are recovered that are either infrequently encountered or that usually represent environmental contamination. Substantial variation in the epidemiology of NTM lung disease has been recognized between countries such that mindfulness of the epidemiologic data is imperative in making assessments of clinical likelihood of disease versus colonization dependent on specific NTM species.

Clinical criteria include respiratory or systemic symptoms attributed to NTM lung disease not attributable to other established diagnoses. Radiographic findings as noted above may vary, especially in the context of whether there is or is not pre-existing lung disease. In the absence of radiographic changes related to pre-existing lung disease or of cavitary change, the most common findings include nodular infiltrates, cylindrical bronchiectasis, and consolidation. Pleural disease, prominent mediastinal/hilar adenopathy, air–fluid levels, and ground-glass opacities on high-resolution chest computed tomography are not commonly seen in non-human immunodeficiency virus (HIV) patients with NTM lung disease. Microbiologic criteria also may vary. If three sputum results are available at least two AFB cultures should be positive, regardless of AFB smear results. In the absence of at least two positive cultures, consideration should be given to repeating three sputum specimens for AFB smear and culture or obtaining bronchoscopy with wash or lavage. If only one bronchial wash or lavage is available, one positive culture regardless of smear is necessary. If the sputum or bronchial wash results are nondiagnostic or another disease cannot be excluded, transbronchial or lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or AFB) and yielding an NTM on culture, or biopsy showing mycobacterial histopathologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washing that is culture positive for an NTM are required.

The preferred staining procedure is the fluorochrome method. Specimens should be cultured on both liquid and solid media. Species that require special growth conditions and/or lower incubation temperatures include *Mycobacterium haemophilum*, *Mycobacterium genavense*, and *Mycobacterium conspicuum*. These species can cause cutaneous and lymph node disease. In general, NTM should be identified to the species level. Methods of rapid species identification include commercial DNA probes (MAC, *M. kansasii*, and *M. gordonae*) and high performance liquid chromatography (HPLC). Routine susceptibility testing of MAC isolates is recommended for clarithromycin only. Routine susceptibility testing of *M. kansasii* isolates is recommended for rifampin only. Routine susceptibility testing, for both taxonomic identification and treatment of RGM (*M. fortuitum*, *M. abscessus*, and *M. chelonae*) should be for amikacin, imipenem (*M. fortuitum* only), doxycycline, the fluorinated quinolones, a sulfonamide or trimethoprim–sulfamethoxazole, cefoxitin, clarithromycin, linezolid, and tobramycin (*M. chelonae* only).

Substantial changes have recently occurred in NTM taxonomy including for *M. abscessus* which underwent a taxonomic change with the identification of two new species, *Mycobacterium massiliense* and *Mycobacterium bolletii*, previously identified as *M. abscessus*. They had otherwise been identical based on the widely adopted mycobacterial speciating technique utilizing sequencing of the 16S ribosomal RNA gene. This gene is highly conserved in the mycobacterial genome such that very small sequence differences can define a new mycobacterial species. It has subsequently come to light that elsewhere in the mycobacterial genome, the organism identified as *M. massiliense* has a smaller, inactive erythromycin methylase or *erm* gene (an inducible gene that causes macrolide resistance and is discussed further below) than *M. abscessus* subsp. *abscessus*, but because the name *M. bolletii* had been applied to this species with the inactive *erm* gene first, the new "official" nomenclature for this organism is currently *M. abscessus* subsp. *bolletii* even though it is widely still referred to as *M. massiliense* in the medical literature. Molecular techniques for organism identification are becoming an increasingly necessary component for informed decision making by the clinician.

DIAGNOSTIC CRITERIA OF NONTUBERCULOUS MYCOBACTERIAL (NTM) EXTRAPULMONARY DISEASE

The diagnosis of extrapulmonary NTM disease also requires a compilation of clinical, microbiologic, and histopathologic test results in the

context of lack of other diagnoses to explain symptoms and findings. Microbiology and histopathology results are generally of most value. Specifically, AFB smear and culture of fluid or tissue is required. Specimens can be obtained by needle aspirate, core biopsy, or excisional biopsy. Tissue biopsy is generally the most sensitive means of obtaining a specimen for culture to establish extrapulmonary NTM disease. In some instances, histopathologic findings of granulomatous inflammation with or without AFB organisms present may be suggestive of NTM disease. However, prior to treatment for extrapulmonary NTM disease definitive identification by culture is recommended.

GENERAL PRINCIPLES OF THERAPY FOR NONTUBERCULOUS MYCOBACTERIA (TABLE 158.1)

The greatest misunderstanding about treatment regimens for NTM pathogens is the result of the expectation that all NTM infections should respond in a predictable manner to antimicrobial therapy, in a manner similar to *Mycobacterium tuberculosis*. That is, treatment regimens should be based on in vitro susceptibility testing and the NTM pathogen should respond to antimicrobial agents based on in vitro susceptibility results. The most difficult and frustrating aspect of NTM therapy for most clinicians is the lack of a clear association between in vitro susceptibility results and clinical (in vivo) response for many NTM pathogens including the most common one, MAC. For many NTM, including MAC, laboratory cutoffs for "susceptible" and "resistant" do not have a demonstrable clinical correlate and have not been confirmed to be clinically meaningful. The situation is complicated further because there is a spectrum of response by NTM pathogens based on in vitro susceptibilities. For instance, diseases caused by *M. kansasii*, *M. fortuitum*, and *M. marinum* respond predictably to treatment regimens based on in vitro susceptibilities. Response of disease caused by MAC correlates with in vitro susceptibility to macrolides (clarithromycin and azithromycin), but not other agents. Lastly, there are a number of NTM species (*M. abscessus, Mycobacterium simiae, Mycobacterium malmoense*, *Mycobacterium xenopi*, etc.) for which there is no established correlation between in vitro susceptibilities and in vivo response for any antimicrobial agents. The explanation(s) for the dichotomy between in vitro susceptibility results and in vivo response (clinical outcome) for many NTM is (are) currently not known.

The presence of the *erm* gene noted above has recently provided a potential explanation for the discordance between in vitro testing and phenotypic response: erythromycin methylase (*erm*) genes encode a diverse collection of methylases that impair binding of macrolides to ribosomes, reducing the inhibitory activity of these agents. The primary mechanism of acquired clinically significant macrolide resistance for some mycobacteria, especially RGM, is the presence of an inducible *erm* gene. All isolates of *M. abscessus* subsp. *abscessus*, *M. fortuitum*, and several other RGM, but not *M. chelonae*, contain an inducible *erm* gene. The most interesting aspect of this inducible gene is that if an *M. fortuitum* or *M. abscessus* subsp. *abscessus* isolate is exposed to macrolide, the *erm* gene activity is induced with subsequent in vivo macrolide resistance which may not be reflected by the initial in vitro minimum inhibitory concentration (MIC) of the organism for the macrolide. It is only with incubation of NTM in the presence of a macrolide that the *erm* gene and the associated macrolide resistance will be identified.

The clinician must use in vitro susceptibility data for many NTM with the awareness that, unlike tuberculosis, NTM disease may not be eradicated in a given patient with therapy based on in vitro susceptibility results.

Lastly, the clinician may not uncommonly encounter different NTM isolates synchronously or metachronously, and should monitor microbiologic response during and microbiologic status after a treatment course.

RECOMMENDED DRUG TREATMENT FOR MAC LUNG DISEASE

As discussed in the general principles of NTM therapy, the macrolides (clarithromycin and azithromycin) are the only antimicrobial agents for which there is a demonstrated correlation between in vitro susceptibility and in vivo response for MAC lung disease. The cornerstones of MAC therapy, therefore, are the macrolides, clarithromycin and azithromycin, with the addition of ethambutol. These agents are then combined with companion drugs, usually a rifamycin and, possibly, an injectable aminoglycoside. It is necessary to include companion drugs with the macrolide to prevent the emergence of macrolide-resistant MAC isolates. The macrolides should

Table 158.1 Treatment of nontuberculous mycobacterial infections (see text for details)

NTM species	Disease	Treatment	Comment
MAC	Pulmonary[a]	Clarithromycin 500 mg BID or azithromycin 250 mg/d plus ethambutol 15 mg/kg/d plus rifampin 600 mg/d Consider streptomycin or amikacin 10–15 mg/kg IM or IV for severe disease	Treat for 1 year of negative AFB cultures Rifabutin 150–300 mg daily may be substituted for rifampin
MAC	Disseminated	Clarithromycin 500 mg BID or azithromycin 500 mg/d with ethambutol 15 mg/kg/d ± rifabutin 300 mg/d	Treatment lifetime or may be stopped with CD4+ T-cell count over 100 cells/mm^3 for 12 months
MAC	Lymph node Involvement	Complete surgical excision of involved nodes usually curative	If adjunctive chemo-therapy necessary, see drugs for pulmonary disease
M. kansasii	Pulmonary	Rifampin 600 mg/d Isoniazid 300 mg/d Ethambutol 15 mg/kg/d	Treat for 1 year of negative AFB cultures Clarithromycin and moxifloxacin also with excellent activity against *M. kansasii*
M. kansasii	Disseminated	Substitute rifabutin 150–300 mg/d for rifampin in HIV +	Treatment duration as for disseminated MAC
M. abscessus subsp. *bolletii*	Pulmonary	Clarithromycin 500 mg BID plus amikacin 10–15 mg/kg 3–5 times per week	Consider second parenteral drug such as cefoxitin or imipenem. Activity of linezolid, tigecycline, and clofazimine is variable
M. abscessus subsp. *bolletii*	Soft tissue	Clarithromycin 500mg BID plus amikacin 10–15 mg/kg 3–5 times per week for a minimum of 2 weeks, 4–6 months for severe infection	Consider second parenteral drug for severe disease. Removal of foreign body and surgical debridement also important. Other agent activity variable including linezolid, tigecycline, or clofazimine
M. abscessus subsp. *abscessus*	Pulmonary	Amikacin 10–15 mg/kg 3–5 times per week plus second parenteral drug such as cefoxitin or imipenem	Other agents with variable activity: linezolid, tigecycline, and clofazimine Role of azithromycin in presence of active *erm* gene is uncertain
M. abscessus subsp. abscessus	Soft tissue	Amikacin 10–15 mg/kg 3–5 times per week plus second parenteral drug such as cefoxitin or imipenem for a minimum of 2 weeks, 4–6 months for severe infection	Other agents with variable activity: linezolid, tigecycline, and clofazimine. Role of azithromycin in presence of active *erm* gene is uncertain. Removal of foreign body and surgical debridement also important
M. chelonae	Pulmonary	Clarithromycin 500 mg BID plus tobramycin 3–5 mg/kg 3–5 times per week	Consider third agent such as imipenem or linezolid. Clofazimine, doxycycline, and quinolone susceptibility varies
M. chelonae	Soft tissue	Clarithromycin 500 mg BID plus tobramycin 3–5 mg/kg 3–5 times per week for a minimum of 2 weeks, 4–6 months for severe infection	Consider third agent for severe disease. Susceptibility to imipenem, linezolid, clofazimine, doxycycline, and quinolone varies. Removal of foreign body and surgical debridement may be important
M. marinum	Soft tissue	Clarithromycin 500 mg BID plus ethambutol 15 mg/kg/d. Treat 1–2 months after resolution of symptoms (usually 3–4 months total)	Susceptible to multiple agents. Surgical debridement may also be important
M. fortuitum	Pulmonary	2 agents to which the organism is susceptible for 6 months. Consider parenteral medication for severe disease	Susceptible to multiple medications including quinolones, doxycycline, trimethoprim/sulfa, macrolides, amikacin
M. fortuitum	Soft tissue	As above. Treatment 3–6 months	
M. simiae, *M. xenopi* *M. malmoense* *M. szulgai*		Too little information to make standard or routine recommendation	Usually a macrolide-based regimen

[a] Consider three times weekly therapy (TIW) with clarithromycin 1000 mg, ethambutol 25 mg/kg/dose, and rifampin 600 mg for mild nodular/bronchiectatic (noncavitary) disease.

never be used as monotherapy for treatment of MAC disease (pulmonary or disseminated). Likewise, the use of macrolide and fluoroquinolone may be associated with cardiac toxicity and puts the patient at risk for development of macrolide-resistant MAC disease.

An important illustration of how the dichotomy between in vitro susceptibility results and in vivo response in MAC disease can be detrimental is provided by the example of ethambutol. There has not been a demonstrated correlation between ethambutol in vitro susceptibility and clinical response in any previous study; however, the duration of ethambutol use is associated with improved microbiologic response for patients receiving an intermittent clarithromycin-containing regimen and the exclusion of ethambutol from treatment regimens is a major risk factor for the development of macrolide-resistant MAC. It would be potentially risky to the patient for a physician to exclude ethambutol from a multidrug MAC treatment regimen based on in vitro susceptibility results.

There is another difficult-to-explain phenomenon associated with MAC drug therapy. Patients who have failed prior MAC therapy, with or without a macrolide, have lower sputum conversion rates with macrolide-containing treatment regimens, even with macrolide-susceptible MAC isolates, than do patients with no prior therapy. Although the explanation for this observation is also not clear, it is evident that the best chance for treatment success in MAC lung disease is the first treatment effort.

The recommended treatment length for MAC pulmonary disease is a duration of therapy that includes 12 months of sputum culture negativity. This treatment goal dictates that patients should have sputum collected for AFB analysis on a regular basis throughout the course of treatment.

The intensity of MAC treatment should be proportionate to the disease burden; other considerations should be individualized patient factors including tolerance to medications, medication cost, and acceptance of necessary monitoring and risks for the multidrug regimens.

For most patients with nodular/bronchiectatic disease, or those with fibrocavitary disease who cannot tolerate daily therapy, or those patients for whom disease suppression is an appropriate goal, intermittent, three times weekly, therapy is recommended. Recommended intermittent drug dosages include: (1) clarithromycin, 1000 mg, or azithromycin, 500 to 600 mg, (2) ethambutol, 25 mg/kg, and (3) rifampin, 600 mg, given three times weekly. Intermittent therapy is not recommended for patients with cavitary disease or patients who have received previous therapy for MAC.

The recommended regimen for patients with fibrocavitary disease or severe nodular/bronchiectatic disease, includes (1) clarithromycin, 1000 mg/day (or 500 mg twice daily) or azithromycin, 250 mg/day, (2) ethambutol, 15 mg/kg/day, and (3) rifampin, 10 mg/kg/day (maximum 600 mg/day). For some patients, the doses of clarithromycin may need to be split (e.g., 500 mg twice daily) because of gastrointestinal intolerance and for patients of small body mass (less than 50 kg) or age over 70 years, the clarithromycin dose may need to be reduced to 500 mg/day or 250 mg twice a day because of gastrointestinal intolerance.

A more aggressive and less well-tolerated treatment regimen for patients with severe and extensive (multilobar), especially fibrocavitary, disease consists of clarithromycin, 1000 mg/day (or 500 mg twice a day), or azithromycin, 250 mg/day, rifabutin, 150 to 300 mg/day, or rifampin, 10 mg/kg/day (maximum 600 mg/day), ethambutol (15 mg/kg/day), and consideration of inclusion of a parenteral agent, either amikacin or streptomycin, for the first 2 or 3 months of therapy (see dosage discussion below). Patients receiving clarithromycin and rifabutin should be carefully monitored for rifabutin-related toxicity, especially hematologic (leukopenia) and ocular (uveitis) toxicity. Active investigations are ongoing attempting to define the role of inhaled amikacin in the treatment of NTM lung disease. To date, although inhaled amikacin is often used there is very little published data supporting the indication, dose, and duration of the best use as a companion drug.

Macrolide-resistant MAC lung disease is associated with a very poor prognosis. The two major risk factors for macrolide-resistant MAC disease are macrolide monotherapy or treatment with macrolide and inadequate companion medications. The treatment strategy associated with the most success includes both the use of a multidrug regimen including a parenteral aminoglycoside (streptomycin or amikacin) and surgical resection ("debulking") of disease. The optimal drug regimen for treating macrolide-resistant strains is unknown but some experts recommend ethambutol, rifabutin, and an injectable agent. The role of other drugs, such as moxifloxacin or clofazimine, is still not known. Likewise, the future role of newer antimicrobials being developed and in

early clinical usage trails for tuberculosis is equally unclear at this time.

Patients whose disease is predominantly localized to one lung and who can tolerate resectional surgery might also be considered for surgery if there is poor response to drug therapy, the development of macrolide-resistant MAC disease or the presence of significant disease-related complications such as hemoptysis. Whenever possible, this surgery should be performed at centers with thoracic surgeons who have considerable experience with lung resectional surgery for mycobacterial disease, which is potentially associated with significant morbidity and mortality.

DISSEMINATED MAC DISEASE

Successful treatment of disseminated MAC in persons with AIDS is based on treatment of both the mycobacterial infection and the HIV infection. Clinicians must, therefore, be aware of the drug–drug interactions between the antimycobacterial and antiretroviral medications. Current guidelines for the use of antimycobacterial drugs with HIV therapies can be found at www.cdc.gov/nchstp/tb/TB_HIV_DRUGS/TOC.htm.

All patients should be treated with clarithromycin, 1000 mg/day or 500 mg twice a day, or as an alternative, azithromycin at a dose of 500 mg daily, and ethambutol at the dose of 15 mg/kg daily. Rifabutin, if added, should be used at a dose of 300 mg daily, with adjustments for interactions with antiretroviral drugs. As with macrolide-resistant MAC lung disease, patients with macrolide-resistant strains are far less likely to be successfully treated. Other drugs that should be considered for inclusion are amikacin and moxifloxacin. Clofazimine has been associated with excess mortality in the treatment of disseminated MAC disease and should not be used. Treatment of MAC in patients with AIDS should be considered lifelong, unless immune restoration is achieved by antiretroviral therapy. MAC treatment may be stopped for patients who are asymptomatic, and have achieved a CD4+ T-cell count of over 100 cells/mm^3 for at least 12 months.

Preventive therapy for disseminated MAC is recommended for all HIV-infected patients with less than 50 CD4+ T-cells/mm^3. Based on efficacy and ease of use, azithromycin – given as 1200 mg once weekly – is the preferred agent. Clarithromycin is also effective; however, it is considered an alternative agent because it must be given twice daily and the risk of breakthrough with macrolide-resistant strains is higher with daily clarithromycin than with weekly azithromycin. Rifabutin is also effective but should only be used when a macrolide cannot be tolerated. Primary MAC prophylaxis should be discontinued among adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ T-lymphocyte counts to more than 100 cells/mm^3 for more than 3 months. Primary prophylaxis should be reintroduced if the CD4+ T-lymphocyte count decreases to less than 50 to 100 cells/mm^3.

MAC LYMPHADENOPATHY

The treatment of choice for MAC lymphadenopathy, as well as localized lymphadenopathy due to most NTM pathogens, is complete surgical resection of the involved lymph nodes. When complete surgical resection is not possible, due for instance to nerve impingement or encasement by the infected nodes, then chemotherapy with MAC treatment regimens similar to those for lung and disseminated disease would be necessary.

M. KANSASII PULMONARY DISEASE

The recommended regimen for treating pulmonary *M. kansasii* disease includes daily rifampin (600 mg/day), isoniazid (300 mg/day), and ethambutol (15 mg/kg/day) for a duration that includes 12 months of negative sputum cultures. Limited data suggests that intermittent therapy with rifampin, ethambutol, and clarithromycin for *M. kansasii* disease can also be successful. The recommended treatment duration, as with MAC lung disease, is a duration that includes 12 months of sputum AFB culture negativity.

Patients whose *M. kansasii* isolates have become resistant to rifampin as a result of previous therapy have been treated successfully with a regimen that consists of high-dose daily isoniazid (900 mg), high-dose ethambutol (25 mg/kg/day), sulfamethoxazole (1 g three times per day) combined with several months of streptomycin or amikacin. The excellent in vitro activity of clarithromycin and moxifloxacin against *M. kansasii* suggests that multidrug regimens containing these agents and at least one other agent based on in vitro susceptibilities, such as ethambutol or sulfamethoxazole, are likely to be even more effective for treatment of a patient with rifampin-resistant *M. kansasii* disease.

DISEMINATED *M. KANSASII*

The treatment regimen for disseminated disease should be the same as for pulmonary disease. Because of the critically important role of rifamycins in the treatment of *M. kansasii* disease, it is important to construct *M. kansasii* and antiretroviral treatment regimens that are compatible (see website in disseminated MAC disease discussion above). An option for treating HIV-infected patients who receive an antiretroviral regimen not compatible with rifamycins is to substitute a macrolide or moxifloxacin for the rifamycin. There is no recommended prophylaxis regimen for disseminated *M. kansasii* disease.

M. abscessus disease

M. abscessus isolates are uniformly resistant to the standard antituberculous agents. *M. abscessus* isolates generally have low or intermediate MICs, compared to achievable drug levels, to clarithromycin, amikacin, and cefoxitin. Some isolates have low or intermediate MICs to linezolid, tigecycline, and imipenem.

For serious skin, soft-tissue, and bone infections caused by *M. abscessus*, clarithromycin 1000 mg/day or azithromycin 250 mg/day should be combined with one or more of the parenteral medications (amikacin, cefoxitin, or imipenem). Macrolide, especially clarithromycin, offers little additional benefit in the presence of an active *erm* gene, e.g., *M. abscessus* subsp. *abscessus*. Intravenous amikacin is given at a dose of 10 to 15 mg/kg daily to adult patients with normal renal function to provide peak serum levels in the low 20 μg/mL range. The lower dose (10 mg/kg) should be used in patients over the age of 50 and/or in patients in whom long-term therapy (greater than 3 weeks) is anticipated. The amikacin combined with high-dose cefoxitin (up to 12 g/day given intravenously in divided doses) is recommended for initial therapy (minimum 2 weeks) until clinical improvement is evident. Cefoxitin availability or intolerance may necessitate the choice of an alternative agent such as imipenem (500 mg two to four times daily), which is a reasonable alternative to cefoxitin. For serious disease, a minimum of 4 months of therapy is necessary to provide a high likelihood of cure. For bone infections, 6 months of therapy is recommended. Surgery is generally indicated with extensive disease, abscess formation, or where drug therapy is difficult. Removal of foreign bodies such as breast implants or percutaneous catheters is important and likely essential to recovery.

In contrast to the efficacy of medication regimens for nonpulmonary disease, no antibiotic regimens based on in vitro susceptibilities have been shown to produce long-term sputum conversion for patients with *M. abscessus* lung disease. The goal of 12 months of negative sputum cultures while on therapy may be optimal, but there is no medication strategy to reliably achieve this goal. Alternative goals of therapy such as symptomatic improvement, radiographic regression of infiltrates, or improvement in sputum culture positivity, short of conversion to negative cultures, are more realistic for *M. abscessus* lung disease. Combination therapy (as outlined above) with or without macrolide plus one or more parenteral agent (amikacin, cefoxitin, or imipenem for 2–4 months) usually produces clinical and microbiologic improvement, but the cost and morbidity are significant impediments to a curative course of therapy. Several recently published series of *M. abscessus* lung disease patients treated with a combination of parenteral and oral agents suggest improved clinical response rates in contrast to historical controls. Linezolid and tigecycline may also have variable activity but also carry costs that are high and tolerance which is limited. For some patients, symptoms can be controlled with intermittent periods of therapy with clarithromycin or azithromycin alone or in combination with one or more parenteral drugs. Curative therapy for *M. abscessus* lung disease is more likely to be obtained with limited disease and a combination of surgical resection of involved lung and chemotherapy (not dissimilar to the approach to macrolide-resistant MAC lung disease). Unfortunately, with current antibiotic options, *M. abscessus* is a chronic incurable infection for most patients and, if disease is present, represents a contraindication for lung transplantation in those with advanced lung disease.

M. chelonae pulmonary and extrapulmonary disease presents in a similar fashion to *M. abscessus* but should be differentiated from *M. abscessus*/*M. chelonae* in the laboratory given the better response to antibiotics for *M. chelonae* than *M. abscessus*. This improved response to antibiotics is, in part, related to the lack of an active *erm* gene in *M. chelonae*.

M. marinum disease

M. marinum isolates are susceptible to rifampin, rifabutin, ethambutol, clarithromycin, sulfonamides, and trimethoprim sulfamethoxazole, intermediately susceptible to streptomycin,

doxycycline and minocycline, and resistant to isoniazid and pyrazinamide.

For skin and soft-tissue infections due to *M. marinum* a reasonable approach is to treat with two active agents for 1 to 2 months after resolution of symptoms, typically 3 to 4 months in total. Some experts believe that minimal disease can be treated with a single agent. Excellent outcomes have also been reported for the combinations of clarithromycin and rifampin, clarithromycin and ethambutol, and the combination of ethambutol and rifampin. Clarithromycin and ethambutol are likely to provide the optimal balance of efficacy and tolerability for most patients, with the addition of rifampin in cases of osteomyelitis or other deep structure infection. Surgical debridement may also be indicated, especially for disease involving the closed spaces of the hand and for disease that has failed to respond to standard therapy.

EMERGING AREAS OF NTM INFECTIONS

Increased numbers of published reports have highlighted several emerging areas of NTM infections over the past decade. These newer and somewhat less common infections are worth noting and have linked growing numbers of individuals developing NTM infections to specific underlying disease conditions or specific home, work, or nosocomial environmental exposures, including CF, hypersensitivity pneumonitis-like lung disease (hot tub lung), and healthcare-associated NTM infections, respectively.

Cystic fibrosis-associated NTM disease

A recent cross-sectional assessment from multiple CF centers across the United States found that approximately 13% of all surveyed CF patients, and 40% over the age of 40, had NTM isolated from sputum. Similar to non-CF NTM pulmonary disease most NTM isolated were MAC (76%) or *M. abscessus* (18%). The explanation for this high prevalence of NTM in CF patients remains uncertain. Ambient exposure to NTM organisms from ubiquitous environmental water and soil sources coupled with abnormal host pulmonary factors such as altered mucociliary clearance and structural abnormalities accompanying advancing bronchiectasis may contribute to the development and phenotypic expression of NTM pulmonary disease commonly encountered in this group of patients. The diagnosis of NTM pulmonary disease in CF patients is similar to that of patients with non-CF NTM disease with the recognition that underlying bronchiectasis and other pathogens are present and may account for respiratory symptoms and radiographic abnormalities. The decision to treat NTM pulmonary infection in CF patients is complicated by a paucity of information about the effect of NTM infection on the natural history of CF, although CF patients with heavy *M. abscessus* growth from sputum appear to be at particular risk for more rapidly progressive disease and, in some instances, respiratory failure. Overall, treatment decisions require consideration of benefits weighed against risks and medication side effects for individual patients. Treatment regimens for CF patients with NTM lung disease are also similar to those for non-CF NTM pulmonary disease. CF patients on azithromycin for noninfective purposes should have surveillance for NTM in sputum prior to and during treatment with macrolides to avoid macrolide monotherapy in a patient with occult or undiagnosed NTM disease. The presence of active or untreated *M. abscessus* lung disease is a contraindication to listing for lung transplantation at many transplant centers in the United States. Recent reports of the transmissibility of *M. abscessus* species in two outpatient CF clinics is worth noting given the previous lack of human-to-human transmissibility of NTM lung disease.

Hypersensitivity pneumonitis-like NTM pulmonary disease

Several series of patients developing hypersensitivity pneumonitis-like lung disease following NTM exposure have been reported over the past decade. Most reports describe development of a typical pattern of hypersensitivity pneumonitis-like lung disease in association with hot tub exposure. Some investigators have used the term "hot tub lung" to describe this presentation. In the cases of exposure to hot tubs, MAC has been the mycobacterial organism isolated from sputum, bronchoalveolar lavage, tissue, and hot tub water. Furthermore, comparison of MAC isolates from the hot tub water and lung specimens when assessed by genotyping methods has demonstrated identical matches. Controversy still exists, however, as to whether hot tub lung is an infectious process, inflammatory process, or a combination of processes.

Hypersensitivity pneumonitis-like lung disease patients tend to be young and without preexisting lung disease. The clinical presentation

varies widely from mild respiratory symptoms to respiratory failure requiring mechanical ventilatory support. Key elements to the diagnosis of MAC hypersensitivity-like lung include a compatible clinical history (subacute onset of respiratory symptoms, hot tub exposure), characteristic radiographic findings, and MAC isolates in sputum, bronchoalveolar lavage, tissue, and hot tub water (and compatible histopathology when available).

Patient prognosis is generally excellent independent of severity on presentation. The most benefit is gained by simply removing the patient from antigen exposure. In the case of hot tub lung, removal from antigen exposure generally involves drainage of hot tub water and complete avoidance of hot tub use. Whether continued exposure to ambient environmental MAC organisms can propagate the hypersensitivity pulmonary reaction is uncertain. For select patients with hypersensitivity pneumonitis-like lung disease, use of systemic corticosteroids may be of benefit and hasten recovery of pulmonary symptoms, gas exchange abnormalities, and radiographic abnormalities. Likewise, antimycobacterial therapy with the same medications as standard pulmonary MAC lung disease may be required in some patients but with shorter durations of therapy, usually 3 to 6 months. Most patients can be expected to have complete or near complete resolution of respiratory symptoms as well as pulmonary function and radiographic abnormalities.

Healthcare-associated NTM disease

Transmission of NTM disease in the healthcare setting has most frequently been linked to tap (municipal) water exposure. While various NTM species (including MAC, *M. kansasii*, *M. xenopi*, and *M. simiae*) have been isolated from municipal water supplies, *M. fortuitum* and *M. abscessus* have most often been implicated in healthcare-associated NTM disease. Even with use of potent disinfectants, including organomercurials, chlorine, bromine, 2% formaldehyde, and glutaraldehyde, after tap water exposure, NTM organisms may persist on equipment or devices. The inability to eliminate these organisms underscores the importance of avoidance of tap water for preventing healthcare-associated NTM disease. Examples of healthcare-associated NTM infections include infections involving median sternotomy, plastic surgery procedures, liposuction, laser-assisted in situ keratomileusis (LASIK), dialysis-related outbreaks, long-term central intravenous catheters, tympanostomy tubes, and prosthetic devices such as heart valves, knee and hip joints, lens implants, and metal rod bone stabilizers. Pseudo-outbreaks have involved bronchoscopes contaminated with *M. abscessus* and *Mycobacterium immunogenum*. Documented outbreaks of hygiene-associated *M. fortuitum* and *Mycobacterium mageritense* furunculosis in association with use of contaminated whirlpool footbaths have been described in nail salons.

As a result of the increased understanding of environmental NTM reservoirs and reports linking the use of tap water to healthcare-associated NTM infections it is recommended that tap water not be used in preparation of surgical procedures, prosthetics, and intravascular catheters; not used in cleaning of fiberoptic endoscopes; and not be used to rinse the mouth out prior to collecting expectorated sputum samples. Moreover, recognition that alternative medicines or unapproved substances for injection may also be at risk of contamination by NTM warrants caution against use of these products as well. Reports of transmissibility of *M. abscessus* in CF clinics as referenced above underscores the need for respiratory isolation and adherence to standard infection control principles.

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159. Vibrios

Duc J. Vugia

Vibrios are motile, rod-shaped, facultative-anaerobic, gram-negative bacteria that can cause gastroenteritis, wound infection, and septicemia in humans. They are naturally found in marine, estuarine, and brackish waters in the United States and in other parts of the world. In the United States, they are recovered from the environment most commonly in summer and fall, when the water is warm. Vibrios have also been isolated from a variety of fish and shellfish, including oysters, clams, mussels, crabs, and shrimp. Human cases of illness associated with *Vibrio* infection occur mostly in summer and fall, and usually follow ingestion of raw or undercooked shellfish, particularly oysters, or exposure of a wound to fish, shellfish, or seawater. In countries with endemic or epidemic cholera, infection with *Vibrio cholerae* may occur after ingestion of any contaminated food or water; in the United States, cholera is endemic along the Gulf Coast.

Analysis of 5S ribosomal ribonucleic acid sequence revealed 34 *Vibrio* spp., 12 of which have been isolated from human clinical specimens. The major clinical presentations associated with infection with these 12 species are shown in Table 159.1. Rarely, vibrios have also been recovered from bone, cerebrospinal fluid, ear, gallbladder, sputum, and urine.

Table 159.1 Association of *Vibrio* species with major clinical presentations

	Clinical presentations		
Species	**Gastroenteritis**	**Wound infection**	**Septicemia**
V. cholerae			
O1	++	+	+
O139	++		+
Other non-O1	++	+	+
V. alginolyticus	+	++	+
V. carchariae		+	
V. cincinnatiensis			+
V. damsela		+	+
V. fluvialis	++	+	+
V. furnissii	+		+
V. hollisae[a]	++	+	+
V. mimicus	++	+	+
V. metschnikovii	+	+	+
V. parahaemolyticus	++	++	+
V. vulnificus	+	++	++

++, Common; +, rare.
[a] Now *Grimontia hollisae*.

GASTROENTERITIS AND CHOLERA

Clinical presentation

Gastroenteritis is the most common clinical presentation of infection with most pathogenic vibrios. The disease ranges in severity from mild, self-limited diarrhea to frank, life-threatening cholera.

Cholera is a profuse, watery diarrhea mediated via an enterotoxin produced by epidemic strains of *V. cholerae* O1 and O139 and by some non-O1 strains. After attachment of toxigenic vibrios to intestinal epithelial cells, the cholera toxin, consisting of one A (activation) subunit and five B (binding) subunits, is generated. It stimulates intracellular cyclic AMP, resulting in a secretory diarrhea. Other symptoms include nausea, vomiting, abdominal cramps, and muscle cramps of extremities; fever is typically not seen because the disease is toxin mediated and there is no invasion of the intestinal epithelium. Illness develops 4 hours to 5 days after ingestion of the bacteria and can rapidly lead to severe dehydration, electrolyte imbalance, metabolic acidosis, and death. Cholera usually lasts less than 7 days even without antibiotic therapy.

Gastroenteritis due to vibrios other than *V. cholerae* O1 and O139 may also be mediated

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via an enterotoxin, but the diarrhea is normally not so severe. However, bloody stool, low-grade fever, and elevated white blood cell count may be noted along with nausea, vomiting, and abdominal cramps. The median incubation period is 1 day, ranging from 4 hours to 5 days, and the duration of illness is typically less than 7 days, ranging from 1 to 15 days.

Therapy

For cholera, prompt replacement of fluid volume and electrolytes with an appropriate intravenous or oral solution is critical. If the patient has severe dehydration (loss of at least 10% of body weight) or cannot drink, intravenous fluid replacement with Ringer's lactate is recommended. Normal saline does not contain appropriate electrolytes to correct metabolic acidosis and is therefore not recommended. If the patient can drink, a solution containing glucose and adequate electrolyte replacement is recommended, such as those prepared with the oral rehydration salts (ORS) endorsed by the World Health Organization or commercially available ORS/electrolyte replacement solutions.

Treatment of cholera with antimicrobials is secondary to fluid and electrolyte replacement and recommended for patients with moderate to severe cholera. Appropriate antibiotics can decrease volume and duration of diarrhea, and shedding of vibrios. Multidrug-resistant strains of *V. cholerae* O1 have been documented in Asia and in Africa, and antibiotic susceptibility testing should be performed on isolates from cholera patients to inform drug choices. For most settings, a single dose of doxycycline (300 mg orally) for adults or a single dose of azithromycin (1 g orally) for adults, including pregnant women, and (20 mg/kg up to a maximum of 1 g orally) for children is effective. Alternatively, ciprofloxacin orally in a single dose (1 g for adults or 20 mg/kg for children) can be used; however, quinolone-resistant strains of *V. cholerae* have been reported in South Asia. As quinolones and macrolides are used more commonly, resistance to these classes of antibiotic may increase and, therefore, cholera patients treated with any antibiotic should have their isolates tested for susceptibility and the patients should be closely followed for appropriate clinical response.

For severe or prolonged gastroenteritis due to other vibrios, fluid and electrolyte replacement along with quinolone or doxycycline treatment is in order. However, mild or moderate gastroenteritis is usually self-limited and may not need therapy other than oral rehydration.

EXTRAINTESTINAL INFECTIONS

Clinical presentations

For extraintestinal sites, wound infection and septicemia are the most common clinical presentations. Wound infection with vibrios occurs after exposure of a break in skin to seawater or after a skin injury from handling fish or shellfish. Wound infection may be mild and self-limited or severe and invasive. Septicemia, which may be primary following ingestion of raw shellfish or secondary following wound infection, indicates severe disease.

Among vibrios causing extraintestinal infections, *Vibrio vulnificus* frequently causes two important clinical syndromes: primary septicemia and wound infections. Primary septicemia occurs predominantly in adults with liver disease, including cirrhosis and hemochromatosis, with alcoholism, with other chronic underlying diseases, including renal failure and diabetes, or with immune suppression, including cancer and human immunodeficiency virus (HIV) infection. In these susceptible persons, septicemia usually follows ingestion of raw shellfish, typically raw oysters. Between 7 and 48 hours after eating shellfish containing *V. vulnificus*, infected patients present with fever, chills, nausea, vomiting, abdominal pain, diarrhea, mental status changes, suggestive skin lesions (including bullae, cellulitis, and ecchymoses), and often hypotension or shock. Mortality for patients with *V. vulnificus* primary septicemia is greater than 50%, and it increases with hypotension within 12 hours of hospitalization or when appropriate antibiotic therapy is delayed.

Vibrio vulnificus wound infection, however, results from injury to the skin from handling fish or shellfish or exposure of a fresh wound to seawater. Any healthy person may acquire this infection, but persons with the underlying diseases listed previously are at higher risk for severe skin and soft-tissue infection, secondary septicemia and death. Infected persons develop inflammation of the wound, fever, and chills 4 hours to 4 days after exposure. Wound infections range from mild cellulitis to severe necrotizing fasciitis and myositis requiring extensive debridement or amputation. Secondary disseminated skin lesions such as bullae may be due to secondary septicemia (Figure 159.1). Case-fatality rate for *V. vulnificus*

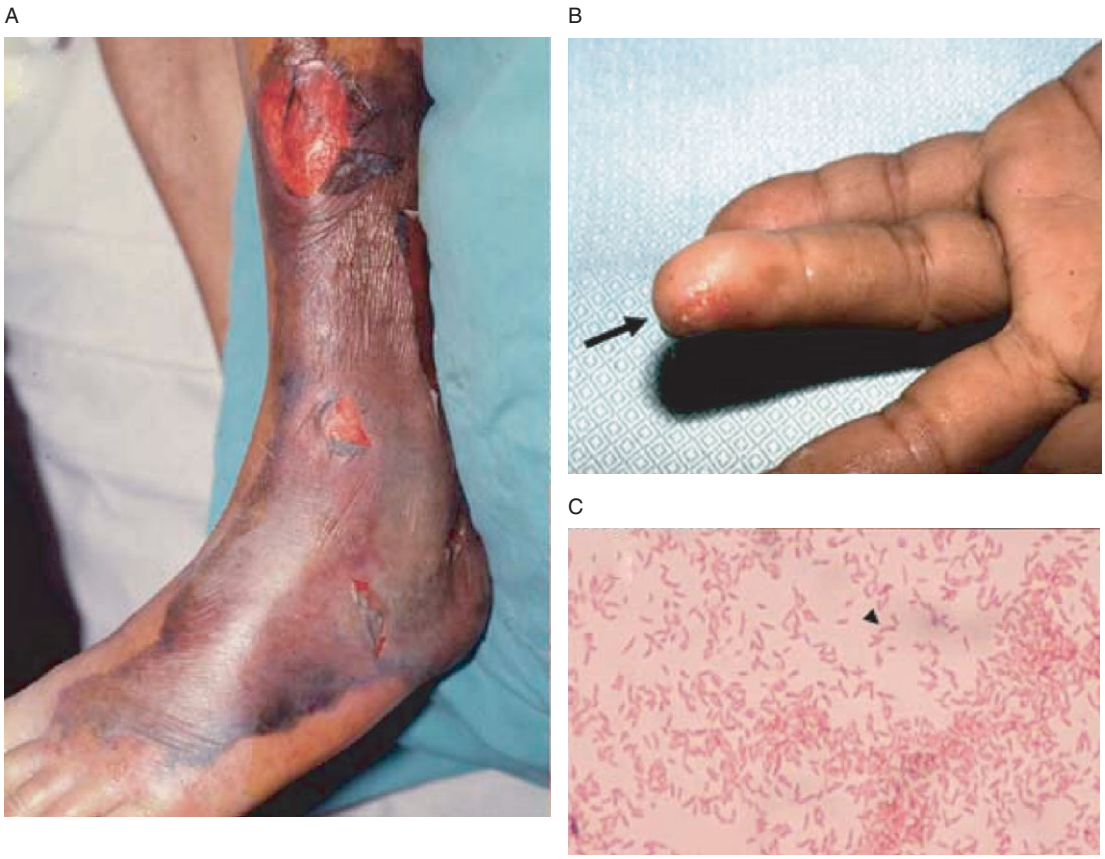

Figure 159.1 **(A)** Characteristic skin lesions associated with *Vibrio vulnificus* infection on the leg of a 75-year-old patient with liver cirrhosis in whom septic shock and bacteremia developed. **(B)** *Vibrio vulnificus* bacteremia developed 1 day after a fish bone injury on the fourth finger of the left hand (arrow) in a 45-year-old patient with uremia. **(C)** Gram-negative curved bacilli isolated from a blood sample of the 45-year-old patient with uremia. (Photos from Hsueh *et al*. *Vibrio vulnificus* in Taiwan. *Emerg Infect Dis*. 2004;10(8):1363–1368.)

necrotizing fasciitis increases when surgical intervention is later than 24 hours after admission or when effective antibiotics are not used.

Therapy

For invasive diseases of *Vibrio*, particularly *V. vulnificus*, prompt treatment with early antibiotic administration (preferably within 24 hours of illness onset), aggressive wound management, and supportive care are crucial. Doxycycline, 100 mg, intravenously every 12 hours combined with a third-generation cephalosporin (e.g., ceftazidime 2 g intravenously [IV] every 8 hours) should be given without delay. Alternatively, a fluoroquinolone such as ciprofloxacin, 400 mg IV every 12 hours, can also be used. The combination of ciprofloxacin and cefotaxime has been found synergistically active against *V. vulnificus* in vitro. The duration of treatment should be individualized to the presentation and clinical course but should be considered for at least 7 to 14 days. Necrotic tissue should be surgically debrided within 24 hours of admission and, occasionally, amputation of an affected limb may be necessary.

LABORATORY DIAGNOSIS

For a patient with a gastrointestinal or cholera-like illness thought to be caused by *Vibrio*, physicians should specify culture for vibrios when ordering stool cultures. Ideally, specimens should be collected before treatment with antimicrobials. Vibrios are isolated by direct inoculation of stool onto a selective medium, such as thiosulfate-citrate-bile salts-sucrose agar.

Selective media are not necessary for extraintestinal infections because common media used to culture blood and wounds contain at least 0.5% sodium chloride, which is adequate to grow halophilic (salt-loving) vibrios.

For cholera patients already treated with antimicrobials and whose stool culture was either negative or not processed for vibrios, *V. cholerae* vibriocidal or antitoxin antibodies can be detected by serologic assays.

PREVENTION

Most *Vibrio* gastroenteritis, cholera, and primary *V. vulnificus* septicemia can be prevented. For prevention of cholera, travelers should be informed on whether cholera is endemic in the country or region being visited and should take appropriate precautions with all foods and drinks. In general, well-cooked foods and hot or carbonated drinks are safe. There is no cholera vaccine available currently in the United States. And, although an oral cholera vaccine is commercially available in some other countries, it is not recommended for most travelers. In the United States, *Vibrio* gastroenteritis can be prevented by avoiding consumption of raw or undercooked shellfish. Patients with underlying liver and other chronic diseases or with immunosuppression, which puts them at increased risk of *V. vulnificus* septicemia, should avoid raw unprocessed oysters and other raw shellfish.

Wound infections are probably not preventable, because vibrios exist naturally in the marine water environment. Nonetheless, a history of exposure to seawater, fish, or shellfish in a patient with an infected wound should raise clinical suspicion and prompt consideration of treatment for possible infection with a *Vibrio*.

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160. *Yersinia*

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INTRODUCTION

The genus *Yersinia* consists of 17 species. Only three species are consistently pathogenic for humans. These are *Yersinia pestis*, the agent of plague, *Yersinia enterocolitica*, and *Yersinia pseudotuberculosis*, which are usually, but not entirely, gastrointestinal pathogens.

YERSINIA PESTIS

An ongoing result of the unfortunate events of September 11, 2001 has been an increase in research on *Yersinia*, particularly, *Y. pestis*. This is an ancient organism and since its divergence from *Y. pseudotuberculosis* 1500 to 20 000 years ago has largely existed as a rodent pathogen with only occasional human transmission. Three well-described pandemics of plague have occurred. The last of these began in the nineteenth century. Alexandre Yersin first isolated *Y. pestis* in 1894. The twentieth century saw major outbreaks in Vietnam and India. The majority of cases currently are seen in sub-Saharan Africa, particularly Madagascar.

The majority of cases seen in the United States are from the southwestern states of New Mexico, Arizona, Colorado, Texas, and California. Climate change may well affect the bacteria, the vector, and the hosts, resulting in potential worldwide changes in the frequency and distribution of disease. In 2010 two human cases were reported in Oregon.

There has been remarkable progress in the understanding of the pathogenesis of *Yersinia* infections, particularly those caused by *Y. pestis*. A partial list of these advances include the effects of *Y. pestis* on flea behavior, and its avoidance of both innate and adaptive (both humeral and cellular) immune response.

Natural infection occurs most commonly through the bite of an infected flea. The majority of these patients present with febrile lymphadenitis or bubonic plague. The incubation period is typically 2 to 6 days. Inguinal and femoral nodes are most frequently involved. Axillary and cervical presentations are less common. Inhalation of respiratory droplets from infected humans or animals, especially cats, may result in primary pneumonic plague. Pneumonic plague may also result from aerosols of bioterrorism agents. The ingestion of infected meat may result in pharyngitis and disseminated infection. Systemic disease without lymphadenitis may present as gram-negative sepsis, often with gastrointestinal symptoms. This usually results from an infected flea bite that does not produce a discernible bubo. A careful epidemiologic history is essential in the evaluation of patients with lymphadenitis, sepsis, or pneumonia.

All suspected *Y. pestis* infections must be reported to public health authorities. Specimens and cultures from suspected *Y. pestis* must be handled with *extreme caution* and in accordance with state and federal law. In the United States *Y. pestis* is a federal select (A) agent.

Smear and culture of lymph node aspirate, sputum, cerebrospinal fluid, buffy coat, and blood should be undertaken expeditiously as dictated by clinical presentation. Gram stain and Wright Giemsa or the preferred Wayson stain should be prepared. The latter if positive will reveal the classic safety pin morphology that in the appropriate clinical setting is virtually diagnostic.

Y. pestis is easily propagated on normal laboratory media aerobically or anaerobically. Identification can be undertaken by the technology available in most modern hospital microbiology laboratories. Difficulty with identification has occurred. All suspected specimens and isolates should be referred to an appropriate public health laboratory.

Most isolates of *Y. pestis* have predictable sensitivity and there is not a trend to increasing antimicrobial resistance. Naturally resistant isolates have been identified. There is also the likelihood

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Table 160.1 Therapy of *Yersinia pestis*

Preferred antibiotic	Classification for use
Streptomycin 15 mg/kg/d (some authorities would double the dose on the first day) Usually given q12h. IM may be given IV if necessary	Availability an issue Call Pfizer Monitor renal, vestibular, and otic toxicity
Gentamicin 5–7 mg/kg/d Given as 2–3 doses IV	Monitor renal, vestibular, and otic toxicity Monitor blood levels and adjust for renal function
Ciprofloxacin 400 mg q8h IV	Not approved for pediatric use <16 yr
Levofloxacin 750 mg qd IV	Not approved for pediatric use <16 yr
Moxifloxacin 400 mg qd IV	Not approved for pediatric use <16 yr May be preferred in renal failure over other fluoroquinolones
Doxycycline 100 mg q12h IV Some authorities would double the dose on the first day	Not approved for pediatrics ≤8 yr or in pregnancy
Chloramphenicol 1 g (25 mg/kg) IV q6h dose reduction to 500 mg (15 mg/kg) q6h as patient improves	Predominantly for patients with meningitis and children. Meropenem may be an alternative in meningitis

that bioterrorism constructs of *Y. pestis* would be resistant to many antimicrobials. According to a recent publication by the Centers for Disease Control and Prevention (CDC) Etest® is equivalent to the reference broth dilution and disk diffusion testing is not recommended.

Therapy (Table 160.1)

Streptomycin has been used as therapy since the 1940s with undeniable success. Streptomycin may or may not be the optimal therapy for plague. Streptomycin availability may be an issue. Other aminoglycosides have been used successfully in the treatment of plague.

There has been significant success with the use of tetracyclines in therapy of *Y. pestis*. In recent years doxycycline has been the tetracycline of choice. A randomized trial comparing gentamicin and doxycycline was conducted in Tanzania. The results were equivalent with less than 5% deaths.

A murine bubonic plague model demonstrated ciprofloxacin was as effective as ciprofloxacin plus gentamicin and possibly more effective than gentamicin monotherapy. A recent in vitro pharmacodynamic model evaluated ciprofloxacin, moxifloxacin, gentamicin, ampicillin, and meropenem against streptomycin. All of the drugs out performed streptomycin. There are countervailing in vitro data that streptomycin and ciprofloxacin may be more active against both extracellular and intracellular organisms than either gentamicin or doxycycline. There are mouse data suggesting that levofloxacin-resistant organisms are significantly less fit than streptomycin-resistant organisms. Lastly, there may be nonantibiotic treatments on the horizon. Typical antibiotic courses are 7 to 10 days. Meningitis may require longer therapy.

YERSINIA ENTEROCOLITICA AND *YERSINIA PSEUDOTUBERCULOSIS*

Yersinia enterocolitica and *Y. pseudotuberculosis* are most frequently associated with enterocolitis. Infection with *Y. enterocolitica* occurs much more often than with *Y. pseudotuberculosis*.

Y. enterocolitica is an important cause of enterocolitis worldwide, especially in colder climates and winter months. This is distinctly different than most enteropathogenic organisms. The frequency of *Y. enterocolitica* in the United States is much lower than that of other similar locales. Food, particularly pork, contaminated milk, and untreated water have long been recognized as sources of infection. More recently, lettuce was reported to be contaminated. Serogroup O:3 is responsible for the majority of disease in the United States. The incubation period is 1 to 14 days, typically at the shorter end of this spectrum. Immunocompromised individuals, those with iron overload or treated with iron-chelating agents, and those with alkalinization of the stomach are at increased risk. Children have a greater risk as compared to adults.

The most common presentation is enteritis or enterocolitis, not unlike shigellosis. Typical symptoms include diarrhea, occasionally bloody, fever, abdominal pain, and vomiting. *Y. pseudotuberculosis* and *Y. enterocolitica* can present with abdominal pain that mimics appendicitis. Careful abdominal imaging with ultrasound or computed tomography can usually distinguish *Yersinia*-induced mesenteric lymphadenitis from appendicitis. *Y. enterocolitica* can cause superative infection, including pharyngitis, pneumonia, empyema, hepatic abscess, lymphadenitis, and

Table 160.2 Therapy for *Yersinia enterocolitica*

Preferred antibiotic for serious infections	Classification of use
Ceftriaxone 1 g (100 mg/kg) Q daily Plus Gentamicin 5–7 mg/kg/d Given 2–3 IV doses or Ciprofloxacin 400 mg q8h if susceptibility is shown	Not approved for pediatrics ≤16 yr
Other agents likely to be effective	
Trimethoprim–sulfamethoxazole TMP–SMX 10 mg/50 mg/kg/d IV as 2 doses	
Doxycycline 100 mg q12h IV	Not approved for pediatrics ≤8 yr

Table 160.3 Therapy for *Yersinia pseudotuberculosis*

Preferred antibiotic for serious infections (sepsis)	Classification of use
Ampicillin 2 g q4h IV (200 mg/kg) Plus gentamicin 5–7 mg/kg/d in 2–3 doses	
Alternative agents Doxycycline 100 mg q12h IV	Not approved for pediatric use ≤8 yr

genitourinary and musculoskeletal infections. Sepsis, endocarditis, pericarditis, and myocarditis have all been reported. Rare cutaneous infections have also been reported.

Y. enterocolitica and *Y. pseudotuberculosis* have both been implicated in immunopathologic disease, including erythema nodosum, uveitis, and reactive arthritis. There may be a link to inflammatory bowel disease. A role for *Y. pseudotuberculosis* in Kawasaki disease has been suggested.

Diagnosis of active infection is primarily by culture. Isolation from blood and sterile sites should not prove challenging in untreated patients. Culture of stool and other contaminated sites is more difficult. Cold enrichment and selective media may be helpful, but this usually requires specific discussion with the microbiology laboratory.

Therapy (Tables 160.2 and 160.3)

Therapy is usually not required for *Y. enterocolitica* and *Y. pseudotuberculosis* gastroenteritis or mesenteric lymphadenitis in immunocompetent hosts. Extraintestinal disease, particularly sepsis, requires antimicrobial therapy. Sepsis with either of the above species has a high mortality.

Y. enterocolitica often produce β-lactamases, precluding the use of penicillin and many cephalosporins. Most *Yersinia* strains are resistant to macrolides. Resistance to fluoroquinolones has been reported in Spain.

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161. Miscellaneous gram-positive organisms

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PEDIOCOCCUS SPECIES

Pediococci are gram-positive cocci that grow in pairs and tetrads and belong to the lactic acid bacteria group. Normal inhabitants of the gastrointestinal tract, they are used extensively in industry to ferment cheese and other dairy products, soy products, and alcoholic beverages. Thirteen species of pediococci are recognized today, but only *Pediococcus acidilactici* and *Pediococcus pentosaceus*, typically found in sugar-rich foods, have been identified as human pathogens. In recent years, these organisms have been increasingly recognized as a cause of bacteremia, endocarditis, and pneumonitis in the immunocompromised host. These organisms have also been isolated from intra-abdominal infections such as peritonitis and hepatic abscesses. Risk factors for *Pediococcus* infections include prior antibiotic therapy, abdominal surgery, and gastric feeding.

Diagnosis is made by isolation and identification of the organism from cultures of blood or other body fluids. *Pediococcus* species may be difficult to distinguish from enterococci and *Leuconostoc* species given its association with food. Approximately 95% of clinical isolates will cross-react with group D streptococcal antisera. Tests that aid in distinguishing pediococci from other organisms include a negative pyrrolidonyl arylamidase (PYRase) test and the absence of gas production from glucose. With newer application of molecular genetic techniques to determine relatedness of food-associated lactic acid bacteria, reorganization of the genus with novel morphologic or phenotypic differentiation of *Leuconostoc* species from *Pediococcus* species is being studied.

Pediococci are intrinsically highly resistant to vancomycin and other glycopeptides. Most strains are moderately susceptible to penicillin and ampicillin. Minimum inhibitory concentrations (MICs) are variable for cephalosporins. Imipenem appears active against all isolates, as does gentamicin. In vitro susceptibility to linezolid and daptomycin has been demonstrated. There have also been case reports of daptomycin being successfully used to treat pediococcocal endocarditis. Resistance to quinupristin–dalfopristin, erythromycin, clindamycin, tetracycline, tobramycin, and amikacin has been described. If a serious *Pediococcus* infection is suspected (e.g., on the basis of the characteristic tetrad morphology on Gram stain), intravenous penicillin at a dosage of 12 million or more units daily or imipenem may be used as empiric therapy. Susceptibility testing, preferably by MIC rather than disk diffusion, should be performed to determine appropriate therapy (Table 161.1).

LEUCONOSTOC SPECIES

Leuconostoc species are catalase-negative, gram-positive coccobacilli that have been increasingly recognized as human pathogens over the last decade. These organisms are normally found in dairy products and vegetable matter and are used in the production of wine, dairy products, and dextrans. *Leuconostoc* species are not considered part of the normal human flora, but they have been isolated from the feces, vagina, and gastric fluid, primarily in hospitalized patients. Immunocompromised patients and those treated with vancomycin, to which leuconostocs are intrinsically resistant, may have gastrointestinal colonization with these organisms.

Leuconostoc species may cause bacteremia in otherwise healthy neonates. At least four *Leuconostoc* species (including *Leuconostoc mesenteroides, Leuconostoc paramesenteroides, Leuconostoc cremoris*, and *Leuconostoc citreum*) may cause human infections. Risk factors for *Leuconostoc* infection include lengthy hospitalization requiring tracheostomy or parenteral nutrition, intravascular catheters, prior antibiotic therapy, prematurity, short gut syndrome, and serious underlying disease. *Leuconostoc* infections have been associated

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Table 161.1 Recommended drug of choice for the miscellaneous gram-positive organisms

Organism	Antibiotic (Ab) (alternative Ab)	Route	Dosage	Duration
Pediococcus	Penicillin G Imipenem (Cephalosporins) (Linezolid)	IV	12 million U	(10–14 d)[a]
Leuconostoc	Penicillin G Ampicillin (Clindamycin) (Erythromycin) (Daptomycin)	IV	≥12 million U	(10–14 d)[a] 4 to 6 wk for endocarditis
Lactobacillus	Penicillin G Penicillin G and gentamicin (Clindamycin) (Erythromycin) (Linezolid)	IV IV IV	12 million U daily 20–24 million U daily for endocarditis 1.0 mg/kg q8h	(10–14 d)[a] 6 wk
Oerskovia	Penicillin G, TMP–SMX (Vancomycin)	IV	(Moderate to high dosage)[a]	4–6 wk for endocarditis
Rothia	Penicillin G, (Vancomycin) (Cephalosporins) (Fluoroquinolones)	IV	20 million U daily for endocarditis	6 wk
Arcanobacterium	Erythromycin Penicillin V Penicillin G ± aminoglycosides (Clindamycin) (Tetracycline) (Linezolid)	PO/IV PO IV	40 mg/kg (4 divided doses) 250–500 mg QID 2 million U q4h (for endocarditis)	10 d Until clinical response 4–6 wk
Rhodococcus	Vancomycin (V) or imipenem plus rifampin (AIDS) or erythromycin (Sulfonamides) (Chloramphenicol) (Linezolid)	IV IV PO IV/PO	1 g q12h 500 mg q6h 600 mg/d 500 mg–1 g QID	2 wk 2–4 wk
Abiotrophia *Granulicatella* *Gemella*	Ampicillin or penicillin + gentamicin			

[a] Suggested by some authorities.

Abbreviations: TMP–SMX = trimethoprim–sulfamethoxazole; AIDS = acquired immunodeficiency syndrome.

with pancreatitis, necrotizing enterocolitis, meningitis, and chylothorax to name a few.

Diagnosis is based on identification of the organism from cultures of blood or other sterile body fluids. On Gram stain the organisms appear as pairs or chains of slightly elongated gram-positive cocci that may appear rod-like. They may be difficult to distinguish from viridans streptococci, enterococci, lactobacilli, or pediococci. Helpful tests include the production of gas from glucose; a negative catalase, oxidase, and PYRase test; and the absence of arginine hydrolysis.

Leuconostoc isolates, like pediococci, are uniformly resistant to vancomycin and other glycopeptides. Most strains are susceptible to penicillin, clindamycin, and gentamicin. Susceptibility to the cephalosporins, quinolones, and trimethoprim–sulfamethoxazole (TMP–SMX) is variable. Daptomycin and linezolid show activity against *Leuconostoc* spp. Resistance to quinupristin/dalfopristin has been demonstrated. Penicillin, the drug of choice, should be given at relatively high dosages (≥12 million units daily). In the case of penicillin allergy or resistance, therapy should be based on results of susceptibility testing. Appropriate therapy may also include removal of potentially infected devices such as indwelling intravascular catheters.

LACTOBACILLUS SPECIES

Lactobacillus species are gram-positive rods that normally inhabit the human mouth, vagina, and gastrointestinal tract. More than 50 species of lactobacilli are recognized, many of which are used in the production of cheese, yogurt, pickles, and fermented beverages. Lactobacilli are widely considered to have low pathogenicity, and over the last decade have been used as probiotic factors (e.g., immunomodulation, microbe–microbe interactions, epithelial barrier protection), as part of prevention and treatment protocols for post-antibiotic enteric infections, vehicles for oral immunization, and as part of treatment policies called *ecoimmunonutrition*. Nevertheless, they have been reported to cause infections, including bacteremia, endocarditis, intra-abdominal and hepatic abscesses, meningitis, and pneumonia. Risk factors for serious infections caused by *Lactobacillus* species include underlying immunocompromised state (including human immunodeficiency virus [HIV] disease) and gastrointestinal surgery. Prior antibiotic therapy, particularly with vancomycin (to which most lactobacilli are resistant), has also been identified as a clinical risk factor. In patients with *Lactobacillus* bacteremia and endocarditis, cancer, recent surgery, and diabetes mellitus were identified as underlying risk factors. Additional history of dental infection or manipulation is common.

Diagnosis is based on identification of the organism from sterile body fluids. Lactobacilli are gram-positive rods, but they may appear coccoid if grown on solid media. Cultures grown in broth are more reliable for assessing morphology. Some *Lactobacillus* isolates may be difficult to distinguish from *Leuconostoc* species and streptococci. The combination of tests for gas production from glucose, arginine hydrolysis, PYRase, and carbohydrate fermentations should allow proper identification.

Intravenous penicillin (≥12 million units daily) is generally the drug of choice for serious infections. Endocarditis should be treated with penicillin 20 million to 24 million units daily plus gentamicin for 6 weeks. Lactobacilli are usually resistant to glycopeptides such as vancomycin. Susceptibility to cephalosporins and quinolones is variable, and most isolates are resistant to tetracycline and TMP–SMX. Most strains are susceptible in vitro to clindamycin, a possible alternative therapy in penicillin-allergic patients, but few clinical data are available. Lactobacilli are usually susceptible in vitro to linezolid but may be resistant to daptomycin and quinupristin–dalfopristin. Because of variable activity, susceptibility testing is critical in developing a treatment regimen. In the patient allergic to β-lactams who has endocarditis, penicillin desensitization should be considered.

OERSKOVIA AND *CELLULOSIMICROBIUM* SPECIES

Oerskovia species are yellow, gram-positive, non-acid-fast organisms with extensively branched filaments. They were first described by Orskov in 1938 as "motile *Nocardia*." Their usual habitat is soil, although they have also been isolated from decaying plant materials and grass cuttings. Two species of *Oerskovia* were originally recognized: *Oerskovia turbata* and *Oerskovia xanthineolytica*. Recently, *O. xanthineolytica* has been reclassified as *Cellulosimicrobium cellulans*, and *O. turbata* has been proposed for reclassification as a novel *Cellulosimicrobium* species. Both are rare causes of opportunistic infection in humans but should be considered as potential pathogens of low virulence, especially in the setting of indwelling devices. Reported infections caused by *Oerskovia* and *Cellulosimicrobium* species include native and prosthetic valve endocarditis, peritonitis, central venous catheter infections, bacteremia in immunocompromised hosts (including patients with acquired immunodeficiency syndrome [AIDS]), acalculus cholecystitis, prosthetic joint infection, keratitis, and endophthalmitis due to a penetrating eye injury. Several reported cases have been associated with exposure to soil, marine sediment, and bacterial contamination of hydrophilic contact lens solutions.

The diagnosis of *Oerskovia* and *Cellulosimicrobium* infections rests on laboratory identification from clinical specimens. Gram stain may reveal pleomorphic gram-positive nonmotile rods that can be mistaken for *Corynebacterium* spp. Culture reveals yellow colonies that are catalase positive when grown aerobically. They may be distinguished from other *Nocardia*-like organisms in that they are facultatively anaerobic and do not produce aerial mycelia. Identification is based on carbohydrate fermentation testing.

Successful treatment of *Oerskovia* infections requires removal of the contaminated foreign body in addition to appropriate antibiotic therapy, although some published cases report treatment without removal of infected vascular or

peritoneal catheters. Antibiotics to which clinical isolates of *Oerskovia* and *Cellulosimicrobium* have been reported to be susceptible include penicillin (including extended-spectrum penicillins), vancomycin, TMP–SMX, cephalothin, and amikacin. Intermediate susceptibility or resistance has been described for ampicillin, ciprofloxacin, doxycycline, erythromycin, gentamicin, clindamycin, and the third-generation cephalosporins. Therapy should be based on susceptibility testing of the isolate. However, if culture results suggest *Oerskovia* infection, empiric parenteral penicillin or TMP–SMX therapy seems prudent while awaiting results of susceptibility testing.

ROTHIA SPECIES

Rothia dentocariosa is a small gram-positive pleomorphic rod belonging to the family Micrococcaceae. These organisms, common components of the normal oral microflora, were first isolated from carious dentine. The first description of human disease due to *Rothia* species was not reported until 1975, when the organism was recovered from a periappendiceal abscess. Over the last decade, a number of case reports have described *Rothia* species as causing native and prosthetic valve endocarditis, aortic root abscess, neck abscess, peritonitis, septic arthritis, osteomyelitis, and pneumonia. The patient often has a history of recent dental infection or dental manipulation or is immunocompromised; however, a recent report includes identification in throat cultures of healthy individuals. *Rothia dentocariosa* has been isolated in lymph nodes of patients with cat scratch disease (CSD), suggesting a possible role, together with *Bartonella henselae*, in the pathogenesis of CSD. Another species of this genus (*Rothia mucilaginosa*, formerly known as *Stomatococcus mucilaginosus*) was found to be a member of the normal oral flora. This species has been described as opportunistic agents of infection in cases of endocarditis, meningitis, peritonitis, and other infections.

Diagnosis of *Rothia* infections depends on identification of the organism from the cultures of blood or other body fluids. *Rothia* species are catalase positive, nonmotile, urease negative, and indole negative. On Columbia chocolate horse blood agar, they appear to be gray and have a mucoid tendency after 48 hours of incubation. The organisms may appear branched, resembling *Actinomyces* or *Nocardia* species. They are distinguished from these genera by carbohydrate fermentation testing. *Rothia mucilaginosa* forms cocci in clusters and displays variable catalase reactions ranging from negative to weakly positive to strongly positive. The inability to grow in 5% NaCl distinguishes *R. mucilaginosa* from members of *Staphylococcus* and *Micrococcus* genera.

Penicillin is the drug of choice for treatment of infections due to *Rothia* spp. Because rare isolates may be resistant to penicillin, susceptibility testing should be performed. For endocarditis due to penicillin-susceptible strains, intravenous penicillin at dosages of 20 million units per day for 6 weeks is recommended. In the case of penicillin resistance or drug allergy, vancomycin, netilmicin, or teicoplanin therapy may be effective. *Rothia* species may also be susceptible in vitro to ciprofloxacin, rifampin, third-generation cephalosporins, vancomycin, chloramphenicol, and gentamicin. Resistance to amikacin, kanamycin, ciprofloxacin, and TMP–SMX has been described. In endocarditis cases due to *Rothia* spp., cardiac surgery may be beneficial when antimicrobial therapy alone is unsuccessful. Dental evaluation should also be considered in patients with infections due to *Rothia* species because carious or infected teeth may be a source of recurrent infection.

ARCANOBACTERIUM SPECIES

Arcanobacterium haemolyticum (formerly known as *Corynebacterium haemolyticum*) are facultatively anaerobic gram-positive to gram-variable pleomorphic rods (slender at first, sometimes clubbed, or in angular arrangements) that are nonmotile and nonsporulating. They are considered commensals of human nasopharynx and skin and are transmitted person to person by the droplet route. *Arcanobacterium* species have been recognized as causes of pharyngitis and cervical lymphadenopathy (indistinguishable from the pharyngitis caused by *Streptococcus pyogenes*) with additional symptoms of fever, pruritus, nonproductive cough, scarlatiniform skin rash with mild desquamation, and occasional formation of peritonsillar abscesses. Cutaneous infections, including ulcers, wound infection, cellulitis, and paronychia, are marked in some cases by the elaboration of lipid-hydrolyzing enzyme (sphingomyelinase D), producing dermonecrosis. Sepsis has been seen in immunocompromised states. Central nervous system (CNS) infections (brain abscess, cerebritis, meningitis), endocarditis, osteomyelitis, otitis media, sphenoidal sinusitis, empyema, and cavitary pneumonia have also been described.

Diagnosis is made by isolation and identification of the organism from cultures of blood, pharynx, skin lesions, or other clinical specimens (e.g., CNS abscess, cerebrospinal fluid [CSF], aortic valve, bone). Isolates of *Arcanobacterium* spp. are weakly acid fast, but this characteristic is typically not used for identification. On Loeffler's medium, the morphology closely resembles *Corynebacterium diphtheriae*. Tests that aid in diagnosis include fermentation of dextrose, lactose, and maltose but not mannitol or xylose. Colonies appear circular, discoid, opaque, and whitish, with a rough surface and friable consistency, a uniform feature at 48 hours of a black opaque dot at the center of each colony, and hemolysis at 24 to 48 hours incubation. Because *Arcanobacterium* species may present as part of polymicrobic infections with typical respiratory pathogens, they are often overlooked. Diagnosis often occurs only after repeated isolation. Increased awareness in microbiology laboratories of this organism may allow further elucidation of its pathogenicity in soft-tissue infections.

Most isolates of *A. haemolyticum* are susceptible to erythromycin, gentamicin, clindamycin, and third-generation cephalosporins. Newer studies report susceptibility to linezolid as well. They are resistant to sulfonamides and nalidixic acid in vitro. The drug of choice is erythromycin, 40 mg/kg orally or intravenously in four divided doses per day (2 g maximum). Although there have been reports of treatment failure with penicillin attributed to tolerance and failure to penetrate the intracellular location of the pathogen, penicillins with or without aminoglycosides are also widely used antibiotics, in most cases with success. In cases of abscess or tissue necrosis, surgical drainage or debridement may be a necesssary adjunct to antibiotic therapy.

RHODOCOCCUS SPECIES

Rhodococcus equi (formerly known as *Corynebacterium equi*), zoonotic organisms readily found in soil contaminated with stool of grazing animals, particularly young horses, are nonfastidious, strict aerobic gram-positive bacteria displaying rod-to-coccus pleomorphism, with fragmenting and occasionally palisading forms. *Rhodococcus* are well-documented veterinary pathogens, causing granulomatous pneumonia in foals. They are opportunistic pathogens found in immunocompromised patients, including transplant patients and HIV-infected persons. Documented clinical presentations include slowly progressive granulomatous pneumonia with lobar infiltrates progressing to cavitating lesions on chest radiograph; abscesses of the central nervous system, pelvis, and subcutaneous tissue; and lymphadenitis. Vertebral osteomyelitis and pulmonary malakoplakia have also been reported. Recently, two cases of nosocomial *R. equi* infection have been associated with ventriculoperitoneal shunts. Mortality exceeds 50% among AIDS patients with documented *R. equi* pneumonia, which is associated with a high rate of relapse despite adequate treatment. A newly described species of *Rhodococcus, Rhodococcus tsukamurella*, may cause multiple lung cavitary lesions in immunosuppressed patients and patients with indwelling foreign bodies.

Rhodococcus equi forms salmon pink colonies on blood agar from clinical specimens after 2 to 3 days of incubation. Colonies can be mucoid and coalescing; growth on Lowenstein–Jensen medium allows earlier detection of pigment. Synergistic hemolysis (resembling the CAMP test), displayed by cross-streaking on sheep blood agar with any of a number of other bacteria, including *A. haemolyticum, Staphylococcus aureus*, and *Corynebacterium pseudotuberculosis*, has been helpful in the diagnosis. In addition, *Rhodococcus* isolates are nonreactive to catalase, urease, and phosphatase and exhibit acid-fast staining. Some diagnostic laboratories use a commercial kit (API CORYNE strip; bioMerieux-Vitek, Hazelwood, MO) for identification. Prompt identification is necessary for optimal patient management.

Most strains are susceptible to inhibition by glycopeptide antibiotics, rifampin, and macrolides. Susceptibility to linezolid has been documented. Resistance to β-lactam antibiotics (except carbapenems) has been reported. The high relapse rate and attributable mortality rate, especially among AIDS patients, makes it difficult to recommend a standard treatment protocol. Repeat cultures are warranted during treatment to discover acquired resistance. A combination of at least two antibiotics parenterally (including a glycopeptide and rifampin) followed by oral maintenance therapy is recommended. Surgical wound resection has been performed in some cases, sometimes in combination with antimicrobial therapy. Antimicrobial prophylaxis may prove of benefit in AIDS patients. Recent data suggest treatment for *R. tsukamurella* infections to be a combination of β-lactam and aminoglycoside, along with removal of affected medical devices.

ABIOTROPHIA AND *GRANULICATELLA* SPECIES

First described in 1961 by Frenkel and Hirsch these were initially thought to be nutritionally variant streptococci (NVS). They are members of normal oral cavity flora and have been documented as agents of bacteremia and endocarditis in immunocompromised patients. They form gram-positive cocci in pairs and chains under optimal nutritional conditions (pyridoxal-supplemented media) but may display pleomorphic cellular morphology when growth conditions are suboptimal. Strains of these genera usually grow as small α-hemolytic colonies on chocolate agar but not on sheep blood agar unless the medium is supplemented or other bacteria are present to provide compounds needed for growth. Most strains exhibit positive PYR and LAP tests. They are susceptible to β-lactam agents, although elevated MICs for β-lactams have been observed for some strains. A combination of ampicillin and gentamicin is recommended for endovascular infections with these organisms.

GEMELLA SPECIES

This genus has recently grown to include a total of six species (*Gemella haemolysans, Gemella morbillorum, Gemella bergeriae*, *Gemella sanguinis, Gemella cuniculi*, and *Gemella palaticanis*). Most strains are PYR and LAP positive. They produce colonies on blood agar that resemble viridans streptococci. Although the cellular morphology of *G. morbillorum* resembles that of streptococci, *G. haemolysans* forms *Neisseria*-like diplococci that may also be arranged in tetrads and clusters and may appear to be gram variable. *Gemella haemolysans* is part of the normal flora of the oral cavity, *G. morbillorum* is part of the normal flora of the gastrointestinal tract, *G. cuniculi* has been reportedly isolated from rabbits, and *G. palaticanis* has been identified only in dogs but recently associated with a case of endocarditis in a child. *Gemella* strains have been isolated from cases of meningitis. It has been shown that these organisms are susceptible to vancomycin, penicillin G, and ampicillin. Synergy is seen between penicillin or vancomycin and gentamicin or streptomycin. Hence, penicillin and gentamicin are recommended for the treatment of *Gemella* endocarditis.

HELCOCOCCUS SPECIES

Helcococcus kunzii is currently the only species in this genus of PYR-positive, LAP-negative cluster-forming cocci that has been isolated from human clinical specimens. It forms small, nonhemolytic, slowly growing colonies on blood agar. This species has been described in recent reports as an agent of wound infection, bacteremia, and endocarditis. They are susceptible to vancomycin and β-lactam agents.

LACTOCOCCUS SPECIES

The genus *Lactococcus* was created to accommodate non-β-hemolytic Lancefield group N streptococci normally isolated from dairy products. Seven species have been currently recognized, with four subspecies. Members of this genus are homofermentators of lactic acid and resemble either streptococci or enterococci in terms of phenotypic traits and are infrequently isolated opportunistic pathogens. Though lactococci are commonly considered food-grade bacteria, they have been isolated from cases of endocarditis and a variety of other infections. They are susceptible to vancomycin and other β-lactam agents.

GLOBICATELLA SPECIES

The description of the species *Globicatella sanguinis* is α-hemolytic, PYR positive, LAP negative, and salt tolerant. They form cocci in chains. *Globicatella* spp. have been identified as a rare cause of shunt-associated meningitis and bacteremia. They are susceptible to vancomycin and β-lactam agents.

AEROCOCCUS GENUS

This genus contains seven species. The most well-known species of this genus, *Aerococcus viridans*, forms clusters and though mostly associated with disease in lobsters, it has been noted as an infrequent cause of infection in compromised hosts. Another species, *Aerococcus urinae*, has been well documented as an agent of urinary tract infections and endocarditis in immunocompromised patients. Aerococci form α-hemolytic colonies on blood agar. *Aerococcus viridans* colonies are larger than those of *A. urinae*. These two species also differ in other phenotypic traits (*A. viridans* is PYR positive and LAP negative, whereas *A. urinae* is PYR negative and LAP positive). *Aerococcus*

urinae is susceptible in vitro to a number of β-lactam agents and vancomycin; time-kill studies suggest a need for combination therapy, including an aminoglycoside for bactericidal therapy in endovascular infection.

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162. Miscellaneous gram-negative organisms

Sampath Kumar and Kamaljit Singh

Most gram-negative infections are caused by organisms in the Enterobacteriaceae or Pseudomonadaceae families; however, a few are caused by a heterogeneous group of gram-negative organisms. These organisms do not fit conveniently into a single genera and have undergone frequent taxonomic changes, making understanding them even more difficult for clinicians. The clinical presentation varies widely, affecting different types of hosts and requiring a variety of antibiotics for therapy (Table 162.1). Varied predisposing environmental and host factors are outlined in Table 162.2.

ACINETOBACTER

Acinetobacter is a member of the family Moraxellaceae, with at least 25 genospecies. *Acinetobacter calcoaceticus*, *Acinetobacter lwoffii*, and *Acinetobacter baumannii* are the species most commonly reported in the clinical literature. Because of problems in phenotypically separating the *Acinetobacter* species, the term *A. calcoaceticus-baumannii* complex is sometimes used. *Acinetobacter* spp. are nonmotile, oxidase-negative, gram-negative coccobacilli often appearing as diplococci and thus are easily confused with *Neisseria* or *Haemophilus* spp. They differ from Enterobacteriaceae in that they do not grow anaerobically or reduce nitrates. They are distinguished from *Neisseria* and *Moraxella* by their negative oxidase reaction. Virulence factors include a polysaccharide capsule that may prevent phagocytosis and fimbriae that potentiate adherence to epithelial cells.

Epidemiology

Acinetobacter spp. are widely distributed in the environment, found in food, soil, water, and sewage. *Acinetobacter* spp. may be found on inanimate surfaces, including hospital equipment such as ventilator tubing, resuscitation bags, humidifiers, sinks, mist tents, dialysis baths, angiography catheters, pressure transducers, and

Table 162.1 Antimicrobial therapy of miscellaneous gram-negative bacilli

Organism	First-line therapy	Alternative therapy
Acinetobacter	Ampicillin–sulbactam, piperacillin–tazobactam, imipenem–cilastatin, meropenem, ceftazidime, amikacin	Fluoroquinolones, trimethoprim–sulfamethoxazole, minocycline, tigecycline, colistin
Achromobacter	Imipenem–cilastatin, meropenem, tigecycline	Piperacillin–tazobactam, ceftazidime, trimethoprim–sulfamethoxazole
Alcaligenes	Imipenem–cilastatin, meropenem, trimethoprim–sulfamethoxazole	Amoxicillin–clavulanate, ceftazidime, piperacillin–tazobactam
Capnocytophaga canimorsus	Penicillin	Clindamycin, imipenem–cilastatin, ampicillin–sulbactam, amoxicillin–clavulanate
Pseudomonas oryzihabitans/luteola	Fluoroquinolones, ceftazidime, piperacillin–tazobactam	Imipenem–cilastin, meropenem, aztreonam, aminoglycosides, trimethoprim–sulfamethoxazole
Chromobacterium	Imipenem–cilastin, ciprofloxacin, tigecycline	Tetracycline, trimethoprim–sulfamethoxazole, gentamicin
Elizabethkingia meningoseptica	Vancomycin, rifampin, levofloxacin	Tigecycline, trimethoprim–sulfamethoxazole
Ochrobactrum anthropi	Imipenem–cilastin	Trimethoprim–sulfamethoxazole, tetracyclines, aminoglycosides, fluoroquinolones

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Table 162.2 Environmental and host factors predisposing to infections with miscellaneous gram-negative bacilli

Organism	Environmental factors	Host factors	Infection
Acinetobacter	Ventilator tubing, resuscitation bags, humidifiers, sinks, mist tents, dialysis bags, angiography and IV catheters, pressure transducers, plasma protein solutions	Severely debilitated, recent surgery, instrumentation	Septicemia, endocarditis, meningitis, pneumonia, UTI, wound infections, abscesses, peritonitis, osteomyelitis, eye infections
Achromobacter	Contaminant in disinfectants, diagnostic tracer solution, IV CT contrast, hemodialysis solutions, ventilators, humidifiers, pressure transducers	Severely debilitated, recent neurosurgery	Community-acquired bacteremia, meningitis, chronic otitis media, hospital-acquired meningitis, bacteremia, ventriculitis, endocarditis, endophthalmitis, corneal ulcers, pharyngitis, pneumonia, wound infections, peritonitis, UTI, abscesses
Alcaligenes	Dairy products, rotten eggs, hospital equipment	Severely debilitated	Septicemia, native and prosthetic valve endocarditis, meningitis, meibomianitis, chronic purulent otitis, pyelonephritis, hepatitis, appendicitis, diarrhea
Capnocytophaga	Normal oral, gastrointestinal, respiratory, and vaginal flora of humans; *C. canimorsus* in canine oral flora	Severely immunocompromised, children with malignancies, neutropenia, mucositis, asplenia, alcohol abuse	Bacteremia, septicemia, keratitis, conjunctivitis, endophthalmitis, corneal ulcer, endocarditis, pericardial abscess, mediastinitis, lung and subphrenic abscess, empyema, peritonitis, abdominal abscess, septic arthritis, lymphadenitis, juvenile periodontitis
Chromobacterium	Enters through the skin or ingestion of contaminated food or water	Neutrophil defects (e.g., chronic granulomatous disease)	Local cellulitis, lymphadenitis, septicemia, osteomyelitis, arthritis, meningitis, ocular infections, and pneumonia
Chryseobacterium	Soil, water, use of contaminated fluids in the hospital, nebulizers, flush solutions, pressure transducers, contaminated disinfectants and anesthetics, ice machines, peritoneal dialysis solutions	Neonates, premature infants, adult immunocompromised patients	Neonates: meningitis, hydrocephalus Adults: endocarditis, pneumonia, peritonitis, keratitis, wound infection, meningitis
Pseudomonas oryzihabitans/ luteola	Soil, water, flushing solutions	Patients with indwelling foreign material, malignancies, immunosuppressive therapy, postsurgical state, history of IVDU, chronic renal failure, bone marrow transplant, cirrhosis	Septicemia, bacteremia, subdural empyema, pneumonia, peritonitis, biliary tract infection, abscesses, wound infection, empyema, line infections, prosthetic joint infections

Abbreviations: UTI = urinary tract infection; CT = computed tomography; IVDU = intravenous drug use.

plasma protein solutions. They are found on the skin of many animal species and humans usually as commensal organisms. They are found as part of the normal oral flora and in the genitourinary and gastrointestinal tracts.

Pathogenesis and clinical syndromes

Acinetobacter baumannii is the most commonly found species in human clinical specimens followed by *A. lwoffii*. *Acinetobacter baumannii* is increasingly recognized as one of the most important causes of nosocomial infections and is of particular concern because of its propensity for multidrug resistance. Most infections due to *A. baumannii* are nosocomial, occurring in severely debilitated patients who have been exposed to broad-spectrum antibiotics in the intensive care unit, mechanical ventilators, and invasive devices (e.g., central venous catheters). In addition, *A. baumannii* is noted as a cause of serious infections among military personnel returning from the Middle East, often with carbapenem-resistant strains of *A. baumannii*. A wide variety of human infections due to *A. baumannii* have been reported, including

pneumonia (most often related to endotracheal tubes), septicemia, endocarditis, meningitis, urinary tract infections, wound infections including necrotizing fasciitis, abscesses, peritonitis, osteomyelitis, and eye infections. Purulent pericarditis has been reported in immunosuppressed patients. The most common sites of isolation of *A. baumannii* are the respiratory and urinary tracts. The mortality can be as high as 40% to 60% in patients with septic shock and up to 30% in patients with ventilator-associated pneumonia, usually associated with underlying disease (e.g., diabetes, malignancy, and renal failure). *Acinetobacter* spp. play a significant role in the colonization of hospitalized patients, making it difficult to differentiate true infection from colonization.

Acinetobacter baumannii is commonly multidrug resistant due to expression of β-lactamases, altered porin channels and efflux pumps. Treatment is best guided by specific antibiotic testing and sensitivity patterns within each hospital. *Acinetobacter lwoffii* tends to be more susceptible than the other *Acinetobacter* spp. Most *A. baumannii* strains are resistant to penicillin, ampicillin, first-generation cephalosporins, gentamicin, and chloramphenicol and show variable susceptibility to second- and third-generation cephalosporins, trimethoprim–sulfamethoxazole, and tetracyclines. Ampicillin–sulbactam and sulbactam alone have intrinsic bactericidal activity and have been used with good success in susceptible strains. In recent years, many institutions have noted increasing resistance to aminoglycosides and carbapenems among *A. baumannii* strains. In addition, New-Delhi metallo-β-lactamase (NDM)-producing strains of *A. baumanni* have also been described. For pan-resistant strains of *A. baumannii*, colistin (or polymyxin B) and tigecycline either singly or in combination may offer reasonable therapeutic alternatives.

ACHROMOBACTER

Epidemiology

Achromobacter spp. are widely distributed in nature, including soil and water. They may be part of the normal flora of the lower gastrointestinal tract. *Achromobacter* spp. have been found as contaminants in disinfectants, diagnostic tracer solutions, intravenous computed tomography contrast solutions, hemodialysis solutions, ventilators, humidifiers, and pressure transducers.

The genus *Achromobacter* consists of a number of species of which two are of clinical relevance: *Achromobacter xylosoxidans* and *Achromobacter denitrificans* (previously *Alcaligenes denitrificans*). These are gram-negative rods that are oxidase positive and grow on MacConkey agar.

Clinical syndromes

Achromobacter spp. have been commonly reported as causative agents in a variety of nosocomial and community-acquired infections. *Achromobacter xylosoxidans* has been isolated from many types of specimens, including blood, cerebrospinal fluid (CSF), bronchial washings, urine, and wounds. It represents an opportunistic pathogen in immunosuppressed patients and has been reported to cause chronic otitis media, meningitis and ventriculitis after neurosurgical manipulation, bacteremia, endocarditis, endophthalmitis, corneal ulcers, pharyngitis, pneumonia, surgical wound infections, peritonitis and urinary tract infections, and abscesses. Mortality can approach 52% in patients with *A. xylosoxidans* bacteremia.

Achromobacter xylosoxidans colonizes the respiratory tract of cystic fibrosis patients and is associated with exacerbations of pulmonary symptoms. Antibiotic selection should be guided by susceptibility testing. Imipenem–cilastatin is the most consistently effective agent in vitro against *A. xylosoxidans*. Trimethoprim–sulfamethoxazole, piperacillin–tazobactam, ticarcillin–clavulanate, fluoroquinolones, and ceftazidime may also be effective. For severe infections, combination therapy may be necessary; however, synergistic activity has not been established. Most strains are resistant to expanded-spectrum cephalosporins (including cefepime) except ceftazidime, and aminoglycosides.

Achromobacter denitrificans is reported to have been isolated from clinical specimens but its pathogenic role remains controversial. It has been reported to cause otitis externa and bacteremia associated with intravenous catheters.

ALCALIGENES

Epidemiology

Alcaligenes consist of gram-negative rods or cocci that are oxidase positive and obligate aerobes. *Alcaligenes faecalis* is the most commonly isolated species in the clinical laboratory. Some *A. faecalis* (previously named *Alcaligenes odorans*) produce a greenish color on blood agar plates and have a characteristic fruity, apple odor. These organisms are found in soil and water as well as on normal

human skin and in gastrointestinal tract flora. Dairy products and rotten eggs have been sources of *Alcaligenes*. These organisms have also been isolated from hospital equipment.

Clinical syndromes

Clinically important infections are found in severely debilitated patients and patients with cystic fibrosis. Most infections are opportunistic and acquired from contaminated hospital equipment (e.g., nebulizers, respirators, and lavage fluid). *Alcaligenes* spp. are a rare cause of bacteremia (blood isolates have also been obtained from patients without clinical evidence of sepsis), native and prosthetic valve endocarditis, meningitis, chronic purulent otitis, keratitis, pyelonephritis, hepatitis, appendicitis, and urinary tract infection. *Alcaligenes* isolated from the blood of patients with septicemia is thought to be associated with contaminated hospital equipment. *Alcaligenes faecalis* isolation from the urine is often considered to be a contaminant and it is also found in diabetic ulcers with mixed flora, and its clinical significance is difficult to determine.

Alcaligenes faecalis is generally susceptible to the β-lactam drugs, fluoroquinolones, aminoglycosides, and trimethoprim–sulfamethoxazole. On the basis of in vitro studies, third-generation cephalosporins or the addition of clavulanic acid to amoxicillin or piperacillin–tazobactam may be more consistently effective. Greater antibiotic resistance is seen in hospitals.

CAPNOCYTOPHAGA

Epidemiology

Capnocytophaga encompasses a group of capnophilic (CO_2 requiring), microaerophilic gram-negative rods. The organisms are slow growing, thin, and often fusiform bacilli that display gliding motility on agar media. There are six clinically relevant human species: *Capnocytophaga ochracea, Capnocytophaga sputigena, Capnocytophaga haemolytica, Capnocytophaga granulosa, Capnocytophaga leadbetteri*, and *Capnocytophaga gingivalis* (formerly CDC DF-1). These species are oxidase, catalase, and indole negative. *Capnocytophaga canimorsus* (formerly DF-2) and *Capnocytophaga cynodegmi* (formerly DF-2-like organism) are part of the normal oral flora of domestic animals. These species are oxidase and catalase positive and indole negative, and they reduce nitrates.

Clinical syndromes

Capnocytophaga are part of the normal flora of humans isolated from the oropharynx, vagina, and gastrointestinal tract. They are causative agents of localized juvenile periodontitis (together with *Aggregatibacter* [formerly *Actinobacillus*] *actinomycetemcomitans*) and other periodontal disease. *Capnocytophaga* may also cause systemic disease in immunocompromised patients with hematologic malignancies and neutropenia, particularly with chemotherapy-associated oral lesions or mucositis. These patients usually present with bacteremia and septicemia. In immunocompetent patients, *Capnocytophaga* may be isolated from polymicrobial infections of the respiratory tract or contaminated wounds (e.g., clenched fist injuries). It has also been reported to cause keratitis, conjunctivitis, endophthalmitis, corneal ulcers, endocarditis, pericardial abscess, mediastinitis, pulmonary abscesses, empyema, septic arthritis, cervical and inguinal lymphadenitis, sinusitis, thyroiditis, osteomyelitis, peritonitis, abdominal abscess, chorioamnionitis, and congenital bacteremia/neonatal sepsis.

Human *Capnocytophaga* species are generally susceptible to clindamycin, erythromycin, tetracycline, chloramphenicol, quinolones, and imipenem–cilastatin. Susceptibilities are variable for penicillin, expanded-spectrum cephalosporins, and metronidazole. In general, these organisms are resistant to aztreonam, aminoglycosides, vancomycin, trimethoprim, and colistin. β-Lactamase production has been reported in 2.5% to 32% of isolates (detected by the nitrocefin test). Clindamycin is thought to be the most active drug in vitro. In immunocompromised patients with bacteremia, antibiotics should be given for 10 to 14 days after documenting negative blood cultures. For immunocompetent patients, the duration of therapy should be dictated by the site and extent of infection and therapy should be given in conjunction with adequate surgical drainage.

Capnocytophaga canimorsus and *C. cynodegmi* are part of the normal oral flora of dogs and cats. *Capnocytophaga canimorsus* is isolated more commonly and appears to be more virulent. It is generally associated with dog bites, causing a wide spectrum of illness ranging from mild to fulminant infection, including sepsis and death. The case-fatality rate is approximately 25%. Predisposing factors to serious infection include underlying illness such as liver cirrhosis, alcohol abuse,

and immunosuppression (steroids or hematologic malignancies). In predisposed persons, particularly asplenic patients, the infection tends to be fulminant, with shock, disseminated intravascular coagulation, hemorrhagic skin lesions mimicking meningococcemia, gangrene, renal failure, and death. More than 75% of cases report exposure to a dog, either through ownership or a bite. The most common clinical manifestations are septicemia and bacteremia, but *C. canimorsus* has been reported to cause meningitis, endocarditis, pneumonia, empyema, corneal ulcer, septic arthritis, cellulitis, and wound infections after a dog bite or cat scratch.

The diagnosis is established by blood cultures, although other specimens may also yield the organism (e.g., wound cultures, CSF). In most reports, cultures become positive within 3 to 7 days. In asplenic patients, the organism may be demonstrated on a Gram stain of the buffy coat. In one alcoholic patient, the organisms were seen on a peripheral blood smear.

Routine susceptibility tests of *C. canimorsus* are difficult to perform because of slow growth and lack of standardized methods. However, it is generally reported to be susceptible to most antibiotics, including penicillins, imipenem–cilastin, erythromycin, vancomycin, clindamycin, third-generation cephalosporins, chloramphenicol, rifampin, doxycycline, and quinolones. Susceptibility to aminoglycosides and trimethoprim is unclear and may depend on the method used. Penicillin is considered the drug of choice for *Capnocytophaga* infections.

CHROMOBACTERIUM

Chromobacterium violaceum is the species most commonly isolated in the clinical laboratory although it is seldom regarded as pathogenic. *Chromobacterium violaceum* is a slightly curved gram-negative rod with an almond-like smell and produces a distinctive water-insoluble violet pigment on blood agar. The organism grows within 24 hours on conventional media. It is motile, with both polar and lateral flagellae that are antigenically distinct. Humans with neutrophil defects (e.g., chronic granulomatous disease) may be particularly susceptible to infections with this organism.

Chromobacterium is generally found in the environment (soil, fresh water, and food). It grows optimally at 20°C to 37°C (68°F to 98.6°F); hence, most infections have been documented in tropical or subtropical climates. It is a rare infection, thought to enter the body through the skin, although ingestion of contaminated food or water may play a role. The most common clinical presentation is a local cellulitis and regional or diffuse lymphadenitis. Hematologic dissemination may occur, resulting in septicemia and multiorgan failure. Mortality is 60% to 70%, depending on the host and accuracy of diagnosis. Other presentations have included fever, skin lesions, abdominal pain, osteomyelitis, arthritis, meningitis, ocular infections, and pneumonia.

Chromobacterium violaceum is generally resistant to most penicillins and cephalosporins. It is susceptible to imipenem–cilastatin, fluoroquinolones, gentamicin, and tetracyclines. Trimethoprim–sulfamethoxazole has been used successfully as outpatient therapy after prolonged intravenous therapy with other agents.

ELIZABETHKINGIA MENINGOSEPTICA

Formerly *Chryseobacterium* spp. (former *Flavobacterium* spp.) these are long, thin, slightly curved, occasionally filamentous, oxidase-positive gram-negative rods. They are common inhabitants of soil and water. *Elizabethkingia meningoseptica* is the species most commonly associated with human infections, but *Chryseobacterium gleum, Chryseobacterium indologenes*, and other *Chryseobacterium* species have also been implicated in human disease. Members of *Chryseobacterium odorans* (*Flavobacterium odorans*) have been renamed *Myroides odoratus* and *Myroides odoratimimus*.

Elizabethkingia meningoseptica is an uncommon pathogen in adults and rarely causes infections in children beyond the newborn period. It is highly pathogenic for premature infants and has been associated with neonatal sepsis and meningitis. The development of meningitis may be insidious. The prognosis is extremely poor, with mortality >60%. Half of the survivors develop significant neurologic complications, including hydrocephalus. Although rarely encountered it is important to diagnose the disease accurately because epidemics may occur in nurseries. Meningitis has also been reported in adult immunocompromised patients. Other clinical presentations in adults include bacteremia, endocarditis, pneumonia, peritonitis, keratitis, and wound infections. Most of the described cases are nosocomial infections associated with the use of contaminated fluids in the hospital (nebulizers, flush solutions for arterial catheters, pressure transducers, ice machines, contaminated disinfectants, contaminated anesthetics, peritoneal dialysis). *Chryseobacterium*

indologenes, although not infrequently isolated in clinical specimens, rarely has clinical significance. Bacteremia has been described with *C. indologenes* particularly in immunocompromised patients, but mortality appears low even when patients are prescribed antibiotics without activity against *C. indologenes*.

Antimicrobial selection is difficult as *Elizabethkingia* and *Chryseobacterium* are inherently resistant to multiple antibiotics, and susceptibilities vary with the method used. Most isolates produce β-lactamases and are resistant to penicillins, third-generation cephalosporins, carbapenems, aminoglycosides, tetracyclines, and chloramphenicol. *Elizabethkingia meningoseptica* and *Chryseobacterium* spp. demonstrate paradoxical susceptibility to agents with activity against gram-positive bacteria (e.g., clindamycin, erythromycin, trimethoprim–sulfamethoxazole, rifampin, and vancomycin). Most earlier reports recommend vancomycin and rifampin for treatment of serious infections due to *E. meningoseptica* meningitis. Erythromycin and rifampin have both been given concurrently intravenously and intrathecally with some success. More recent studies have recommended use of levofloxacin based on in vitro results demonstrating low minimum inhibitory concentrations (MICs). Development of resistance on therapy has been demonstrated with erythromycin, rifampin, ciprofloxacin, and trimethoprim–sulfamethoxazole. Tigecycline has been reported to have in vitro activity against some *E. meningoseptica* strains. Antimicrobial therapy should be continued for at least 2 weeks after sterilization of the CSF. Recovery is the rule in immunocompetent older patients infected with contaminated materials; however, the prognosis is poor in immunocompromised patients.

PSEUDOMONAS ORYZIHABITANS, *PSEUDOMONAS LUTEOLA*, *PSEUDOMONAS FLUORESCENS*, *PSEUDOMONAS PUTIDA*, AND *PSEUDOMONAS STUTZERI*

Pseudomonas oryzihabitans and *Pseudomonas luteola* are oxidase-negative, aerobic gram-negative rods with a distinct yellow pigment. After 48 hours of incubation, colonies are typically rough or wrinkled. They are found in water, soil, and other damp environments. Eighty-four percent of the reported cases have been associated with the presence of a foreign material, including intravascular catheters, dialysis catheters, or artificial grafts. Other associated host factors include malignancy, immunosuppressive therapy, postsurgical state, chronic renal failure, previous antibiotic therapy, intravenous drug use, long-term corticosteroid use, liver cirrhosis, and bone marrow transplantation. Infections associated with these organisms include sepsis, bacteremia, line infections, pneumonia, prosthetic joint infections, subdural empyema, peritonitis, biliary tract infections, surgical wound infections, abscesses, and empyema.

In many studies, resistance has been shown to the first- and second-generation cephalosporins, and most isolates are also resistant to ampicillin and tetracycline. They are sensitive to the ureidopenicillins, third-generation cephalosporins, carbapenems, aminoglycosides, and quinolones. There is a difference in susceptibility to trimethoprim–sulfamethoxazole: *P. luteola* is resistant and *P. oryzihabitans* is sensitive. Clinically, most patients have been treated with ciprofloxacin with a favorable outcome.

The increase in number of reported cases of *Pseudomonas fluorescens* and *Pseudomonas putida* infection is frequently related to the presence of intravascular catheters in immunocompromised patients and dialysis catheters in continuous ambulatory peritoneal dialysis. *Pseudomonas fluorescens* can be isolated from the skin of blood donors and result in contaminated blood transfusions, infected flushes, pseudobacteremia and pseudo-outbreaks. *Pseudomonas putida* has been implicated in nosocomial bacteremia, pneumonia, peritonitis, and neonatal sepsis. *Pseudomonas stutzeri* infections are uncommon but this organism has been reported as a cause of bacteremia, nosocomial brain abscess, and meningitis in immunocompromised patients. Infections such as osteomyelitis, septic arthritis, and endophthalmitis after cataract surgery have also been reported. These organisms are generally susceptible to most antipseudomonal antibiotics.

OCHROBACTRUM

These are oxidase- and urease-positive, gram-negative coccobacilli formerly designated CDC group Vd-1 and Vd-2 and *Achromobacter* groups A, C, and D. Currently there are two designated *Ochrobactrum* species, *Ochrobactrum anthropi* and *Ochrobactrum intermedium*, although it is very difficult to differentiate the two species in the routine clinical microbiology laboratory. Both *Ochrobactrum* species are closely related to *Brucella* species, leading to occasional misidentification by automated systems. *Ochrobactrum anthropi*

is a low-virulence pathogen affecting immunocompromised patients and is often associated with vascular device-related infections, hemodialysis, urinary and respiratory tract infections, continuous ambulatory peritoneal dialysis peritonitis, activation-induced cell death, and pacemaker infections. Cases have been described where resolution of bacteremia has occurred without antibiotic administration or despite administration of resistant antibiotics. *Ochrobactrum anthropi* is usually resistant to most penicillins and cephalosporins and susceptible to carbapenems, aminoglycosides, fluoroquinolones, trimethoprim–sulfamethoxazole, and tetracyclines.

OLIGELLA, *RALSTONIA*, *RHIZOBIUM*, *SHEWENELLA*, *SPHINGOMONAS*, *ROSEOMONAS*, *WEEKSELLA*, AND *BERGEYELLA*

Oligella are small coccobacilli and consist of two species, *Oligella urethralis* (formerly *Moraxella urethralis*) and *Oligella ureolytica*. Most isolates have been isolated from human urine often associated with indwelling Foley catheters and can rarely cause bacteremia, septic arthritis, and pyelonephritis. *Oligella* spp. are susceptible to most antibiotics including penicillin. *Ralstonia pickettii* has been implicated in pseudobacteremias and nosocomial infections due to contaminated infusions.

Rhizobium spp. (former *Agrobacterium*) are occasionally isolated from clinical specimens but rarely linked with human infection. *Rhizobium radiobacter* has been most commonly isolated from blood followed by peritoneal dialysate, mainly associated with infections of transcutaneous devices in immunocompromised patients. Antibiotic susceptibility is variable, and treatment should be guided by individual susceptibility testing. Most isolates are susceptible to broad-spectrum cephalosporins, carbapenems, piperacillin–tazobactam, fluoroquinolones, and gentamicin (but not tobramycin).

Shewanella putrefaciens and *Shewanella algae* are the type species most commonly isolated from human clinical specimens. They are associated with skin and soft-tissue infections and bacteremia, especially in immunocompromised patients. They are usually susceptible to most antibiotics except for penicillin and first-generation cephalosporins.

Sphingomonas (formerly *Pseudomonas*) *paucimobilis* is a yellow-pigmented, weakly oxidase-positive, gram-negative rod that classically infects immunocompromised patients and is isolated from a variety of clinical specimens, including blood, CSF, urine, wounds, and the hospital environment. Most strains are susceptible to vancomycin, tetracycline, trimethoprim–sulfamethoxazole, aminoglycosides, and imipenem–cilastin with variable susceptibility to penicillins and quinolones.

Roseomonas are the most frequently isolated pink-pigmented gram-negative coccobacilli. They are an uncommon cause of human infection but are occasionally isolated from blood, usually due to device-associated bacteremia. They are also associated with intra-abdominal abscesses and urinary tract infections. Most infections have been treated with imipenem–cilastatin, amikacin, and fluoroquinolones. *Roseomonas* spp. are usually resistant to penicillins and cephalosporins.

The genus *Weeksella* contained two species *Weeksella virosa* and *Weeksella zoohelcum*, now reclassified as *Bergeyella zoohelcum*. Both species are oxidase negative and susceptible to penicillin. *Bergeyella zoohelcum* is part of the normal oral flora of dogs and cats, and human isolates frequently result from dog or cat bites.

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PART XIX

Specific organisms: spirochetes

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163. Syphilis and other treponematoses

Arlene C. Seña and Adaora A. Adimora

Treponemes are members of the family Spirochaetaceae, which also contains *Borrelia* and *Leptospira*. Although most treponemes do not cause disease in human beings, a few cause substantial morbidity. This chapter briefly reviews the clinical manifestations and treatment of syphilis in adults and the nonvenereal treponematoses, yaws, pinta, and bejel.

SYPHILIS

Transmission and stages of infection

Syphilis is primarily transmitted through sexual contact with infectious mucocutaneous lesions in primary and secondary syphilis. Mother-to-child transmission can occur from transfer of the spirochete through the placenta or, less commonly, from contact with infectious exudates or blood through the birth canal. Transmission of syphilis through blood products is now rare due to routine screening of donors.

Like other treponemal diseases, the clinical manifestations of syphilis are divided into early and late stages. Early syphilis is further divided into primary, secondary, and early latent stages. During the latent syphilis stage, patients have positive serologic tests for syphilis but no other signs of disease. The Centers for Disease Control and Prevention (CDC) classifies patients in the latent stage as having early syphilis if they acquired infection during the preceding year. Otherwise, persons with latent disease are classified as having either late latent syphilis or latent syphilis of unknown duration. Although clinical staging is useful for diagnosis and treatment, it is also imprecise; overlap between stages is relatively common.

PRIMARY AND SECONDARY SYPHILIS

Treponema pallidum subsp. *pallidum*, the causative agent of syphilis, usually enters the body through breaks in the epithelium that occur during sexual contact. Some organisms persist at the site of entry, whereas others disseminate via the lymphatic system throughout the body, proliferating and stimulating an immune response. The incubation period of primary syphilis is usually about 21 days, although extremes of 10 to 90 days have been noted.

The first clinical manifestation is usually a chancre at the site of genital trauma. The chancre begins as a red macule that subsequently becomes papular and then ulcerates. The lesion is painless with a well-defined margin and thickened, rubbery base. If untreated, the chancre persists for 3 to 6 weeks and then heals. Nontender regional lymphadenopathy also develops.

In untreated individuals, *T. pallidum* disseminates throughout the body, and secondary syphilis develops about 4 to 10 weeks after the chancre's onset. Common symptoms include malaise, headaches, sore throat, fever, musculoskeletal pains, and weight loss. Physical examination of persons with secondary syphilis reveals rash in 75% to 100%, regional or generalized lymphadenopathy in 50% to 85%, and mucosal ulceration in 5% to 30%. The appearance of the rash can vary greatly, but lesions are often maculopapular or papulosquamous and often involve the entire body, including the palms and soles (Figure 163.1). Broad, flat lesions, known as *condylomata lata*, may develop in warm, moist areas, such as the scrotum, vulva, or perianal regions. Patchy alopecia and shallow painless mucosa ulcerations, called *mucous patches*, may also be seen.

The diagnosis of primary or secondary syphilis is based on the characteristic chancres or mucocutaneous lesions, along with demonstration of *T. pallidum* by direct detection methods. Like the chancre, these manifestations of secondary syphilis resolve spontaneously with or without therapy. However, a small proportion of patients develop complications, such as hepatitis, syphilitic glomerulonephritis with nephrotic

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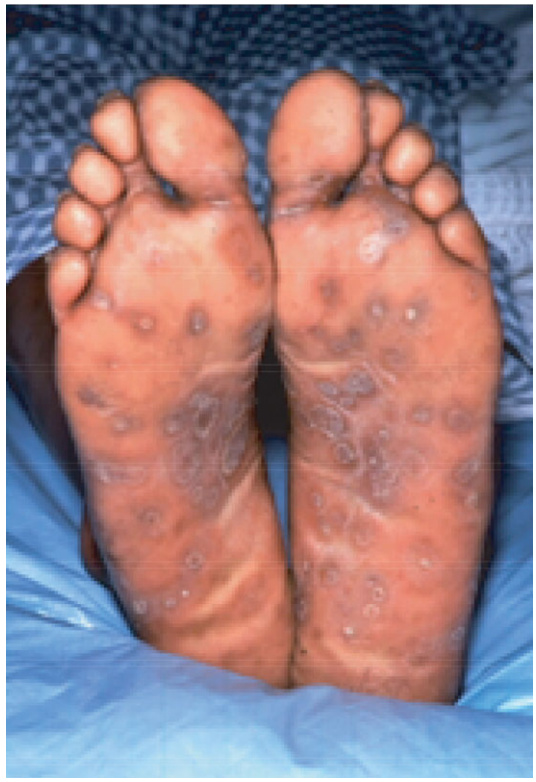

Figure 163.1 Secondary syphilis. Papulosquamous lesions on soles. (Courtesy of David Schlossberg, MD.)

syndrome, anterior uveitis, choroiditis, arthritis, bursitis, or osteitis.

NEUROSYPHILIS

T. pallidum can invade the central nervous system during any stage of syphilis. Asymptomatic neurosyphilis can occur with laboratory abnormalities in the cerebrospinal fluid (CSF) during primary or secondary syphilis. These abnormalities may resolve spontaneously or with treatment, or result in early symptomatic neurosyphilis in 5% of patients.

Syphilitic meningitis most commonly occurs during the first year of infection. Patients may present with headache, fever, stiff neck, and photophobia. Cerebral involvement may result in seizures or hemiplegia. Cranial nerve palsies are especially common. Characteristic CSF findings include a lymphocytic pleocytosis, increased protein, and hypoglycorrhachia in slightly less than half of cases. The diagnosis is confirmed by a reactive serum non-treponemal antibody test and the Venereal Disease Research Laboratory (VDRL) test in CSF. Other manifestations of early neurosyphilis may include cranial neuritis or ocular involvement.

Meningovascular syphilis usually occurs about 5 to 12 years after infection in patients between the ages of 30 and 50 years and may involve the cerebrum, brainstem, or spinal cord. The pathophysiology involves chronic meningitis and infarction due to syphilitic endarteritis. In cerebrovascular syphilis, the middle cerebral artery is most commonly involved, and hemiparesis, aphasia, and seizures commonly occur. CSF usually reveals a lymphocytic pleocytosis with increased protein and a positive CSF VDRL. Spinal syphilis, a relatively uncommon entity, may present as meningomyelitis or transverse myelitis.

The major parenchymatous forms of neurosyphilis are general paresis and tabes dorsalis, which tend to occur between 2 and 30 years and 3 and 50 years, respectively, after initial infection. Both are now uncommon diseases.

General paresis is a chronic meningoencephalitis that results from direct invasion of the brain by *T. pallidum* and combines both psychiatric and neurologic manifestations. Early symptoms, such as irritability, memory loss, headache, and personality changes, may evolve into emotional lability, paranoia, and confusion. Pupillary abnormalities occur in more than half of patients with general paresis. Abnormal reflexes, slurred speech, and tremors are also common. In untreated patients, the interval between onset of symptoms and death can range from a few months to about 5 years.

Serum non-treponemal serologic tests are reactive in 95% to 100% of patients with generalized paresis. CSF VDRL is usually positive, but a negative result alone does not exclude the diagnosis. Differential diagnosis includes Alzheimer's disease, chronic alcoholism, and multiple sclerosis.

Tabes dorsalis is characterized by lightning pains and various combinations of other neurologic signs and symptoms, such as ataxia; bladder disturbances; pupillary abnormalities; absent ankle or knee reflexes; Romberg's sign; impaired vibratory and position sense; and development of extremely large, unstable, painless joints known as Charcot's joints. Lightning pains are paroxysms of severe stabbing pains, which usually occur in the legs. Although most patients have positive serum non-treponemal tests, 10% of patients with tabes will have nonreactive non-treponemal titers but positive treponemal tests.

CSF may be normal or may reveal lymphocytic pleocytosis and elevated protein.

NONNEUROLOGIC MANIFESTATIONS OF TERTIARY SYPHILIS

Syphilitic heart disease, now an uncommon cause of cardiovascular disease, occurs 15 to 30 years after initial infection. During the early phases of infection, *T. pallidum* can disseminate to the heart and lodge in the aortic wall, where they may cause endarteritis of the vasa vasorum of the aorta with resultant scarring and destruction of the vessel's wall. Major cardiac manifestations include thoracic aneurysm, aortic regurgitation (without associated aortic stenosis), and coronary ostial stenosis.

Late benign syphilis is another now uncommon form of tertiary syphilis. It results from the chronic inflammatory response to *T. pallidum* and the formation of a granulomatous type of lesion called a *gumma*. Gummas may be ulcerative, nodular, or noduloulcerative and most commonly occur in the skin and bones but may also invade the viscera, muscles, and other structures.

SYPHILIS IN PERSONS WITH HIV INFECTION

Because syphilis and human immunodeficiency virus (HIV) infection share means of transmission and other risk factors, both infections often coexist. Moreover, syphilis, like other genital ulcer diseases, facilitates HIV transmission. Clinical observation and case reports suggest that HIV-infected patients may experience a more aggressive course of syphilis, with more frequent occurrence of neurosyphilis especially in the early stages of infection. Occasional unusual serologic reactions can occur in HIV-infected patients including very high or fluctuating non-treponemal antibody titers; false-positive non-treponemal tests and false-negative treponemal tests have also been documented. Nevertheless, available data suggest that HIV infection does not significantly change the presentation, clinical course, or response to treatment of syphilis.

SYPHILIS IN PREGNANCY

The clinical manifestations of syphilis are not altered in pregnancy; however, syphilis has widespread complications for both the infected mother and the fetus. Adverse pregnancy outcomes include early fetal loss, preterm delivery, low birth weight, and congenital syphilis in the neonate.

Laboratory tests

DIRECT EXAMINATION

Direct microscopic examination can provide immediate diagnosis of primary and secondary syphilis. Dark-field microscopy must be used because *T. pallidum's* narrow width (0.15 μm) renders the organism below the level of resolution of light microscopy. Wet preparations can be made from the skin or mucous membrane lesions of primary or secondary syphilis. Examination reveals tightly coiled organisms 6 to 14 μm long and 0.25 to 0.30 μm wide, with corkscrew motility. When examination of specimens must be delayed or oral lesions evaluated, direct fluorescent antibody testing can be useful. This test specifically detects *T. pallidum* and eliminates confusion with oral treponemal saprophytes whose morphology is similar to that of *T. pallidum*. Polymerase chain reaction (PCR) assays for diagnosis of syphilitic lesions have been developed and used in research studies; however, none are yet commercially available.

SEROLOGIC TESTS

Serologic tests for syphilis measure either nonspecific non-treponemal antibody or specific treponemal antibody. Non-treponemal antibody tests measure immunoglobulin G (IgG) and immunoglobulin M (IgM) to lipoidal material released from damaged host cells as well as to lipoprotein-like material and cardiolipin released by the treponemes. Non-treponemal antibody titers generally correlate with disease activity; titers fall progressively over time and are expected to decrease 4-fold in response to therapy. The following non-treponemal tests are commonly used: VDRL test, rapid plasma reagin (RPR), the toluidine red unheated serum test (TRUST), and the unheated serum reagin test (USR). Biologic false-positive non-treponemal test results occur in 1% to 2% of the general population, and are associated with several conditions including viral infections, pregnancy, malignancy, autoimmune diseases, and advanced age. False-negative results can occur from the prozone phenomenon in which patients with high non-treponemal titers can have weak or negative results at low dilutions due to excess antibody, although this is rare.

Specific treponemal antibody tests are needed to confirm a current or past diagnosis of syphilis. These tests detect antibodies formed in response to treponemal antigens. Treponemal tests usually

remain reactive after treatment, but a small proportion of infected persons can become seronegative. Commonly used treponemal tests include the fluorescent antibody absorption (FTA-ABS), microhemagglutination assay for *T. pallidum* (MHA-TP), and the *T. pallidum* particle agglutination (TP-PA) test for syphilis.

Several new automated treponemal enzyme immunoassays (EIAs), chemiluminescence immunoassays, and immunoblots for *T. pallidum* that detect treponemal IgM and/or IgG have been US Food and Drug Administration (FDA) approved as screening and confirmatory tests for syphilis diagnosis. The majority of the newer assays use recombinant *T. pallidum* antigens to detect treponemal antibodies from patient specimens. Rapid, point-of-care tests which can provide results within 20 minutes have also been developed primarily for detection of treponemal antibodies; one of the rapid tests has received FDA approval and may be useful in settings with limited laboratory capabilities.

Traditionally, non-treponemal tests are used for screening followed by a treponemal test for confirmation. However, with the development of automated EIAs, some larger laboratories are using a reverse screening algorithm for syphilis testing. In the reverse algorithm, a positive treponemal test result is followed by a non-treponemal test to determine active infection. If the non-treponemal test is negative, then a second treponemal assay is recommended to confirm the results of the initial treponemal test. An individual with a positive treponemal test but negative non-treponemal titer may have early syphilis, late latent syphilis, past treated syphilis, or a false-positive treponemal test. Therefore, obtaining a thorough patient history to determine risks for recent exposures or past infections is critical to determining patient management. Treatment is usually indicated for persons with positive treponemal tests and non-reactive non-treponemal tests, unless a history of treatment exists.

CSF EVALUATION

CSF should be examined in all syphilis patients with neurologic signs or symptoms (e.g., acute or chronic meningitis, ophthalmic or auditory symptoms, cranial nerve palsies, motor or sensory deficits, cognitive dysfunction), evidence of active tertiary syphilis, and in those with probable treatment failure, especially among HIV-infected persons. Performance of lumbar puncture among asymptomatic HIV-infected patients is controversial, but may be considered among coinfected persons with a non-treponemal titer $\geq$1:32 and CD4 count of $\leq$350 cells/mm^3.

When CSF specimens are free of blood contamination, a positive CSF VDRL test confirms the diagnosis of neurosyphilis. However, the sensitivity of the CSF VDRL is limited and a negative test does not rule out neurosyphilis, especially in the presence of CSF pleocytosis and increased CSF protein levels. The CSF FTA-ABS is more sensitive than the CSF VDRL, but false-positive results have been reported.

Treatment and follow-up

Treatment and follow-up are outlined in Tables 163.1 and 163.2 for HIV-uninfected and HIV-infected adults. Penicillin is the drug of choice for all stages of syphilis infection. Alternative treatment regimens are available for patients with penicillin allergies, but there are limited data on efficacy. Therefore, pregnant women who are allergic to penicillin should be desensitized and treated with penicillin. HIV-positive patients with syphilis should be treated with penicillin if at all possible. Azithromycin 2 g orally in a single dose results in similar cure rates as benzathine penicillin in HIV-uninfected patients with early syphilis; however, its routine use is not recommended due to widespread resistance of *T. pallidum* to macrolides.

Clinical and serologic follow-up of patients after syphilis treatment is essential due to the potential for treatment failure. For HIV-negative persons, repeat evaluation should be performed at 6 and 12 months after therapy for early syphilis, and at 6, 12, and 24 months for latent syphilis. For pregnant women, serologic titers should be repeated at 28–32 weeks' gestation and at delivery as recommended for the disease stage. Although non-treponemal titers may fall more slowly among HIV-positive patients than in individuals who are HIV negative after treatment, more frequent follow-up in HIV-infected patients is recommended (see Table 163.2) due to the potential for treatment failure. Vigilant follow-up for patients coinfected with HIV is important to document resolution of infection or to prompt immediate evaluation if relapse, reinfection, or other complications occur.

Serologic response to therapy is demonstrated by at least a 4-fold decrease in non-treponemal titers from baseline (two dilution decrease, i.e.,

Table 163.1 Management of syphilis in adults including pregnant women without known HIV infection

Primary, secondary, or early latent syphilis (duration ≤1 yr)

Treatment

- Benzathine penicillin G, 2.4 million U IM once
- If penicillin allergy:[a]
  - Doxycycline 100 mg PO BID for 2 wk *or* tetracycline 500 mg PO QID for 2 wk
  - Ceftriaxone 1 g IM *or* IV for 10–14 d (caution: some patients with penicillin allergy are also allergic to ceftriaxone)

Treatment (for pregnant women)

- Benzathine penicillin G, 2.4 million U IM once (if penicillin allergic, patients should be desensitized and treated with penicillin); some experts follow with benzathine penicillin G, 2.4 million U IM administered 1 wk after the initial dose

Management and follow-up

- HIV testing
- If evidence of neurologic or ophthalmic disease, evaluate for neurosyphilis and do slit-lamp examination
- Repeat serology and clinical examination at 6 and 12 mo for HIV-negative persons
- Repeat serology at 28–32 weeks' gestation and at delivery for pregnant women
- If symptoms persist or recur, or if 4-fold increase in RPR or VDRL titer occurs, consider treatment failure or reinfection. Repeat HIV testing, consider LP, and retreat
- If RPR or VDRL titers do not fall 4-fold within 6–12 mo of treatment, conduct additional clinical and serologic follow-up

Late latent syphilis or syphilis of unknown duration

Treatment

- Benzathine penicillin G, 2.4 million U IM every wk, for 3 wk
- If penicillin allergy:[a]
  - Doxycycline, 100 mg PO BID for 4 wk or tetracycline, 500 mg PO QID for 4 wk

Treatment (for pregnant women)

- Benzathine penicillin G, 2.4 million U IM every wk for 3 wk (if penicillin allergic, patients should be desensitized and treated with penicillin)

Management and follow-up

- HIV testing
- Examine CSF before treatment if any of the following are present:
  - Neurologic or ophthalmic signs or symptoms
  - Evidence of active tertiary syphilis (e.g., aortitis or gumma)
  - Treatment failure
- Repeat quantitative VDRL or RPR at 6, 12, and 24 mo. Repeat serology at 28–32 weeks' gestation and at delivery for pregnant women
  - Patients with a normal CSF examination should be retreated for latent syphilis if:
    - Serologic titers increase 4-fold or
    - An initially high titer (≥1:32) fails to fall at least 4-fold within 12–24 mo or
    - Patient develops signs or symptoms consistent with syphilis

Tertiary syphilis (gumma or cardiovascular syphilis without neurosyphilis)

Treatment

- Benzathine penicillin G, 2.4 million U IM weekly for 3 wk
- If penicillin allergy, use treatment for late latent syphilis[a]

Treatment (for pregnant women)

- Benzathine penicillin G, 2.4 million U IM every wk for 3 wk (if penicillin allergic, patients should be desensitized and treated with penicillin)

Management

- HIV testing
- Examine CSF

Neurosyphilis

Treatment

- Aqueous crystalline penicillin G, 3 million to 4 million U IV q4h for 10–14 d; some experts follow with benzathine penicillin G, 2.4 million U IM weekly for 3 wk
- Alternative (if compliance is certain):
  - Procaine penicillin, 2.4 million U IM every day for 10–14 d, plus probenecid, 500 mg PO QID for 10–14 d; some experts follow with benzathine penicillin G, 2.4 million U IM weekly for 3 wk

Management

- HIV testing
- Repeat CSF examination every 6 mo until CSF cell count is normal
- Consider retreatment if cell count has not decreased after 6 mo or if CSF is not normal after 2 yr

Abbreviations: HIV = human immunodeficiency virus; RPR = rapid plasma reagin; VDRL = Venereal Disease Research Laboratory test; LP = lumbar puncture; CSF = cerebrospinal fluid.

[a] HIV-infected, penicillin-allergic patients who receive alternative therapies should be closely monitored. If compliance cannot be ensured, patients should be desensitized and treated with penicillin.

Table 163.2 Treatment of HIV-positive patients with syphilis

Primary and secondary syphilis

Treatment

- Benzathine penicillin G, 2.4 million U IM once
- If penicillin allergy: manage according to recommendations for HIV-negative patients with primary and secondary syphilis (see Table 163.1)

Management

- Clinical and serologic evaluation 3, 6, 9, 12, and 24 mo after therapy
- Examine CSF if RPR or VDRL titers fail to show a 4-fold decrease within 6–12 mo or there is other evidence of treatment failure
  - If CSF normal, retreat with penicillin G, 2.4 million U IM weekly × 3 wk
  - If CSF suggests neurosyphilis, treat for neurosyphilis as in Table 163.1

Early latent syphilis

Manage and treat according to recommendations for HIV-negative patients with primary and secondary syphilis (see Table 163.1). Patients with penicillin allergy whose compliance with therapy or follow-up cannot be ensured should be desensitized and treated with penicillin

Late latent syphilis or latent syphilis of unknown duration

Treatment and management

- Consider CSF examination
  - If CSF normal, give benzathine penicillin G, 2.4 million U IM weekly × 3 wk
    - If penicillin allergy: manage according to recommendations for HIV-negative patients with late latent syphilis or latent syphilis of unknown duration. However, patients with penicillin allergy whose compliance with therapy or follow-up cannot be ensured should be desensitized and treated with penicillin
  - If CSF suggests neurosyphilis, treat for neurosyphilis as in Table 163.1

Management

- Clinical and serologic evaluation 6, 12, 18, and 24 mo after therapy
- Examine CSF and retreat accordingly if:
  - Clinical symptoms develop or RPR or VDRL titers rise 4-fold at any time or RPR or VDRL titer fails to fall 4-fold between 12 and 24 mo

Neurosyphilis

Treatment and management as in Table 163.1

Abbreviations: CSF = cerebrospinal fluid; RPR = rapid plasma reagin; VDRL = Venereal Disease Research Laboratory test; HIV = human immunodeficiency virus.

from 1:64 to 1:16) or seroreversion to a nonreactive non-treponemal test. However, despite appropriate treatment, approximately 20% of patients with early syphilis may remain serofast (indicated by a less than 4-fold decline in non-treponemal titers or persistent low-level titers over time). Serofast patients may warrant subsequent clinical and serologic monitoring; however, whether they need to receive retreatment remains unclear. Patients who have evidence of treatment failure based on recurrent signs or symptoms, or a sustained 4-fold increase in non-treponemal titers should undergo HIV testing and CSF examination, especially when there are symptoms suggestive of neurosyphilis.

For patients with neurosyphilis and evidence of CSF pleocytosis, follow-up CSF examination should be repeated every 6 months after treatment. The CSF white cell count should decrease within 6 months; this may occur more slowly in HIV-infected patients than in HIV-negative persons. Regardless of HIV status, retreatment should be considered if the CSF cell count has not decreased after 6 months or if the CSF parameters do not normalize 2 years after therapy.

NONVENEREAL TREPONEMATOSES

Yaws, pinta, and bejel (endemic syphilis) are caused respectively by *T. pallidum* subsp. *pertenue; Treponema carateum*; and *T. pallidum* subsp. *endemicum*. These diseases, seen mainly in tropical and subtropical regions, are transmitted by direct contact with infected skin lesions and not primarily by sexual contact. Like venereal syphilis, these diseases have self-limited primary and secondary stages, a latent stage, and a late stage with destructive lesions. The causative agents are morphologically indistinguishable from *T. pallidum* subsp. *pallidum*, and the serologic responses they elicit are identical to those of venereal syphilis. Diagnosis can be made by dark-field examination of lesions or serologic testing. Long-acting penicillin G, the treatment of choice, has dramatically decreased the incidence of these diseases in endemic regions.

Yaws occurs in the tropical regions of Africa, Southeast Asia, South America, and Oceania. About 3 to 5 weeks after infection, papules develop, which enlarge, erode, and then spontaneously heal. A generalized secondary eruption of similar lesions occurs weeks to months later,

sometimes associated with osteitis or periostitis. In the late stage, infected persons may develop hyperkeratoses on the palms and soles; plaques, nodules, and ulcers of the skin; and gummatous bone lesions.

Pinta occurs in remote parts of Mexico, Central America, and Colombia. About 7 to 21 days after infection, small, red, pruritic papules develop, which enlarge, become squamous, and merge with other primary lesions. These lesions eventually heal, but residual hypopigmentation persists. Three to 12 months after the appearance of the primary lesions, small scaly papules known as *pintids* appear. These may eventually become brown, gray, or blue and may recur as long as 10 years after initial infection. Depigmented lesions develop in the late stage.

Bejel occurs in Africa and western Asia. Unlike yaws and pinta, bejel is spread not only by direct contact but also by eating and drinking utensils. Primary lesions are seldom seen. Secondary manifestations include mucous patches, condylomata lata, split papules at the angles of the mouth, and lymphadenopathy. Gummatous lesions of the skin, nasopharynx, and bones are common in the late stage.

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164. Lyme disease

Janine Evans

Lyme disease, a systemic illness caused by the spirochete *Borrelia burgdorferi*, is the most common tick-borne disease in the United States. In 2011, 48 states reported 24 364 cases of Lyme disease using the Council of State and Territorial Epidemiologists (CTSE)/Centers for Disease Control and Prevention (CDC) surveillance case definition. Since the original discovery of Lyme arthritis in the mid 1970s the clinical spectrum of Lyme disease has expanded to include a wide variety of organ systems, primarily the skin, joints, nervous system, and heart. Protean symptoms, uncertainty in diagnosis due to lack of definitive testing methods, and public fear of late sequelae of disease often lead to overdiagnosis and overtreatment. Although optimal therapy of some of the clinical features of Lyme disease is unclear, better understanding of the natural history, epidemiology, and pathogenesis of Lyme disease helps in the often confusing and difficult decisions related to diagnosis and treatment.

B. burgdorferi has been isolated from blood, skin, cerebrospinal fluid (CSF) specimens, and (rarely) other specimens from infected patients although, with the exception of skin biopsy specimens, culture of *B. burgdorferi* from sites of infection is a low-yield procedure. *B. burgdorferi* displays phenotypic and genotypic diversity and has been classified into separate genospecies, five of which are pathogenic to humans: *Borrelia burgdorferi sensu stricto*, which includes all strains studied thus far from the United States and some European and Asian strains, and *Borrelia garinii*, *Borrelia afzelii, Borrelia spielmanii*, and *Borrelia bavariensis*, which are found in Europe and Asia. *B. afzelii* seems primarily associated with a chronic skin lesion, acrodermatitis chronica atrophicans, rare in the United States, and *B. garinii* is predominant among CSF isolates.

Lyme disease occurs in three principal foci in the United States: the Northeast, the upper Midwest, and the Pacific Coast. These areas correspond to the distribution of the predominant tick vectors of Lyme disease in the United States, *Ixodes scapularis* in the East and Midwest, and *Ixodes pacificus* in northern California. Lyme disease also occurs widely in Europe, where it is transmitted by the sheep tick, *Ixodes ricinus*, and *Ixodes persulcatus*, the taiga tick. The latter is distributed throughout eastern Europe and Asia.

The largest number of reported cases of Lyme disease in Europe are from Germany, Austria, Slovenia, Sweden, the Czech Republic, and the Baltic states. *I scapularis* have a 3-stage, 2-year life cycle. Transovarial passage of *B. burgdorferi* occurs at a low rate. Ticks become infected with spirochetes by feeding upon a spirochetemic animal, typically small mammals, during larval and nymphal stages. In highly endemic areas from 20% to more than 60% of *I. scapularis* carry *B. burgdorferi*. Humans are only an incidental host of the tick; contact is typically made in areas of underbrush or high grasses, but may occur in well-mown lawns in endemic areas. Lyme disease occurs most commonly during April through July when nymphal *I. scapularis* feed. Animal models show that transmission is unlikely to occur before a minimum of 36 hours of tick attachment and feeding.

CLINICAL MANIFESTATIONS

Clinical features of Lyme disease are typically divided into three general stages termed early localized, early disseminated, and late persistent infection. These stages may overlap, and most patients do not exhibit all stages. Direct invasion of the organism with a resultant vigorous inflammatory reaction has been demonstrated to be responsible for many of the clinical manifestations associated with Lyme disease, so the manifestations respond to antibiotic therapy. Some features, such as late neurologic deficits and chronic arthritis, may respond poorly to treatment. It is not absolutely clear that live organisms are responsible for these later symptoms.

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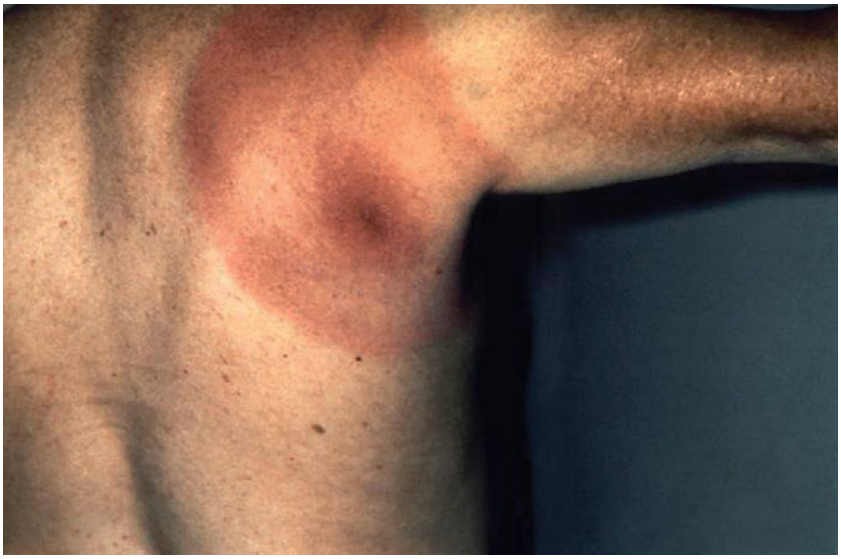

Figure 164.1 Classic erythema migrans lesion.

Seroconversion can occur in asymptomatic individuals, but is rare with strict surveillance.

Early localized disease

Erythema migrans (EM), the hallmark of Lyme disease, begins at the site of a deer tick bite after 3 to 32 days (Figures 164.1 and 164.2). It is reported by 60% to 80% of patients, appearing as a centrifugally expanding erythematous macule or papule, often with central clearing. The thigh, groin, and axilla are common sites. The lesion may be warm, pruritic, and painful, but is often asymptomatic and easily missed if out of sight. Occasionally, these lesions may develop blistering or scabbing in the center, remain an even, intense red without clearing, or develop a bluish discoloration. Spirochetes are present in the EM lesion and can be readily cultured from the expanding edge. Mild musculoskeletal flu-like symptoms such as a low-grade fever, chills, malaise, headache, fatigue, arthralgias, and myalgias may accompany EM lesions. Theoretically such symptoms can occur without dissemination of the organism, via local generation of cytokines. Untreated EM resolves after several weeks and treated lesions clear within several days.

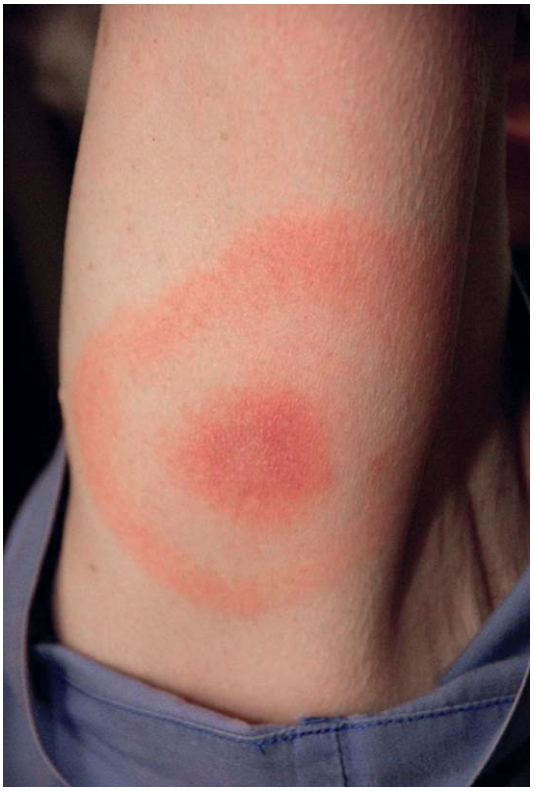

Figure 164.2. Erythema migrans lesion.

Early disseminated

In some patients the spirochete disseminates hematogenously to multiple sites causing characteristic clinical features. Secondary annular lesions, sites of metastatic foci of *Borrelia* in the skin, develop within days of onset of EM in about half of US patients. They are similar in appearance to EM, but are generally smaller, migrate

less, and lack indurated centers. In addition to musculoskeletal flu-like symptoms, mild hepatitis, splenomegaly, sore throat, nonproductive cough, testicular swelling, conjunctivitis, and regional and generalized lymphadenopathy may sometimes occur during early stages.

Diagnosis of early localized and early disseminated Lyme disease is based on clinical presentation, because serologic confirmation is often lacking and culture is not readily available. EM is diagnostic of Lyme disease although atypical lesions and rashes mimicking EM may be confusing. A history of a tick bite and residence or travel in an endemic area should be sought in patients presenting with rashes compatible with EM or a flu-like illness in summer. Specific immunoglobulin (Ig)M antibody responses against *B. burgdorferi* develop 2 to 6 weeks after the onset of EM. Immunoglobulin (Ig)G antibody levels appear approximately 6 weeks after disease onset but may not peak until months or even years into the illness. The highest titers occur during arthritis. Antibodies are typically detected using indirect immunofluorescence, enzyme-linked immunosorbant assay (ELISA), and immunoblotting (Western blot). Antibody responses may persist for months to years after successful eradication of infection. Two-tier testing is recommended, with ELISA screening done first and if positive an immunoblot performed.

Late disease

Late manifestations of Lyme disease typically occur months to years after the initial infection. In the United States, arthritis is the dominant feature of late Lyme disease, reported in approximately 60% of untreated individuals. Less often, individuals develop late chronic neurologic disease. Another late finding (years) associated with this infection is a chronic skin lesion, acrodermatitis chronica atrophicans, well known in Europe but rare in the United States. These late manifestations are discussed below.

THERAPY

Early Lyme disease

The symptoms of early Lyme disease resolve spontaneously in most cases; therefore, the goals of therapy for early localized and mild early disseminated Lyme disease are to shorten the duration of symptoms and reduce the risk of developing serious late manifestations of infection. Treatment of these stages with oral antibiotics is adequate in the majority of patients (see Table 164.1). In patients with acute disseminated Lyme disease but without meningitis, oral doxycycline appears to be equally effective as parenteral ceftriaxone in preventing the late manifestations of disease. Initial studies of treatment for early Lyme disease reported therapy with phenoxymethyl penicillin, erythromycin, and tetracycline, in doses of 250 mg four times a day for 10 to 20 days, shortened the duration of symptoms of early Lyme disease. Phenoxymethyl penicillin and tetracycline were superior to erythromycin in preventing serious late manifestations of disease. Subsequent clinical trials have proven amoxicillin and doxycycline to be equally efficacious. Amoxicillin has largely replaced use of penicillin because of greater in vitro activity against *B. burgdorferi*. It is the preferred antibiotic choice in children under the age of 8 years. Concomitant use of probenecid has not been definitively shown to improve clinical outcome and is associated with a higher incidence of side effects. Doxycycline is usually selected over tetracycline because of its twice-daily dose schedule, increased gastrointestinal absorption and tolerability, and greater central nervous system (CNS) penetration. Doxycycline is effective in treating *Anaplasma phagocytophilum* (formerly known as *Ehrlichia phagocytophila*), an organism also transmitted by *I. scapularis* ticks; amoxicillin is not. Cefuroxime axetil, an oral second-generation cephalosporin, has been shown to be about as effective as amoxicillin and doxycycline in treating early Lyme disease; azithromycin, an azilide analog of erythromycin, somewhat less so. Macrolide antibiotics are not recommended as first-line therapy for early Lyme disease. Long-term follow-up of patients treated during early stages of Lyme disease support the current dosing regimens. Patients who received a 14- to 21-day course of a recommended antibiotic rarely developed late manifestations of illness. Recent studies have indicated that a 10-day course of doxycycline is adequate therapy for EM. Jarisch–Herxheimer-like reactions, an increased discomfort in skin lesions and temperature elevation occurring within hours after the start of antibiotic treatment, have been encountered in 14% of patients treated for early Lyme disease. They typically occur within 2 to 4 hours of starting therapy, are more common in severe disease, and are presumably due to rapid killing of a large number of spirochetes.

Minor symptoms including arthralgia, fatigue, headaches, and transient facial palsy

Table 164.1 Treatment guidelines

Antibiotic regimen	Comments
Erythema migrans	
Amoxicillin, 500 mg 3 times daily for 14–21 d	Pediatric dose is 25–50 mg/kg/d three times daily
Doxycycline (Vibramycin), 100 mg twice daily for 10–21 d	Also effective against *Anaplasma phagocytophium*; not recommended for children under 8 years of age, pregnant or lactating women
Cefuroxime axetil (Ceftin), 500 mg twice daily for 14–21 d	Pediatric dose 30 mg/kg/d twice daily
Azithromycin (Zithromax), 500 mg daily for 7–10 d	Not recommended as first-line therapy; less effective than other regimens
Early disseminated disease (without neurologic, cardiac, or joint involvement)	
Initial treatment is the same as for erythema migrans except duration of treatment may be extended to 21–28 d	
Neuroborreliosis	
Isolated seventh nerve palsy	
Initial treatment is the same as for erythema migrans except duration of treatment is 21–28 d. The need for cerebrospinal fluid examination remains controversial	
All other neurologic manifestations (including meningitis, radiculoneuritis, peripheral neuropathy, encephalomyelitis, chronic encephalopathy)	
Ceftriaxone (Rocephin), 2 g daily for 14–30 d	30-d regimen associated with fewer relapses in patients with chronic encephalopathy
Penicillin G, 20 million units daily for 14–28 d	Pediatric dose 200 000–400 000 units/kg/d every 4 h
Cefotaxime sodium (Claforan), 2 g every 8 h	Pediatric dose 150–200 mg/kg/d in 3–4 divided doses for 14–28 d
Doxycycline, 100 mg twice daily (oral or intravenous) for 14–28 d	No published experience in the United States
Carditis	
Doxycycline, 100 mg orally twice daily for 21 d	For first degree heart block, PR interval <0.3 s
Amoxicillin, 500 mg three times daily for 21 d	For first degree heart block, PR interval <0.3 s
Ceftriaxone, 2 g daily for 14–21 d	Optimal duration of therapy is unknown
Penicillin G, 20 million units daily for 14–30 d	Optimal duration of therapy is unknown, given in divided doses every 4 h
Arthritis	
Amoxicillin 500 mg four times daily for 30–60 d	Oral regimens should be limited to patients without evidence of neurologic involvement. Oral treatment may be extended for 60 d if no response to 30-d course
Doxycycline 100 mg two times daily for 30–60 d	
Cefuroxime axetil, 500 mg twice daily for 30–60 d	For patients with doxycycline and penicillin allergy
Ceftriaxone, 2 g daily for 14–30 d	
Lyme disease in pregnancy	
Amoxicillin, 500 mg three times daily for 21 d	For early localized disease only
Ceftriaxone, 2 g daily for 14–28 d	
Penicillin G, 20 million units daily for 14–28 d	Given in divided doses every 4 h
Asymptomatic tick bite	
No treatment or single dose of 200 mg doxycycline	For pregnant women, a 10-d course of amoxicillin may be considered
Asymptomatic seroconversion	No treatment necessary

are common following treatment and generally resolve over a 6-month period. Patients with disseminated disease are most likely to experience persistent symptoms. These symptoms may be due to retained antigen rather than due to ongoing infection with *B. burgdorferi*, since longer courses of antibiotics have not been shown to shorten their duration. Prolonged courses of antibiotics should be reserved for those patients with evidence of persistent infection with *B. burgdorferi*.

Lyme carditis

Cardiac involvement occurs in up to 10% of untreated patients. Transient and varying degrees of atrioventricular block several weeks to months after a tick bite are the most common manifestations. Other features are pericarditis, myocarditis, ventricular tachycardia, and on rare occasions, a dilated cardiomyopathy; valvular disease is not seen. Carditis is typically mild and self limited although patients may present quite dramatically

in complete heart block, and some require the insertion of a temporary pacemaker. In most cases, carditis resolves completely, even without treatment with antibiotics. Studies examining endomyocardial biopsy specimens from patients with Lyme carditis have indicated that direct invasion of *B. burgdorferi* into myocardium and an associated inflammatory reaction are responsible for the clinical events. Although optimal treatment of carditis is unknown, oral therapy for mild forms of cardiac involvement is usually sufficient. Intravenous antibiotics and cardiac monitoring are recommended for patients with varying, high-degree heart block and more serious cardiac involvement. The benefit of concomitant use of aspirin or prednisone and antibiotics in treating patients with Lyme carditis is uncertain. Despite the generally benign course of Lyme carditis, several cases of permanent heart block have been reported, presumably caused by a vigorous inflammatory response. Short courses of prednisone may be considered in patients with prolonged dense heart block despite adequate antibiotic therapy.

Dilated cardiomyopathy is a rare complication of Lyme disease reported in Europe but not yet in the United States. The majority of the patients were from endemic areas for Lyme disease, had other clinical features of disease, and were seropositive for anti-*B. burgdorferi* antibodies. Their myopathy was cured by antibiotic treatment.

Early neurologic disease

Early neurologic involvement occurs in 15% to 20% of untreated patients and appears within 2 to 8 weeks after the onset of disease. Manifestations include cranial nerve palsies, meningitis or meningoencephalitis, and peripheral neuritis or radiculoneuritis, often appearing in combination. Unilateral or bilateral seventh nerve palsies are the most common neurologic abnormalities. Presenting symptoms depend upon the area of the nervous system involved: patients with meningitis present with fever, headache, and a stiff neck; those with Bannwarth's syndrome (primarily in Europe) develop severe and migrating radicular pain lasting weeks to several months; and those with encephalitis have concentration deficits, emotional lability, and fatigue. In patients with early CNS involvement analysis of CSF typically reveals a lymphocytic pleocytosis. Specific antibodies against *B. burgdorferi* may also be present and concentrated in the CSF relative to the serum concentration; they are useful to confirm disease.

Intravenous antibiotics are recommended for all cases of neuroborreliosis except isolated seventh nerve palsy. Patients presenting with a Bell's-like palsy who have features that suggest possible CNS involvement, such as high fever, headache, or stiff neck, should undergo a lumbar puncture looking for evidence of more extensive disease. The most experience in the treatment of CNS Lyme disease has been with aqueous penicillin and third-generation cephalosporins. Although optimal duration of therapy is unknown, it is recommended that patients be treated for two to four weeks. Ceftriaxone, in doses of 1 to 2 g/day, is the agent of choice because of better CNS penetration and ease of administration. Patients with persistent symptoms after recommended antibiotic therapy pose a particular management problem. It is often unclear whether these symptoms are due to resolving inflammation or ongoing infection. Meningitis and sensory symptoms usually resolve within days to weeks; other features may take months to improve. In most cases it is not necessary to continue antibiotic therapy until complete recovery.

Late manifestations

ARTHRITIS

Arthritis is the dominant feature of late Lyme disease, occurring in up to 60% of untreated patients days to years after initial infection (mean of 6 months). The initial pattern of involvement may be migratory arthralgias (early) followed in 60% of patients by intermittent attacks of arthritis lasting from days to months. Large joints, particularly the knee, are most commonly involved. Swelling is often prominent, with large effusions and Baker's cysts. Serologic testing in patients presenting with arthritis is positive in almost all cases.

Lyme arthritis has been treated successfully with oral and intravenous antibiotics. In early studies examining response to intravenous benzathine penicillin, 2.4 million units intramuscularly weekly for 3 weeks, 7 of 20 patients responded compared with 0 out of 20 in the control group. Intravenous ceftriaxone 2 to 4 g daily for 2 to 4 weeks has been thought to be superior to benzathine penicillin. Oral regimens using doxycycline, 100 mg twice a day for 4 weeks, and amoxicillin plus probenecid, 500 mg of each orally four times a day for 4 weeks, have reported success in 18 of 20 patients and 16 of 18 patients, respectively. Response to antibiotics is typically excellent but effusions may take months to

resolve completely. An additional 4 weeks of oral antibiotic therapy has been recommended for patients with persistent arthritis following initial 4-week treatment.

A small subgroup of Lyme arthritis patients develop a chronic, potentially erosive arthritis unresponsive to antibiotics. These patients often have major histocompatability class II gene products, HLA DR4, accompanied by strong serum IgG responses to *Borrelia* outer surface proteins A or B (OspA or OspB). Repeated courses of antibiotics have not been shown to improve clinical outcome. Treatment with anti-inflammatory medications and intra-articular steroid injections can be helpful in reducing joint swelling. Surgical synovectomy has cured a number of such patients. Resolution of the arthritis eventually occurs; in some patients it may take up to 3 to 5 years.

LATE NEUROLOGIC LYME DISEASE

Chronic neurologic syndromes, which are relatively uncommon, may occur months to years after initial infection. Cognitive dysfunction, affective changes, seizures, ataxia, peripheral neuropathies, and chronic fatigue have all been reported. The most common late-stage neurologic syndrome reported in the United States, called Lyme encephalopathy, is characterized by subtle cognitive impairment. Because these complaints are often nonspecific and may be associated with post-Lyme syndromes, it is important to look for and document evidence of ongoing *B. burgdorferi* infection. Lymphocytic pleocytosis is uncommon in late neurologic disease, but increased intrathecal *B. burgdorferi*-specific antibodies may well be present. Careful evaluation with neuropsychological testing can help to distinguish cognitive abnormalities in Lyme disease from those associated with chronic fatigue states and depression. Chronic neurologic dysfunction usually improves with antibiotics but may not completely reverse. Late neurologic manifestations of Lyme disease are treated with intravenous antibiotics. Agents with demonstrated efficacy are aqueous penicillin and third-generation cephalosporins. Doxycyline, both oral and intravenous forms, have been reported to be successful in treating late CNS Lyme disease in Europe.

OCULAR DISEASE

Ocular lesions in Lyme disease are rare, but have involved every portion of the eye and vary depending on the stage of the disease. The most common ophthalmic presentations in early disease include conjunctivitis, photophobia, and neuro-ophthalmologic manifestations due to cranial nerve palsies. The incidence of seventh nerve palsies is similar in Europe and the United States. The most severe ocular manifestations occur in late stages; they include episcleritis, symblepharon, keratitis, iritis, choroiditis, panuveitis, and retinal vasculitis. Serologic testing in these patients is typically positive.

Experience treating late ocular lesions in Lyme disease is scanty. The most success has been with the use of intravenous ceftriaxone in doses of 2 to 4 g daily for 10 to 14 days.

PREGNANCY

Intrauterine transmission of *B. burgdorferi* is uncommon, usually occurring in cases of obvious disseminated infection during pregnancy. No uniform pattern of congenital anomaly has been reported. Prenatal exposure to Lyme disease has not been found to be associated with an increased risk of adverse pregnancy outcome. Optimal treatment of the pregnant patient with Lyme disease is unknown, but the recommended regimens have not been associated with adverse outcomes. Oral antibiotics for early localized disease is sufficient, and intravenous antibiotics are recommended for patients with symptoms suggesting disseminated disease.

TICK BITES

The risk of infection from a deer tick bite in a Lyme disease endemic area is low. In mice, infected ticks have been attached for over a 36-hour period before significant risk of developing Lyme disease occurred. In a controlled double-blind study in patients with tick bites, no patient asymptomatically seroconverted, no treated patient developed EM, and the 2 of 182 untreated patients who did develop EM were successfully treated with oral antibiotics. These results support marking and watching a tick bite, and should EM develop, treating it early, when antibiotics are most effective. A single dose of doxycycline has been shown to be effective in reducing the development of Lyme disease. The Infectious Diseases Society of America (IDSA) guidelines recommend offering the single-dose doxycycline if the attached tick can be reliably identified as an adult or nymphal *I. scapularis* tick, it is estimated to have been attached for >36 hours, prophylaxis can be started within 72 hours after tick detachment, and the local rate of infection of these ticks

with *B. burgdorferi* is greater than 20%. Doxycycline prophylaxis for children under 8 years is not recommended.

SEROPOSITIVE PATIENT WITH NONSPECIFIC SYMPTOMS

Patients with nonspecific symptoms such as myalgias, arthralgias, concentration difficulties, and fatigue are frequently tested for Lyme disease. Some patients, especially those from endemic areas, test positively and are treated for presumed Lyme disease, often without improvement in their symptoms. In several studies over 50% of patients reporting to Lyme disease clinics did not have evidence of Lyme disease, and the reason for a lack of response to antibiotics was an incorrect diagnosis. Objective clinical evidence in support of the diagnosis of Lyme disease should be sought prior to initiating antibiotics, treatment should be given for the recommended duration and then discontinued, and the patient observed for resolution of symptoms.

POST-LYME DISEASE SYNDROME

Some patients continue to have subjective symptoms after completion of recommended courses of antibiotics for Lyme disease. Symptoms typically include arthalgias, myalgias, fatigue, and neurocognitive difficulties. A study of patients treated for EM reported that approximately 5% to 15% of patients experienced subjective symptoms when evaluated 6 to 12 months after treatment. Such symptoms may persist for 5 or more years after treatment. This postinfectious syndrome does not appear to be related to persistent infection with *B. burgdorferi*. In a study of patients with post-Lyme disease syndrome there were no significant outcome differences between the groups who received either intravenous ceftriaxone for 30 days followed by oral doxycycline for 60 days and those that received placebo. The IDSA guidelines do not recommend antibiotic therapy for patients with chronic (>6 months) subjective symptoms after recommended treatment regimens for Lyme disease.

PREVENTION OF LYME DISEASE

Recommended personal protective measures against tick bites include wearing light-colored clothing, long-sleeve shirts, and long pants; tucking pant legs into socks; using a tick repellent on clothing and exposed skin; and performing regular body checks for ticks, strategies that require significant self-motivation. Environmental strategies include the application of acaricides onto vegetation where the ticks live, acaricides delivered directly to tick hosts to kill ticks on the animals, and excluding deer from areas. The last is not practical in most environments.

Public interest in human and veterinary vaccines prompted researchers to develop a safe and effective vaccine for the prevention of Lyme disease. The results of two large safety and efficacy trials using recombinant OspA preparations reported the vaccine to be safe and effective in preventing Lyme disease in most people. LYMErix^{tm} was approved by the US Food and Drug Administration (FDA) for use in individuals aged 15 and older in 1999. The vaccine manufacturer discontinued production in 2002, citing insufficient consumer demand. Protection provided by this vaccine diminishes over time. Individuals that received the Lyme disease vaccine prior to 2002 are probably no longer protected against Lyme disease.

SUMMARY

Antibiotic regimens are recommended according to results of clinical trials and evolving clinical judgments, and depend upon the stage of infection and the organ system involved. Successful eradication of the infecting organism, *B. burgdorferi*, appears to occur in the majority of patients with Lyme disease using these treatment guidelines. Patients with persistent symptoms following antibiotic therapy, particularly those with previous evidence of disseminated disease, pose a difficult management problem. Most persistent symptoms are likely due to retained antigens and not the result of persistent infection or to noninfectious sequelae such as fibromyalgia. In the former patients, resolution of symptoms occurs over the course of weeks to months and does not require prolonged courses of antibiotics; in the latter, treatment is that of the associated syndrome. Rarely, persistent or recurrent symptoms are due to continued or recurrent infection and require additional courses of antibiotics. Such patients require careful diagnostic evaluation to determine the need for additional treatment.

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165. Relapsing fever borreliosis

Sally J. Cutler

HISTORY

The relapsing fever spirochetes comprise a number of different species (Table 165.1) with many transmitted by specific tick species. *Borrelia recurrentis* is the notable exception in that it is transmitted by clothing lice.

CLINICAL PRESENTATION

The chief sign is that of fever, often accompanied by chills, headaches, arthralgia, myalgia, and tachycardia. Other signs may include jaundice, petecheal rash, conjunctivitis, nausea, hepatosplenomegaly, and epistaxis. Infection with *Borrelia*

Table 165.1 Characteristics of relapsing fever borrelliae

Organism name	Arthropod vector/reservoir	Vertebrate reservoirs	Clinical infection	Geographic region
B. recurrentis	*Pediculus humanus humanus*	Man	LBRF – human	Africa (formerly worldwide)
B. baltazardii	Unknown	Unknown	TBRF – human	Iran
B. crocidurae	*Ornithodoros sonrai*	Rodents	TBRF – human	West Africa
B. duttonii	*Ornithodoros moubata*	Man	TBRF – human	Africa (Central, Eastern)
B. hermsii	*Ornithodoros hermsi*	Rodents	TBRF – human; canine	Canada, Western USA
B. hispanica	*Ornithodoros marocanus; Ornithodoros occidentalis; Ornithodoros kairouanensis* (formerly *Ornithodoros erraticus*[a])	Rodents	TBRF – human	Algeria, Morocco, Portugal, Spain, Tunisia
B. latyschewii	*Ornithodoros tartakovskyi*	Rodents; reptiles	TBRF – human	Central Asia, Iran, Iraq
B. mazzottii	*Ornithodoros talaje*	Armadillos; rodents	TBRF – human	Southern USA, Mexico, Guatemala
B. merionesi	*Ornithodoros costalis* *Ornithodoros merionesi*	Rodents	Unknown	North Africa
B. microti	*Ornithodoros erraticus*[b]			Africa, Iran
B. parkeri	*Ornithodoros parkeri*	Rodents	TBRF – human	Western USA
B. persica	*Ornithodoros tholozani*	Rodents; bats	TBRF – human; cat	Asia, Middle East
B. turicatae	*Ornithodoros turicata*	Rodents	TBRF – human; canine; birds	USA, Mexico
B. venezuelensis	*Ornithodoros rudis*	Rodents	TBRF – human	Central and South America

[a] *Ornithodoros erraticus* represented a complex. Recent taxonomic molecular studies redressed the phylogeny suggesting that *O. erraticus sensu stricto* is not an efficient vector for *Borrelia*.

[b] Molecular confirmation of *O. erraticus* identity unavailable at time of writing.

Abbreviations: LBRF = louse-borne relapsing fever; TBRF = tick-borne relapsing fever.

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Table 165.2 Treatment of relapsing fever borreliosis

Antibiotic	Dosage used	Duration	Comments
Penicillin	400 000–600 000 IU daily	7 to 14 d	Single dose can be curative for LBRF CNS involvement
Tetracycline	200–250 mg BID to 500 mg QID	7 to 14 d	Single dose can be curative for LBRF
Doxycycline	200-250 mg 4 mg/kg/d	7 to 14 d	Can be used as prophylaxis (200 mg d 1, then 100 mg daily 4 d post exposure)
Erythromycin	500 mg QID (50 mg/kg children)	7 to 14 d	During pregnancy or children
Chloramphenicol	500 mg QID (12.5 mg/kg children)	7 to 14 d	During pregnancy or children
Ceftriaxone	2 g daily	7 to 14 d	CNS involvement

Abbreviation: CNS = central nervous system.

duttonii has been associated with significant perinatal mortality in endemic regions such as Tanzania.

Although eventually eliminated by the adaptive immune response, repeat infections can occur in a previously infected individual.

TREATMENT (TABLE 165.2)

Cases are usually managed with penicillin, doxycycline, or tetracycline treatment. Some prefer penicillin as it is believed that this makes Jarisch–Herxheimer reactions (JHR) less likely. Less frequently, cephalosporins, erythromycin, and chloramphenicol have been used.

JHR

The JHR was first described by Adolf Jarisch in 1895 and later by Karl Herxheimer in 1902, in relation to another spirochetal infection, syphilis, but this also occurs in approximately 5% of relapsing fever patients upon treatment. Patients may show an exacerbation of symptoms or "therapeutic shock" during the initial 24 hours post commencing treatment. The JHR is mediated by a release of pyrogenic cytokines (including tumor necrosis factor-α [TNF-α], interleukin [IL]-6, and IL-8) and is treated symptomatically.

TRANSMISSION AND PATHOGENESIS

Transmission of tick-borne relapsing fever (TBRF) occurs during the feeding of *Ornithodoros* soft ticks (up to 20–30 minutes), generally whilst their host is sleeping. The spirochetes may be present within the tick salivary glands, coxal fluid, and feces, facilitating transmission to their vertebrate host. Transovarial transmission occurs for some TBRF borreliae.

Unlike TBRF, in louse-borne relapsing fever (LBRF) the borreliae within the louse vector penetrate the louse's gut epithelium where they can multiply in the louse hemolymph and are also able to be excreted in louse feces, but do not undergo transovarial transmission. Human transmission occurs through crushing lice or their feces into skin abrasions often through scratching.

Once the human is infected, spirochetes multiply in the blood, sometimes to levels of up to $100\,000/mm^3$. This spirochetemia evokes the typical febrile response after which this infection is named. The induced antibody response clears the bloodborne infection; however, the spirochetes soon re-emerge having undergone antigenic variation. A new wave of infection follows that again is eventually controlled through the host's antibody response. Clinically, up to 4 to 5 febrile episodes can occur in LBRF, whilst up to 13 relapses have been recorded for TBRF. Persistence within the human host is a result of a complex interplay of antigenic variation, complement evasion strategies, erythrocyte rosetting, and potentially other mechanisms.

The spirochetes show varying neurotropic potential. This can promote cerebral hemorrhage, for example with *B. recurrentis*. They cross the placenta with associated fetal loss through abortion or congenital infection, particularly *B. duttonii*. Myocarditis and hepatic failure may complicate infection with some of the more virulent members of the relapsing fever borreliae (*B. recurrentis/B. duttonii*), where mortality can reach 10% in untreated cases.

LABORATORY DIAGNOSIS

Microscopy has been the primary diagnostic approach, with demonstration of the spirochetes in blood with Wright's or Giemsa stains, silver staining, or the use of dark-field microscopy for observing motile spirochetes (Figure 165.1). Whilst these methods can detect the causative species, sensitivity is poor, particularly for some species such as *Borrelia crocidurae* where the blood burden is lower than for example *B. recurrentis*. This is further complicated by the need to collect blood during febrile episodes. It is not possible to differentiate species using microscopy.

Animal inoculation can recover and identify cultivable strains. Cultivation can also be achieved from clinical samples into specialized media (such as BSKII) but this is technically demanding. This has been largely superseded by molecular identification approaches, and molecular diagnostics are currently the mainstay for both detection and typing of relapsing fever borreliae.

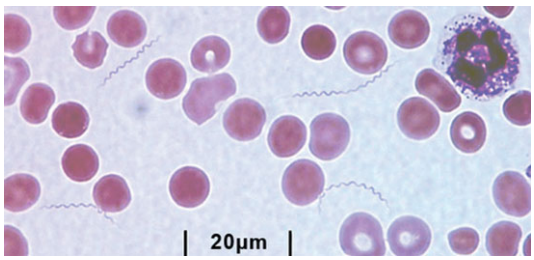

Figure 165.1. Motile spirochetes.

CURRENT EPIDEMIOLOGY

The relapsing fever spirochetes have been divided into those in the Old World and New; however, with improving phylogenetic tools, this division now appears artificial. The prevalence of tick-borne strains correlates with specific regions, particularly African TBRF, probably resulting from climatic conditions conducive for its tick vector. This has not been the case for louse-borne *B. recurrentis*, which was formerly worldwide, but now is restricted to areas where clothing lice persist.

Figure 165.2 depicts the global location of relapsing fever.

It is increasingly apparent that the burden of relapsing fever infections in endemic regions is underdiagnosed. Recent reports from Senegal have suggested that this is the cause of some 13% of fevers presenting at local dispensaries, representing an alarming 11 to 25 cases per 100 person-years. Studies of febrile patients in Morocco have suggested that 20.5% were TBRF cases. Although not at these levels, cases are more frequently being detected in the USA.

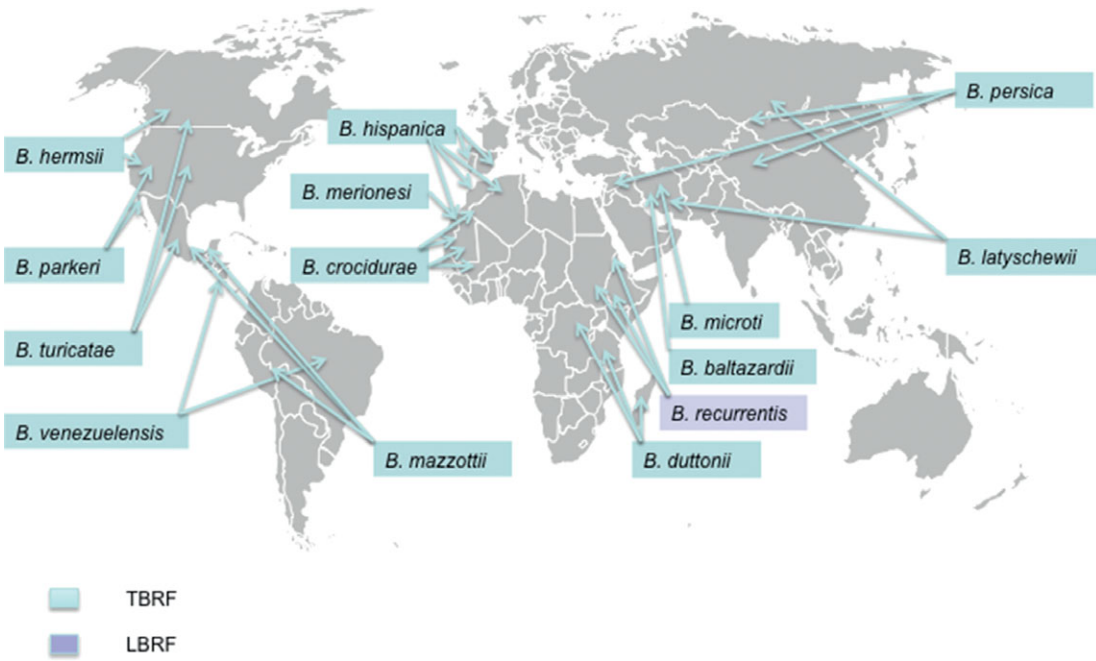

Figure 165.2. Global location of relapsing fever.

Epidemiology of LBRF has changed drastically with the reduced level of infestation with clothing lice. The infection remains in areas of extreme poverty such as Ethiopia, sometimes spilling into adjacent regions, such as an outbreak in the Darfur region of Sudan. During this outbreak between 1999 and 2000 some 20 000 cases occurred with a 10% mortality rate.

RESERVOIRS OF INFECTION

The majority of relapsing fever spirochetes are zoonoses with vertebrate reservoir species (Table 165.1). In the majority of cases, these reservoir species are rodents; however, bats, birds, and reptiles may also have a reservoir role. The notable exceptions are *B. recurrentis* and *B. duttonii*, both of which have an exclusive human reservoir. Many also consider the tick vector a reservoir of infection for TBRF, facilitated by the impressive longevity of these ticks that can survive for many years with their infecting spirochetes.

RISK GROUPS

Both LBRF and TBRF have their greatest burden among those living in extreme poverty.

Occupational contact with tick-infested environments has resulted in clusters of infection, particularly among military personnel who have used caves during training activities, with a resulting clinical burden of up to 6.4 cases/100 000 in Israel. Similarly, conservation workers are at risk. Imported cases have been encountered through migration and tourism, typically in rural regions where intermittently used holiday accommodation has provided refuge for reservoir hosts and their associated tick vectors.

CONTROL AND PREVENTION

Relapsing fever spirochetes remain susceptible to penicillin, tetracycline/doxycycline, chloramphenicol, ceftriaxone, and erythromycin (Table 165.2). Wide use of antimicrobials coupled with improvements in living conditions has reduced the incidence of infection. This is not so apparent for the tick-borne forms of disease that persist in their longer-lived tick vector/reservoirs and through zoonotic vertebrate reservoir species. The burden of TBRF among subsistence agro-pastoralist communities in developing nations remains substantial. Use of acaricides has met with some success, but costs are prohibitive. If contact is unavoidable, doxycycline prophylaxis has been used for short-term prevention.

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166. Leptospirosis

Christopher D. Huston

Leptospirosis is an infection with spirochetes from the genus *Leptospira*. Infections are most commonly caused by *Leptospira interrogans*, of which more than 200 serovars infect humans. People become infected by exposure to animal urine or urine-contaminated surface water. *Leptospira* penetrate intact mucous membranes and abraded skin and disseminate widely via the bloodstream. Symptoms develop 7 to 12 days after exposure. Most patients have an abrupt onset of a self-limited, 4- to 7-day anicteric illness characterized by fever, headache, myalgias, chills, cough, chest pain, neck stiffness, and/or prostration (Table 166.1). An estimated 10% of patients will present with jaundice, hemorrhage, renal failure, and/or neurologic dysfunction (Weil's disease). The major clinical manifestations of disease result from infection of capillary endothelial cells leading to vasculitis (Table 166.2).

Classically, leptospirosis has been considered a biphasic illness. However, many patients with mild disease will not have symptoms of the secondary "immune" phase of illness, and patients with very severe disease will have a relentless progression from onset of illness to jaundice, renal failure, hemorrhage, hypotension, and coma. The illness is biphasic in about half of patients, with relapse occuring approximately 1 week after resolution of the initial febrile illness. A late complication is anterior uveitis, seen in up to 10% of patients months to years after convalescence. Leptospirosis in pregnancy is associated with spontaneous abortion, but it is not known to increase the rate of congenital anomalies.

Case-fatality rates for leptospirosis are less than 1%, and the illness is usually self-limited. Liver and renal dysfunction are reversible, with return to normal function over 1 to 2 months. The mortality rate for icteric disease has been reported in different studies to be 2.4% to 11.3%, with deaths resulting from renal failure, gastrointestinal and pulmonary hemorrhage, and the adult respiratory distress syndrome.

Table 166.1 Symptoms and signs of leptospirosis

Abrupt onset (70%–100%)
Fever, chills, rigors (98%)
Headache (93%–97%)
Myalgias, muscle tenderness (40%–80%)
Vomiting, diarrhea, abdominal pain (30%–95%)
Conjunctival suffusion (33%–100%)
Hepatomegaly (5%–22%; 80% of icteric cases)
Splenomegaly (5%–25%)
Meningeal signs (12%–44%)
Mental status changes (7%–21%)
Oliguria (10%)
Cough (10%–20%)
Chest pain (11%)
Skin rash (9%–18%)
Jaundice (1.5%–6%)

DIAGNOSIS

Leptospirosis most often manifests as a nonspecific flu-like illness, so recognition of epidemiologic risk factors is essential (Table 166.3). Occupational exposure to animal urine (e.g., veterinarians) has classically been considered the chief epidemiologic risk, but recent outbreaks highlight the importance of recreational water use (e.g.,

Table 166.2 Pathogenesis of leptospirosis

Infectious vasculitis with damage to capillary endothelial cells resulting in the following:
Renal tubular dysfunction
Hepatocellular dysfunction
Pulmonary hemorrhage
Muscle focal necrosis
Coronary arteritis
Extravascular fluid shifts

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Table 166.3 Epidemiology of leptospirosis

Leptospira are excreted in animal urine and survive in the environment for up to 6 mo
Disease is common in the tropics, especially in urban slums
Incubation period ranges from days up to 4 wk after exposure (mean 10–12 d)
Recreational exposures include windsurfing, kayaking, swimming, and adventure tourism
Occupational exposures: New Zealand dairy farmers (incidence of 1.1 infections/10 person-years), Glasgow sewer workers (3.7/10 person-years), and US Army soldiers undergoing jungle warfare training in Panama (4.1/10 person-years) Veterinarians, abattoir workers, and others with exposure to rat urine/bites (homeless people, rodent control workers)
Outbreaks seen after floods

Table 166.4 Laboratory findings of leptospirosis

Renal failure – acute interstitial nephritis (15%–70%)
Jaundice with only 2- to 3-fold elevations in transaminases and alkaline phosphatases, conjugated bilirubinemia (2%–60%)
Myositis with elevated creatine phosphokinase (MM band) (20%–62%)
Thrombocytopenia (50%)
Cerebrospinal fluid pleiocytosis (80%–90%): $\leq$300 cells/mm^3, lymphocyte predominance
Abnormal chest radiographs (20%–70%) Patchy alveolar pattern in lower lobes with or without interstitial/alveolar hemorrhage
Electrocardiogram abnormalities: sinus tachycardia, myocarditis, first-degree atrioventricular block
ELISA for IgM antibodies most sensitive test in first week of illness, but limited specificity
Microagglutination test (MAT) for leptospirosis antibodies positive within first 1–2 wk of illness

reservoirs) and risks associated with travel, especially to Southeast Asia or for adventure tourism. Epidemiologic risks should be sought in patients with a flu-like illness, respiratory illness, aseptic meningitis, acute hepatitis, acute renal failure, pericarditis, atrioventricular block, or anterior uveitis. In some developing countries, leptospirosis is more common than hepatitis A as a cause of acute hepatitis. The prominent myalgias, conjunctival suffusion, elevated serum creatine phosphokinase, and the relatively mild (2- to 3-fold) elevations in transaminases seen in leptospirosis may help to distinguish icteric leptospirosis from acute viral hepatitis (Table 166.4). Although prolonged incubation ($\geq$1 week) may be required, it is sometimes possible to grow the organism from blood or cerebrospinal fluid collected during the first 7 to 10 days of illness. Urine cultures may also be intermittently positive for up to 3 months. However, the diagnosis is usually made retrospectively by a 4-fold rise in IgG antibody titer as measured by the microscopic agglutination test (MAT). Serovar-specific agglutinins appear within the first 1 to 2 weeks of illness and peak at 3 to 4 weeks. The sensitivities of culture and the MAT are low, and, although not species or serovar specific, enzyme-linked immunosorbent assay (ELISA) kits to detect immunoglobulin M (IgM) antibodies enable diagnosis during the first week of illness.

Table 166.5 Treatment of leptospirosis

Outpatient treatment: doxycycline, 100 mg PO BID for 7 d in adults
Severe infection requiring hospitalization: penicillin, 6 million U IV qd or ceftriaxone, 1 g IV/IM qd
Chemoprophylaxis: 200 mg doxycycline PO 1$\times$/wk
Jarisch–Herxheimer reaction rare

THERAPY

Antibiotic treatment is most beneficial when started within 4 days of illness. Doxycycline, 100 mg orally twice daily for 7 days started within 48 hours of illness, decreased the duration of illness by 2 days in one study, and is recommended for mild illness. Penicillin at a dosage of 6 million units per day has been successful for early treatment of severe disease, and ceftriaxone (1 g daily) appears to be equally efficacious and has the benefits of simpler dosing schedules and potential intramuscular administration (Table 166.5). A benefit of antibiotic therapy given later in the disease course has not been uniformly seen. Jarisch–Herxheimer reactions (fever, rigors, hypotension, and tachycardia) rarely occur on initiation of antibiotic therapy. Supportive care and treatment of the hypotension, renal failure (including dialysis), and hemorrhage that can complicate leptospirosis are crucial for a good outcome.

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PART XX

Specific organisms: *Mycoplasma* and *Chlamydia*

167. ***Mycoplasma*** 1076
Ken B. Waites

168. ***Chlamydia pneumoniae*** 1086
Margaret R. Hammerschlag

169. ***Chlamydia psittaci*** (psittacosis) 1089
Alfred E. Bacon III

167. *Mycoplasma*

Ken B. Waites

Mycoplasmas are the smallest free-living organisms and are unique among prokaryotes in that they lack a cell wall, a feature that is largely responsible for their biologic properties and lack of susceptibility to many commonly prescribed antimicrobial agents. Mycoplasmas are usually mucosally associated, residing primarily in the respiratory and urogenital tracts and rarely penetrating the submucosa, except in the case of immunosuppression or instrumentation, when they may invade the bloodstream and disseminate to many different organs and tissues throughout the body. Intracellular localization occurs in some species and may contribute to chronicity that characterizes many mycoplasmal infections.

There are at least 17 species of mycoplasmas and ureaplasmas for which humans are believed to be the primary host, and numerous others of animal origin that have been detected occasionally, most often in the setting of immunosuppression. Several human mycoplasmal species are commensals in the upper respiratory or lower urogenital tracts. Five species are responsible for the majority of clinically significant infections which may come to the attention of the practicing physician. These species are *Mycoplasma pneumoniae*, *Mycoplasma hominis*, *Mycoplasma genitalium*, *Ureaplasma urealyticum*, and *Ureaplasma parvum*. *Mycoplasma fermentans* is another mycoplasma of human origin that may behave as an opportunist. *M. fermentans* has been detected in throat cultures of children with pneumonia, in some cases when no other etiologic agent was identified, but the frequency of its occurrence in healthy children is not known. This mycoplasma has also been detected in adults with an acute influenza-like illness and in bronchoalveolar lavage specimens from patients with the acquired immunodeficiency syndrome and pneumonia. *Mycoplasma amphoriforme* is the newest human mycoplasma to be described. It has been detected in a small number of patients with recurrent bronchitis, but its true role as a human pathogen has not yet been established. Other mycoplasmas of animal origin occasionally cause zoonotic infections.

MYCOPLASMA PNEUMONIAE RESPIRATORY DISEASE

M. pneumoniae occurs endemically and occasionally epidemically in persons of all age groups, most commonly in school-age children, adolescents, and young adults. The common misconception that *M. pneumoniae* disease is rare among very young children and older adults has sometimes led to failure of physicians to consider this organism in differential diagnoses of respiratory infections in these age groups. Failure to consider *M. pneumoniae* as an etiologic agent in cases of severe pneumonia may also lead to misdiagnosis since this organism can cause severe respiratory disease that has caused death in a few cases. *M. pneumoniae* is perhaps best known as the primary cause of "walking or atypical pneumonia," but the most frequent clinical syndrome is tracheobronchitis or bronchiolitis, often accompanied by upper respiratory tract manifestations. Typical complaints can persist for weeks to months and include hoarseness, fever, cough which is initially nonproductive but later may yield small to moderate amounts of non-bloody sputum, sore throat, headache, chills, coryza, and general malaise. The throat may be inflamed but cervical adenopathy is uncommon. Bronchopneumonia, involving one or more lobes, often develops in infected persons, accounting for 20% or more of community-acquired pneumonias overall, and an even greater percentage in closed populations such as college dormitories, military barracks, and prisons. The incubation period is generally 1 to 3 weeks and spread throughout households often occurs. Epidemiologic studies have shown *M. pneumoniae* was second only to *Streptococcus pneumoniae* as an etiologic agent of pneumonia in adults requiring hospitalization.

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Hospital admission may be necessary in about 10% of children and adults, but recovery is usually complete without sequelae. Some people may experience extrapulmonary complications at variable time periods after onset of or even in the absence of respiratory illness. Such complications most commonly include skin rashes, pericarditis, hemolytic anemia, arthritis, meningoencephalitis, peripheral neuropathy, and pericarditis. Other nonspecific manifestations include nausea, vomiting, and diarrhea. Mycoplasmal infection may also be associated with exacerbations of asthma. Whether the organism can act independently in the pathogenesis of asthma has not been firmly established, but the fact that it can induce a number of inflammatory mediators such as IgE and that administration of macrolide antibiotics improves lung function of asthmatic persons with evidence of mycoplasmas in their airways suggests this possibility is worthy of further study. Some cases of fulminant mycoplasmal infection resulting in death, usually in otherwise healthy persons, have been described. It seems likely that serious disease occurs more often than is currently appreciated, but goes undetected when specific tests to detect *M. pneumoniae* are not performed. A major advance in the understanding of the mechanisms behind the clinical manifestations of *M. pneumoniae* disease is the discovery of an exotoxin similar to pertussis toxin that induces ciliostasis and airway vacuolization, elicits a lymphocytic and eosinophilic airway exudate, and upregulates various cytokines and chemokines.

Autoimmune reaction is thought to be responsible for many of the extrapulmonary complications associated with mycoplasmal infection. However, *M. pneumoniae* has been isolated from extrapulmonary sites such as synovial fluid, cerebrospinal fluid (CSF), pericardial fluid, and skin lesions and it has also been detected by polymerase chain reaction (PCR) assays in various extrapulmonary sites. Therefore, direct invasion must always be considered. The frequency of direct invasion of these sites is unknown because the organism is rarely sought.

The hemogram is often normal, but about one-fourth of patients may develop leukocytosis and one-third may demonstrate an elevated erythrocyte sedimentation rate. The cellular response of the sputum is mononuclear, with no bacteria visible by Gram stain. In about 50% of patients, a cold agglutinin titer of $\geq$1:32 may develop by the second week of illness, disappearing by 6 to 8 weeks. This is not a specific test for *M. pneumoniae*, since other microorganisms may induce

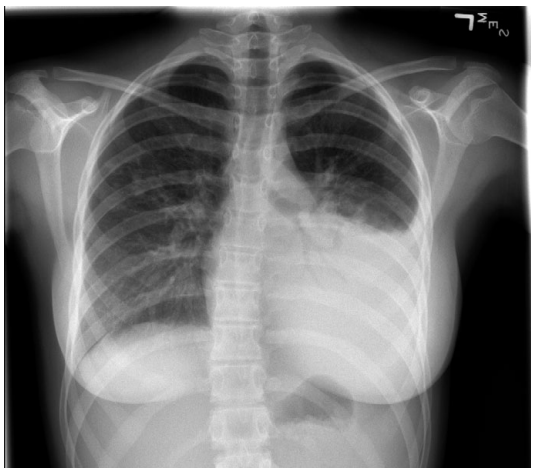

Figure 167.1 Chest radiograph of a female adolescent with PCR-proven mycoplasmal pneumonia, demonstrating bilateral infiltrates. (Radiograph courtesy of T. Prescott Atkinson, MD.)

similar reactions. Several viruses, *Chlamydia pneumoniae*, *S. pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Legionella* species, and even some mycobacteria or fungi can produce infections which are clinically indistinguishable, and which may occur simultaneously with mycoplasmal infection.

Lung involvement tends to be unilateral, but can be bilateral. Diffuse reticulonodular or interstitial infiltrates involving the lower lobes appearing as streaks radiating from the hilus to the base of the lung are the most common radiographic abnormalities. True lobar consolidation is uncommon, but pleural effusion may develop in about 25% of cases. Abnormalities on chest radiographs often appear more severe than the clinical condition of the patient would predict. A typical radiographic presentation of mycoplasmal pneumonia is shown in Figure 167.1.

Due to widespread lack of diagnostic services, length of time until results can be obtained, impracticality of obtaining diagnostic specimens, and similarity of clinical syndromes due to different microorganisms, clinicians often do not attempt to obtain a microbiologic diagnosis in mild to moderately ill outpatients suspected of having *M. pneumoniae* infection and elect to treat empirically. However, if the illness is of sufficient severity to require hospitalization, search for a specific microbiologic etiology is justified. If mycoplasmal respiratory infection is to be confirmed, culture, molecular-based, and/or serologic tests are necessary. Clinical laboratories may offer culture service through a reference laboratory familiar with the

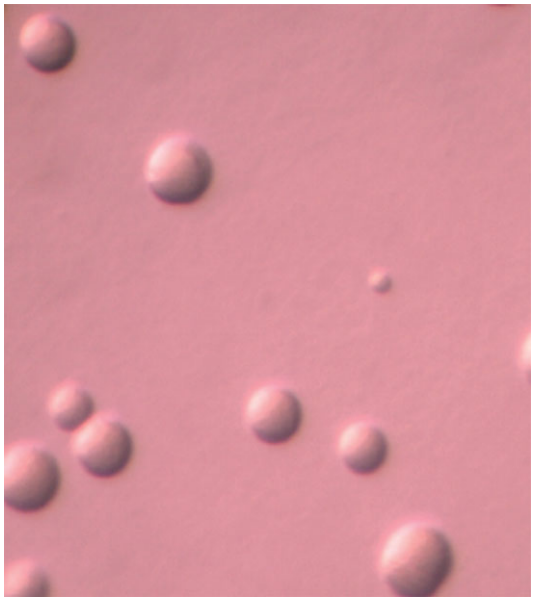

Figure 167.2 Spherical colonies of *Mycoplasma pneumoniae* approximately 100 μm in diameter growing on SP4 agar. Magnification: 126×.

complex cultivation requirements of mycoplasmas. Respiratory tract specimens suitable for culture include throat swabs, sputum, tracheal aspirates, bronchial lavage fluid, pleural fluid, or lung biopsy tissue according to the patient's clinical condition. Care should be taken in specimen collection, inoculation into a suitable transport medium, such as SP4 broth, at bedside whenever possible, and not allowing desiccation. Freezing at −70°C is advised if specimens cannot be transported to the diagnostic laboratory immediately after collection. Growth in culture is slow, requiring ≥3 weeks in some cases. Growth of a glucose-fermenting mycoplasma in SP4 broth and development of microscopic spherical colonies approximately 100 μm in diameter on SP4 agar as shown in Figure 167.2 are presumptive evidence of *M. pneumoniae*. Since some of the upper respiratory commensal mycoplasmal species may also grow on this medium, it is advisable to confirm the identity of the organisms using the PCR assay. Due to the turnaround time, expense, and limited availability, culture is rarely used for routine diagnosis of *M. pneumoniae* infection.

Serology has been used historically to confirm *M. pneumoniae* infection. Enzyme-linked immunosorbent assays are preferred over complement fixation assays or cold agglutinin titers. Since primary infection does not guarantee protective immunity against future infections and residual antibody may remain from earlier encounters with the organism, there has been a great impetus to develop sensitive and specific tests that can differentiate between acute or remote infection. Definitive diagnosis requires seroconversion documented by paired serum specimens obtained 2 to 4 weeks apart and assayed at the same time. Although single-titer qualitative and quantitative IgM or IgA assays purported to detect current infection have now become available, IgM can sometimes persist for many weeks after acute infection and as many as 50% of adults may not mount a detectable IgM response. Conversely, some children may not mount a measurable IgG response. Therefore, reliance on a single serologic test can be clinically misleading and paired assays for both IgM and IgG are recommended. Even then, the interpretation of serologic results can sometimes be complex and inconclusive.

Molecular-based systems for rapid detection of *M. pneumoniae* alone or in combination with other respiratory pathogens are now available through reference laboratories. Some of these assays are commercially sold and others have been developed by individual laboratories for their own use. Given the limitations of culture and serology, molecular-based detection, when available, is the method of choice for detection of acute *M. pneumoniae* infection.

TREATMENT OF *MYCOPLASMA PNEUMONIAE* INFECTIONS

Formerly it was believed that mycoplasmal respiratory infections were entirely self-limited and no antimicrobial treatment was indicated. More recently it has been shown that appropriate antimicrobial therapy will shorten the symptomatic period and hasten radiologic resolution of pneumonia and recovery, even though organisms may be shed for several weeks. In general, the clinical efficacy of antimicrobial therapy is correlated with severity of pneumonia and elapsed time of illness before treatment is begun. A summary of treatment alternatives for *M. pneumoniae* respiratory infections is provided in Table 167. 1.

M. pneumoniae is generally susceptible to macrolides, ketolides, tetracyclines, and fluoroquinolones such that in vitro susceptibility testing to guide therapy is not indicated at present. Susceptibility testing would also be impractical most of the time because clinical isolates are generally not available. Macrolide resistance in *M. pneumoniae* has been known to occur for many years, but

Table 167.1. Treatment options for respiratory tract infections caused by *Mycoplasma pneumoniae*[a]

Drug	Route	Dosage/24 h		Comments
		PEDIATRIC	ADULT	
Doxycycline	PO	4 mg/kg loading dose d 1, then 2–4 mg/kg/d in 1–2 doses × 10–14 d	200 mg loading dose d 1, then 100 mg q12h × 9–13 d	Pregnancy category D Tetracyclines are contraindicated in children under 8 years of age unless there is no other alternative
	IV	Same as PO	Same as PO	
Tetracycline	PO	25–50 mg/kg/d in 4 doses × 10–14 d	250–500 mg q6h × 10–14 d	Pregnancy category D Tetracyclines are contraindicated in children under 8 years of age unless there is no other alternative
	IV	10–20 mg/kg/d in 2–4 doses × 10–14 d	500 mg–1 g q6–12h × 10–14 d	
Erythromycin	PO	20–50 mg/kg/d in 3–4 doses × 10–14 d	250–500 mg base/stearate q6h or 400–800 mg ethylsuccinate q6h × 10–14 d	Pregnancy category B
	IV	25–40 mg/kg/d in 4 doses × 10–14 d	Same as PO	
Azithromycin	PO	10 mg/kg/d on d 1, then 5 mg/kg/d × 4 d; not to exceed 250 mg/d	500 mg d 1, then 250 mg qd × 4 d or 2 g given as a single dose	Pregnancy category B IV formulation is not approved for use in persons under 16 years of age
	IV	Not recommended	500 mg qd IV × 2 d, then 500 mg PO qd × 7–10 d	
Clarithromycin	PO	15 mg/kg/d in 2 doses × 7–14 d	250–500 mg q12h × 7–14 d (immediate release) or 1 g qd × 7 d (extended release)	Pregnancy category C No IV formulation is available
Levofloxacin	PO	Not recommended	750 mg qd × 5 d	Pregnancy category C Fluoroquinolones are not approved for use in persons under 18 years of age
	IV	Not recommended	Same as PO	
Moxifloxacin	PO	Not recommended	400 mg qd × 7–14 d	Pregnancy category C Fluoroquinolones are not approved for use in persons under 18 years of age
	IV	Not recommended	Same as PO	
Gemifloxacin	PO	Not recommended	320 mg qd × 7 d	Pregnancy category C Fluoroquinolones are not approved for use in persons under 18 years of age. No IV formulation is available

[a] Treatment recommendations are primarily for management of community-acquired pneumonia with antibiotics approved for treatment of this condition, although they are also appropriate for tracheobronchitis due to this organism. Choice of routes for administration is dependent on the severity of the clinical condition being treated. Most *M. pneumoniae* infections can be adequately treated with oral medication.

it was believed to be quite rare and of minimal clinical significance. Over the past decade, the emergence of macrolide-resistant *M. pneumoniae* infections in Asia that have resulted in diminished clinical response to macrolide therapy is worrisome. This resistance now affects the majority of *M. pneumoniae* isolates in China and Japan. Limited data suggest that such resistant organisms also occur in the United States and various countries in Europe, but are still relatively uncommon. Recent data suggest 10% macrolide resistance in the USA. Oral erythromycin has long been a drug of choice for mycoplasmal respiratory infections, but its use has been reduced due to the availability of better-tolerated drugs in this class with improved pharmacokinetics and shorter treatment durations.

The macrolides clarithromycin, azithromycin, and dirithromycin are broad-spectrum agents used primarily for treatment of community-acquired respiratory infections caused by a wide array of bacteria. These agents are very active in vitro against *M. pneumoniae* and inhibit its growth at comparable or lower minimum inhibitory concentrations (MICs) than those of erythromycin, unless the strain has ribosomal mutations conferring macrolide resistance. All of these drugs have proven clinical efficacy and approved therapeutic indications for pneumonia caused by this organism. Care must be taken because of numerous

potential drug interactions with these macrolides. Clarithromycin and azithromycin are available as pediatric oral suspensions and azithromycin is also available as an intravenous formulation in addition to the oral formulations. Tetracycline and its analogs are also effective in vivo and in vitro, but should not be used in children due to potential bone and tooth toxicity. Clindamycin is effective in vitro, but limited reports suggest it may not be active in vivo and should not be considered a first-line treatment. None of the β-lactams, sulfonamides, or trimethoprim is effective in vitro or in vivo against *M. pneumoniae*.

Fluoroquinolones exhibit bactericidal antimycoplasmal activity, but are less potent in vitro than the macrolides against *M. pneumoniae*. Development of quinolones with documented clinical efficacy and approved indications for treating *M. pneumoniae* has been driven largely by the need for therapeutic alternatives for β-lactam- and macrolide-resistant *S. pneumoniae*, and the desire for agents that can be used as empiric monotherapy for respiratory infections due to other typical and atypical organisms. At the present time, quinolones are not approved for use in persons under 18 years of age, but these drugs are rapidly achieving widespread use for treatment of respiratory infections in adults, mainly in the ambulatory setting, and represent reasonable alternative therapies for *M. pneumoniae* disease, particularly in the setting of macrolide resistance.

Mycoplasmas are slow-growing organisms; thus one would logically expect respiratory infections to respond better to longer treatment courses than might be offered for other types of infections. Thus, a 14- to 21-day course of oral therapy is appropriate for some drugs, but some of the newer agents have shown clinical efficacy against mycoplasmal pneumonias with shorter durations. For example, a 5-day course of oral azithromycin is approved for treatment of community-acquired pneumonia due to *M. pneumoniae*.

In addition to the administration of antimicrobials for management of *M. pneumoniae* infections, other measures such as cough suppressants, antipyretics, and analgesics should be given as needed to relieve the headaches and other systemic symptoms. Since most extrapulmonary manifestations are diagnosed late in the course of disease, the benefit of early treatment is unknown. However, limited information suggests that high-dose steroid therapy and/or intravenous immunoglobulin therapy may help reverse neurologic symptoms, if present. If treatment of extrapulmonary mycoplasmal infections is necessary, and/or the patient is immunosuppressed, selection of an agent that exhibits bactericidal activity such as a fluoroquinolone may be most appropriate and administration of the drugs for longer durations may be required.

Fortunately, the treatments of choice for *M. pneumoniae* are appropriate for many of the other microbial agents responsible for community-acquired respiratory infections. This is especially important in view of the fact that in the major proportion of ambulatory patients seeking medical care, the identity of their infectious organism is never determined.

GENITAL *MYCOPLASMA* AND *UREAPLASMA* INFECTIONS

Ureaplasma spp. and *M. hominis* can be isolated from the lower genital tract in the majority of sexually active women; their occurrence is somewhat less frequent in men. The presence of genital mycoplasmas in so many asymptomatic persons has made it difficult to prove their pathogenic potential. For some conditions such as cystitis, male urethritis, and urinary calculi for *Ureaplasma* spp. and pelvic inflammatory disease (PID) for *M. hominis*, evidence is sufficient to implicate these organisms as etiologic agents in a portion of clinical cases. For other conditions such as prostatitis and bacterial vaginosis the evidence is not as clear-cut. Only a subgroup of otherwise healthy adult men and women who are colonized will develop clinically significant genitourinary disease due to these organisms, but the risk factors are poorly understood. Table 167.2 summarizes diseases believed to be associated with or caused by genital mycoplasmas and ureaplasmas.

The ability of genital mycoplasmas to be transmitted vertically from mother to offspring in utero or at the time of delivery has led to considerable efforts to ascertain their role as perinatal pathogens. Isolation of *Ureaplasma* spp. from the chorioamnion of pregnant women has been consistently associated with histologic chorioamnionitis and is inversely related to birth weight, even when adjusting for duration of labor, rupture of fetal membranes, and presence of other bacteria. *Ureaplasma* spp. can be isolated from endometrial tissue of healthy, nonpregnant women, indicating that they may be present at the time of implantation and might therefore be involved in early pregnancy losses. Numerous studies have shown that the presence of ureaplasmas alone or with other bacteria in the chorioamnion is independently

Table 167.2. Diseases associated with or caused by genital mycoplasmas

Disease	*Ureaplasma* spp.	*M. hominis*	*M. genitalium*
Male urethritis	+	−	+
Chronic prostatitis	±	−	±
Epididymitis	±	−	−
Urinary calculi	+	−	−
Cystitis/pyelonephritis	+	+	−
Bacterial vaginosis	±	±	−
Cervicitis	−	−	+
Pelvic inflammatory disease	−	+	+
Infertility	±	−	−
Chorioamnionitis	+	±	−
Spontaneous abortion	±	±	−
Prematurity/low birth weight	+	−	−
Intrauterine growth retardation	+	−	−
Postpartum/postabortal fever and endometritis	+	+	−
Neonatal pneumonia	+	+	−
Neonatal chronic lung disease	+	−	−
Neonatal bacteremia/meningitis	+	+	−
Neonatal abscesses	+	+	−
Extragenital disease in adults[a]	+	+	−

− = no association or causal role demonstrated. In some conditions for *M. genitalium* this may reflect the fact that no studies using appropriate techniques to detect this organism have been performed.

+ = causal role.

± = significant association and/or strong suggestive evidence, but causal role not proven.

[a] These include conditions such as septic arthritis, bloodstream invasion, abscesses, wound infections, lung infections, endocarditis, and osteomyelitis.

associated with birth at <37 weeks of gestation regardless of the duration of labor. The ability of ureaplasmas to invade the amniotic fluid early in gestation and initiate inflammation provides the setting through which they can also produce inflammation in the lower respiratory tract of the developing fetus and neonate. Over the past several years there has been increasing evidence that these organisms may cause congenital pneumonia and initiate events leading to chronic lung disease of prematurity or bronchopulmonary dysplasia.

Superficial mucosal colonization in the newborn period tends to be transient and without sequelae, but neonates, especially those born preterm, have been shown to be susceptible to development of a variety of systemic conditions due to either *M. hominis* or ureaplasmas, including bacteremia and meningitis.

For many years *U. urealyticum* was the only species known to infect humans. However, this organism was eventually subdivided into two separate species, *U. urealyticum* and *U. parvum*, based on 16S rRNA sequences. *U. parvum* is the more common species isolated from clinical specimens, but both species may occur simultaneously. Most clinical studies have not distinguished between the two species except in very recent years because sophisticated nucleic acid amplification tests are necessary to discriminate between them. Evidence is accumulating that suggests *U. urealyticum* may be more pathogenic in some conditions such as male urethritis.

Extragenital infection with *M. hominis* and/or *Ureaplasma* spp. beyond the neonatal period is usually associated with some degree of immunocompromise, such as congenital hypogammaglobulinemia, iatrogenic immunosuppression following solid organ transplantation, or with invasive procedures such as instrumentation of the urinary tract. Ureaplasmas and other mycoplasmas are the most common etiologic agents of septic arthritis in the setting of congenital antibody deficiencies and should be considered early when attempting to diagnose these conditions.

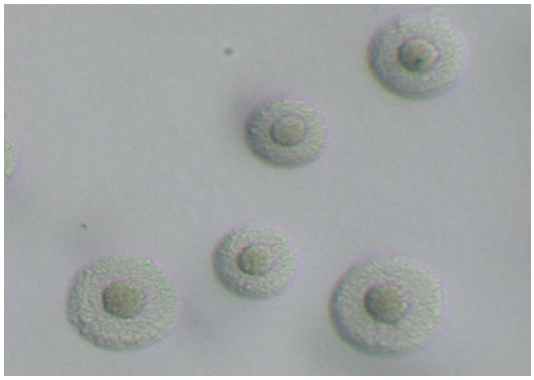

Figure 167.3 Fried egg-type colonies of *Mycoplasma hominis* up to 110 μm in diameter. Magnification: 132×.

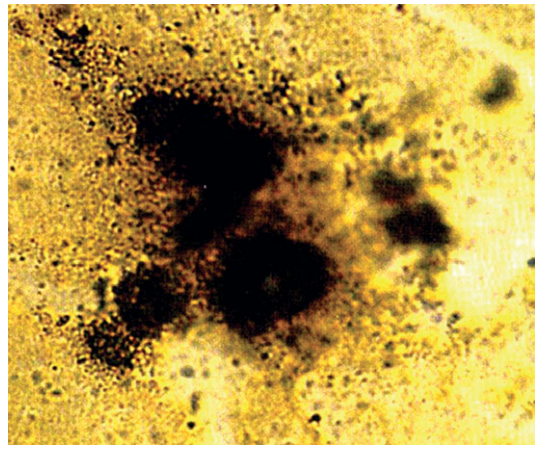

Figure 167.4 Granular brown urease-positive colonies of *Ureaplasma* species 15 to 60 μm in diameter from a vaginal specimen growing on A8 agar. Magnification: 100×.

M. genitalium was first isolated from urethral specimens in men with urethritis. This mycoplasma occurs much less commonly in the lower urogenital tract of asymptomatic persons than *M. hominis* or *Ureaplasma* spp. Availability of the PCR assay has greatly enhanced understanding of the role of *M. genitalium* in human disease. Several clinical studies support a causal role in male urethritis, indicating it may be responsible for 15% to 25% of all cases, as well as female cervicitis, and PID.

Both *M. hominis* and ureaplasmas grow more rapidly and can therefore be detected in cultures of appropriate specimens within 2 to 5 days. Proper handling and bedside inoculation of transport broth enhance recovery of these organisms. Urethral or wound swabs, cervicovaginal or prostatic secretions, urine, respiratory specimens such as those described for *M. pneumoniae*, CSF, and blood or other body fluids or tissues are appropriate for culture, depending on the clinical setting. Cultures are available mainly through larger hospital laboratories or reference laboratories. *M. hominis* produces typical fried-egg colonies on agar and can be presumptively identified by rate of growth, colony morphology (Figure 167.3), and arginine hydrolysis. Definitive identification requires characterization by PCR. Ureaplasmas can be identified to genus level by typical colony morphology on A8 agar and urease activity (Figure 167.4). At present there are no commercial serologic assays or rapid detection tests available for routine diagnostic studies for any of the genital mycoplasmas in the USA, but several PCR-based assays are sold in various European countries. Techniques for isolation of *M. genitalium* in culture have been described, but its extremely slow growth, sometimes requiring several weeks to form colonies, and difficult cultivation have essentially limited diagnostic measures to PCR assays. PCR tests to detect *M. genitalium* for clinical diagnostic purposes are available through reference laboratories, though such testing is still uncommonly performed at the present time.

Genitourinary or extragenital diseases from mycoplasmas warrant appropriate diagnostic tests when available and treatment if infection is confirmed. This is of particular importance if the organisms are recovered in the absence of other possible microbial etiologies and if the infection is present in a normally sterile site. Practitioners will usually have to rely upon familiarity with clinical syndromes typically due to genital mycoplasmas and treat empirically if facilities for laboratory diagnosis are not readily available. Many of the conditions associated with a mycoplasmal etiology can also be due to a variety of microbial agents and some conditions such as PID can be polymicrobial. Therefore, the selection of drugs must take into account multiple causes.

TREATMENT OF GENITAL *MYCOPLASMA* AND *UREAPLASMA* INFECTIONS

Oral tetracyclines have historically been the drugs of choice for use against urogenital infections due to *M. hominis*, but resistance now occurs in 20% to 50% of isolates. A survey of clinical isolates of *Ureaplasma* spp. from various states found that 45% possessed the *tetM* transposon conferring resistance to this class of drugs. The degree of resistance may vary according to geographic area, type of patient population, and

Table 167.3 Treatment options for urogenital and systemic infections in adults caused by *Mycoplasma hominis*, *Mycoplasma genitalium*, and *Ureaplasma* species[a]

Drug	Route	Dosage/24 h	Comments
Doxycycline	PO IV	200 mg loading dose d 1, then 100 mg q12h × 7 d Same as PO	Pregnancy category D. Tetracyclines are contraindicated in children <8 yr of age unless no other alternative is available. Activity may be inhibited in some strains of *M. hominis* and *Ureaplasma* spp. possessing *tetM*. Treatment failures have been described for *M. genitalium* urethritis
Tetracycline	PO IV	250–500 mg q6h × 7 d 125–500 mg q6–12h × 7 d	Pregnancy category D. Tetracyclines are contraindicated in children <8 yr of age unless no other alternative is available. Activity may be inhibited in some strains of *M. hominis* and *Ureaplasma* spp. possessing *tetM*
Erythromycin	PO IV	250–500 mg q6h × 7 d Same as PO	Pregnancy category B. Not active against M. *hominis*
Azithromycin	PO IV	500 mg × 1 d then 250 mg × 4 d or 1 g as a single dose 500 mg/d × 2 d, then 500 mg PO qd	Pregnancy category B. Not active against *M. hominis*. In vitro resistance and treatment failures have been described for *M. genitalium* urethritis
Clindamycin	PO IV	150–450 mg q6h × 7 d 150 – 900 mg q6–8h × 7 d	Pregnancy category C. Not active against *Ureaplasma* spp.
Ofloxacin	PO IV	200 – 400 mg q12h × 7 d Same as PO	Pregnancy category C. Fluoroquinolones are not approved for use in persons under 18 yr of age
Levofloxacin	PO IV	500 mg qd × 7–14 d Same as PO	Pregnancy category C. Fluoroquinolones are not approved for use in persons under 18 yr of age
Moxifloxacin	PO IV	400 mg q12h × 10 d Same as PO	Pregnancy category C. Fluoroquinolones are not approved for use in persons under 18 yr of age. Moxifloxacin does not have approved indications for treatment of urogenital infections, but it has been effective in men with *M. genitalium* urethritis who failed treatment with azithromycin

[a] Treatment options are based on accepted regimens for urogenital infections involving other microorganisms that are expected to be suitable for infections caused by genital mycoplasmas based on in vitro susceptibility data in circumstances where there are no approved microbiologic indications. Route and duration of treatment are dependent on the severity of the clinical condition being treated. For extragenital and/or systemic infections, particularly those involving immunocompromised persons, a longer duration of treatment may be necessary than those listed. Joint infections may require several weeks to months of antimicrobial administration. Recommendations are based primarily on published case reports due to the lack of objective data from clinical trials.

previous exposure to antimicrobial agents. Recent reports of fluoroquinolone resistance in both *M. hominis* and *Ureaplasma* spp. in the United States and Europe lend support to the recommendation that in vitro susceptibility testing is indicated when these organisms are recovered from a normally sterile body site, from immunocompromised hosts, and/or from persons who have not responded to an initial treatment. Susceptibility testing can be accomplished in 3 to 5 days by a reference laboratory once the organism is isolated. Treatment alternatives for urogenital infections in adults and neonatal infections are provided in Tables 167.3 and 167.4, respectively.

Clindamycin is an alternative treatment for *M. hominis* and is effective against tetracycline-resistant strains, but it is much less active against *Ureaplasma* spp. In contrast, macrolides are generally active against ureaplasmas, but *M. hominis* is typically resistant to macrolides. Occasional macrolide-resistant ureaplasmas have been reported. A single dose of azithromycin is approved for treatment of urethritis due to *Chlamydia trachomatis*, and has been shown to work as well clinically as doxycycline in persons with urethritis due to *Ureaplasma* spp. Despite in vitro susceptibility, tetracycline or erythromycin treatment of vaginal mycoplasmas is not always successful.

Clinical studies have encountered treatment failures with the tetracyclines for urethritis caused by *M. genitalium* and it was initially believed azithromycin would be a better option. However, reports of treatment failures with azithromycin and detection of *M. genitalium* isolates with elevated MICs to this drug indicate it may not always be effective. Macrolide-resistant *M. genitalium* infections have been successfully treated with fluoroquinolones (e.g., moxifloxacin), but resistance has also been documented.

Table 167.4. Treatment options for neonatal infections with *Mycoplasma hominis* and *Ureaplasma* species[a]

Drug	Route	Dosage/24 h	Comments
Doxycycline	PO IV	4 mg/kg loading dose d 1, then 2–4 mg/kg/d in 1–2 doses × 10–14 d Same as PO	Tetracyclines are contraindicated in children <8 yr of age unless no other alternative is available. Activity may be inhibited in some strains of *M. hominis* and *Ureaplasma* spp. possessing *tetM*. This drug has been used to successfully treat neonatal meningitis due to *M. hominis* and *Ureaplasma* spp., but treatment failure has been reported with *Ureaplasma* spp.
Tetracycline	PO IV	25–50 mg/kg/d in 4 doses 10–20 mg/kg/d in 2–4 doses	Tetracyclines are contraindicated in children <8 yr of age unless no other alternative is available. Activity may be inhibited in some strains of *M. hominis* and *Ureaplasma* spp possessing *tetM*
Chloramphenicol	PO IV	Not recommended For neonates up to 2 wk of age, use 25 mg/kg/d in 1 dose, thereafter 50 mg/kg/d in 1 dose	Chloramphenicol has been used successfully to treat neonatal meningitis due to *M. hominis* and *Ureaplasma* spp., but there has also been a report of treatment failure with *M. hominis*. Frequent monitoring of hematologic parameters and blood levels of the antibiotic are necessary due to its potential toxicity.
Erythromycin	PO IV IV	20–50 mg/kg/d in 3–4 doses 25–40 mg/kg/d in 4 doses Same as PO	Not active against *M. hominis*. Despite poor CSF penetration, this drug has been used successfully to treat neonatal meningitis due to *Ureaplasma* spp., but treatment failure has also been reported
Clindamycin	PO IV	10–25 mg/kg/d in 3–4 doses × 10–14 d 10–40 mg/kg/d in 3–4 doses. Do not exceed 15–20 mg/kg/d	Not active against *Ureaplasma* spp. This drug has been used to successfully treat neonatal infections due to *M. hominis*

[a] No treatment guidelines for neonatal infections with genital mycoplasmas are available. Treatment options have been compiled based on in vitro susceptibility data and information described in published case reports. No dosages have been established or approved for neonates, so amounts listed are based on data applicable to older infants and children.

Despite occasional reports of resistance, fluoroquinolones have become useful alternatives for treatment of certain infections caused by *M. hominis*, *M. genitalium*, and *Ureaplasma* spp. within the urogenital tract and in some extragenital locations. Activity of fluoroquinolones is not affected by tetracycline or macrolide resistance. Ciprofloxacin and ofloxacin are generally less active in vitro against these organisms than levofloxacin and moxifloxacin. Very few clinical antibiotic trials have included microbiologic data specific for genital mycoplasmas and there have been no systematic comparative evaluations of treatment regimens for extragenital infections in adults or for neonatal infections. Thus, treatment recommendations in Tables 167.3 and 167.4, including dosages and duration, are based largely on in vitro susceptibility data, outcomes of treatment trials evaluating clinical response to syndromes such as PID and urethritis that may be due to genital mycoplasmas, and individual case reports. For infections such as urethritis that may be venereally transmitted, sexual contacts of the index case should also receive treatment.

Experience with mycoplasmal or ureaplasmal infections in immunocompromised patients, especially those with hypogammaglobulinemia who have been the best studied, demonstrate that even though mycoplasmas are primarily noninvasive mucosal pathogens in the normal host, they have the capacity to produce destructive and progressive disease. Infections may be caused by resistant organisms refractory to antimicrobial therapy and require prolonged administration of a combination of intravenous antimicrobials, intravenous immunoglobulin, and/or antisera prepared specifically against the infecting species for weeks to months. Even with aggressive therapy, relapses are still likely to occur. Repeat cultures of affected sites may be necessary to monitor in vivo response to treatment.

Isolation of *M. hominis* or *Ureaplasma* spp. from CSF in neonates with pleocytosis, progressive hydrocephalus, or other neurologic abnormality; pericardial fluid; pleural fluid; tracheal aspirate in association with respiratory disease; abscess material; or blood are justification for specific treatment in critically ill neonates when no other verifiable microbiologic etiologies of the clinical condition are apparent. Parenteral tetracyclines have been used to treat neonatal meningitis due to either *M. hominis* or *Ureaplasma* spp., despite contraindications, but erythromycin or other macrolides such as azithromycin for *Ureaplasma* spp., clindamycin for *M. hominis*, or chloramphenicol for either species are alternatives. No single drug has been successful in every

instance in eradication of these organisms from CSF of neonates. Even though azithromycin has a number of advantages over erythromycin from the pharmacokinetic standpoint, there has been minimal clinical experience with this drug in treatment of neonatal ureaplasmal infections and there are no guidelines for its use in this setting. Overall treatment guidelines for neonates are the same as for urogenital and systemic mycoplasmal infections in adults with appropriate dosage modifications based on weight, except that the intravenous route should be used for serious systemic infections. Duration of treatment and drug dosages for neonatal mycoplasmal infections have not been critically evaluated, but a minimum of 10 to 14 days of therapy is suggested based on experience in individual cases where microbiologic follow-up has been assessed.

Other mycoplasmal species

A variety of mycoplasmal species can be isolated from the upper respiratory tract or urogenital tracts of humans. Some of them occur fairly commonly as commensals in healthy persons, whereas others are found less often. Some of these organisms have been implicated in case reports as agents of invasive disease, usually in immunosuppressed persons. No guidelines for their detection or treatment are possible due to the infrequency of isolation and lack of clinical isolates on which in vitro susceptibility tests have been performed. In the case of *M. fermentans*, its antimicrobial susceptibilities are generally similar to those of *M. hominis*, but scant information is available for other species. If a clinical isolate of one of these opportunistic mycoplasmal species is available, in vitro susceptibility tests can sometimes be performed to guide treatment, providing the organism will grow well enough in vitro to perform the test. Otherwise, empiric use of drugs shown to be effective against other mycoplasmal species as shown in Tables 167.1, 167.3, and 167.4 should be considered, with the choice being based on the type of infection encountered and status of the host.

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168. *Chlamydia pneumoniae*

Margaret R. Hammerschlag

The first isolates of *Chlamydia pneumoniae* were obtained serendipitously during trachoma studies in the 1960s. After the recovery of a similar isolate from the respiratory tract of a college student with pneumonia in Seattle, Grayston and colleagues applied the designation TWAR after their first two isolates, TW-183 and AR-39. *C. pneumoniae* appears to be a common human respiratory pathogen. The mode of transmission remains uncertain but probably involves infected respiratory tract secretions. Spread of *C. pneumoniae* within families and enclosed populations, such as military recruits, prisons, and nursing homes, has been reported. The proportion of community-acquired pneumonia in children and adults associated with *C. pneumoniae* infection has ranged from 0% to >44%, varying with geographic location, the age group examined, and the diagnostic methods used. Early studies that relied on serology suggested that infection in children younger than 5 years was rare; however, subsequent studies using culture and/or polymerase chain reaction (PCR) have found the prevalence of infection in children beyond early infancy to be similar to that found in adults.

Studies that have used culture have found a poor correlation with serology, especially in children. Although 7% to 13% of children 6 months to 16 years of age enrolled in two multicenter pneumonia treatment studies were culture positive and 7% to 18% met the serologic criteria for acute infection with the microimmunofluorescence (MIF) test, they were not the same patients. Only 1% to 3% of the culture-positive children met the serologic criteria, and approximately 70% were seronegative. By age 20, approximately 50% of persons will have detectable anti-*C. pneumoniae* immunoglobulin G (IgG). Seroprevalence may exceed 80% in some populations.

Prolonged culture positivity lasting from several weeks to several years after acute infection has been reported. Asymptomatic nasopharyngeal carriage also occurs in 2% to 5% of adults and children. The role that asymptomatic carriage plays in the epidemiology of *C. pneumoniae* is not known, but possibly these persons serve as a reservoir for spread of infection.

Most *C. pneumoniae* infections are probably mild or asymptomatic. Initial reports emphasized mild atypical pneumonia clinically resembling that associated with *Mycoplasma pneumoniae*. Generally, pneumonia associated with *C. pneumoniae* is not clinically indistinguishable from other pneumonias. Coinfection with other pathogens, especially *M. pneumoniae* and *Streptococcus pneumoniae*, are frequent. *C. pneumoniae* pneumonia has been associated with severe illness and even death, although the role of pre-existing chronic conditions as contributing factors in many of these patients is difficult to assess. In some cases, however, *C. pneumoniae* clearly appears to be implicated as a serious pathogen, even in the absence of underlying disease. *C. pneumoniae* has been isolated from the empyema fluid in several patients with severe pneumonia.

The role of host factors in *C. pneumoniae* infection remains to be determined. *C. pneumoniae* appeared to be responsible for 14% to 19% of episodes of acute chest syndrome in children with sickle cell disease. *C. pneumoniae* infection in these patients appeared to be associated with more severe hypoxia than infection with *M. pneumoniae*. *C. pneumoniae* is also an inflammatory trigger for asthma.

The role of *C. pneumoniae* in upper respiratory infections is less well defined. *C. pneumoniae* has been isolated from the middle ear fluid of children and adults with otitis media and has also been implicated as a cause of pharyngitis. *C. pneumoniae* infection has been implicated in a wide variety of chronic diseases and conditions, including atherosclerosis, Alzheimer's disease, macular degeneration, and arthritis. However, many of these studies are hampered by the lack of standardized methods for the diagnosis of *C. pneumoniae* infection.

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LABORATORY DIAGNOSIS

A specific laboratory diagnosis of *C. pneumoniae* infection can be made by identification of the organism from nasopharyngeal or throat swabs, sputa, or pleural fluid, if present, by culture or nucleic acid amplification test (NAAT). The nasopharynx appears to be the optimal site for isolation of the organism. The relative yield from throat swabs and sputum is not known. Isolation of *C. pneumoniae* requires culture in tissue; the organism cannot be propagated in cell-free media. *C. pneumoniae* grows readily in cell lines derived from respiratory tract tissue, specifically, HEp-2 and HL cells. Culture with an initial inoculation and one passage should take 4 to 7 days.

Nasopharyngeal cultures can be obtained with Dacron-tipped, wire-shafted swabs. Each lot of swabs should be treated in a mock infection system to ensure that no inhibitory effects occur on either the viability of cells or recovery of chlamydiae. Specimens for culture should be placed in appropriate transport media, usually a sucrose phosphate buffer with antibiotics and fetal calf serum, and stored immediately at 4°C for no longer than 24 hours. Viability decreases if specimens are held at room temperature. If the specimen cannot be processed within 24 hours, it should be frozen at –70°C until culture can be performed. After 72 hours of incubation, culture confirmation can be performed by staining with either a *C. pneumoniae* spp.-specific or a *Chlamydia* genus-specific (antilipopolysaccharide [anti-LPS]) fluorescein-conjugated monoclonal antibody.

NAATs, specifically real-time PCR, appear to be the most promising technology in the development of a rapid, nonculture method for detection of *C. pneumoniae*. More than 25 in-house PCR assays for detection of *C. pneumoniae* in clinical specimens have been reported in the literature. None of these assays is standardized or extensively validated in comparison to culture for detection of *C. pneumoniae* in respiratory specimens. Recently, a new PCR assay for the detection of *C. pneumoniae* became commercially available, and was US Food and Drug Administration (FDA) cleared in July 2012. The FilmArray assay detects *C. pneumoniae*, *M. pneumoniae*, and *Bordetella pertussis* on the same platform. The system combines nucleic acid extraction, nested PCR, detection, and data analysis in a single-use pouch. However, clinical data on the use of this assay are limited.

Because isolation of *C. pneumoniae* was initially considered to be difficult and limited, emphasis was placed on serologic diagnosis. The microimmunofluorescence (MIF) test is not standardized or FDA approved. Although enzyme immunoassay (EIA) serology test kits offer the promise of standardized performance and objective end points, none have been evaluated adequately in comparison to culture or PCR. Most have been compared only with MIF. None have FDA clearance or approval for use in the United States. One commercial assay, the Medac rELISA, uses a recombinant LPS antigen; others are based on LPS-extracted EBs or synthetic peptides. These kits can measure IgG, immunoglobulin M (IgM), and immunoglobulin A (IgA) antibodies, but cutoffs vary from kit to kit, and the criteria for a positive result (acute infection, past infection) can be very complex. The Centers for Disease Control and Prevention (CDC) has proposed modifications of the serologic criteria for diagnosis of *C. pneumoniae* infection. Although the MIF test was considered to be the only serologic test currently acceptable, the criteria were made significantly more stringent. Acute infection as determined by MIF was defined as a 4-fold rise in IgG or an IgM titer of 16 or greater, and the use of a single elevated IgG titer was discouraged. However, the use of paired sera also affords only a retrospective diagnosis, which is of little help in terms of deciding how to treat a patient. An IgG titer of 16 or greater was considered to indicate past exposure, but neither elevated IgA titer nor any other serologic marker was thought to be a validated indicator of persistent or chronic infection. The CDC did not recommend the use of any EIA for detection of antibody to *C. pneumoniae*.

THERAPY

Chlamydia pneumoniae is susceptible to tetracyclines, macrolides, and quinolones. Most of the treatment studies of pneumonia caused by *C. pneumoniae* published thus far have relied entirely on diagnosis by serology; consequently, microbiologic efficacy could not be assessed. Anecdotal reports have suggested that prolonged courses, up to 3 weeks, of either tetracyclines or erythromycin may be needed to eradicate *C. pneumoniae* from the nasopharynx of adults. The results of two pediatric multicenter pneumonia treatment studies found that 10-day courses of erythromycin and clarithromycin and 5 days of azithromycin suspension were equally efficacious; they eradicated the organism in 79% to 86% of children. Quinolones, including levofloxacin

Table 168.1 Regimens for respiratory tract infection caused by *C. pneumoniae*

Adults	Children
Doxycycline, 100 mg 2 × a day for 14–21 d	Erythromycin suspension, 50 mg/kg/d for 10–14 d
Tetracycline, 250 mg 4 × a day for 14–21 d	Clarithromycin suspension, 15 mg/kg/d for 10 d
Azithromycin, 1.5 g over a period of 5 d	Azithromycin suspension, 10 mg/kg on day 1 followed by 5 mg/kg/d once daily on days 2 to 5
Levofloxacin, 500 mg/d orally or intravenously for 7–14 d	
Moxifloxacin, 400 mg/d orally for 10 d	

and moxifloxacin, also have been demonstrated to have 70% to 80% efficacy in eradicating *C. pneumoniae* from adults with community-acquired pneumonia. Most patients improved clinically despite persistence of the organism. Persistence does not appear to be secondary to the development of antibiotic resistance.

Based on these limited data, regimens for respiratory tract infection caused by *C. pneumoniae* are listed in Table 168.1. Some patients may require retreatment.

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169. *Chlamydia psittaci* (psittacosis)

Alfred E. Bacon III

Chlamydia psittaci was identified simultaneously by three investigators in 1930. It is one of four species within the genus *Chlamydia*. Based on RNA sequencing, it is currently considered distinct from *Chlamydia pneumoniae* and *C. trachomatis*, despite phenotypic and physiologic similarities that have taxonomically bound them for many years. The organism is an obligate intracellular pathogen that contains both RNA and DNA but lacks a classic cell wall. These characteristics contribute to both the clinical manifestations and the determination of therapeutic options. *C. psittaci* has a wide range of host species, including birds, humans, and lower mammals. *C. pneumoniae*, however, is found only in humans and *C. trachomatis* only in humans and mice.

The systemic illness associated with *Chlamydia psittaci* has been termed *psittacosis* because of its association with parrots and psittacine birds. Subsequently, many avian species have been found to harbor *C. psittaci* and to transmit the organism to humans, causing disease. The term *ornithosis* would be more appropriate; however, it is not traditional. The organism can be carried for years in birds, remaining latent and causing disease many years after acquisition. Transmission to humans can occur even in the absence of disease in the bird. Excretion in the feces with aerosolization is the typical mode of transmission. Human-to-human transmission has been documented rarely and usually in the setting of severe disease. Healthcare workers have acquired the disease, but it is not felt warranted to isolate patients when hospitalized. Cases of mammal-to-human acquisition have been described in the setting of placental aeration at birth, but these cases are likely caused by the now separate species *Chlamydophila abortus*.

Individuals epidemiologically at risk for *Chlamydia psittaci* infection include abattoir and veterinary workers as well as those exposed to aviaries. Poultry breeders (particularly turkey farmers) are at significant risk, accounting for most outbreaks. A variable degree of illness exists in the birds infected with *C. psittaci*, ranging from asymptomatic to full-blown disease manifested by anorexia, dyspnea, and diarrhea. Birds may resolve the illness spontaneously, and a waxing and waning clinical course is not unusual. Therefore, a history of contact with birds is pertinent even if the bird is seemingly healthy. Up to 20% of patients may not recall bird exposure, but contact as innocuous as mowing a lawn or being exposed to airborne feces is adequate exposure. It remains a distinctly unusual cause of pneumonia with only four cases reported to the Centers for Disease Control and Prevention (CDC) in 2010, compared to an average of 16 cases per year in the preceding decade. New criteria for the diagnosis also contributed to this drop. Underreporting in the setting of accepted clinical criteria may play a role in this lack of recognition.

Vigilance in the workplace and prevention in at-risk bird populations play an increasing role. Quarantine and treatment of imported birds is a mainstay.

CLINICAL SYNDROMES

Following inhalation in aerosol form, the organism travels to the alveoli and then disseminates to regional lymph nodes and the reticuloendothelial system. Dissemination does not always occur, limiting disease to the chest. The organism invades and even multiplies successfully in a wide range of host cells, including macrophages and neutrophils. Multiple organ involvement is not uncommon, and the systemic nature of this disease cannot be overstated.

The classic presentation is one of an atypical pneumonia, although systemic infection in the absence of pneumonia has been well described as a typhoidal disease, even with cutaneous manifestations such as Horder's spots. Cough is often a later clinical sign, preceded by fever, malaise, and often severe headache by a number of

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days. The presence of severe headache is felt to be a sentinel component of the disease. The incubation period ranges from 5 to 21 days, and in up to 20% of patients no history of exposure to a bird can be elicited. Diarrhea is very common.

Neurologic involvement and encephalopathic features have been reported. Endocarditis, myocarditis, and septicemia can occur. Rash, panniculitis, and even joint disease seen as human leukocyte antigen (HLA)-B27 reactive arthritis occur rarely. Recently, a follicular conjunctivitis has been described caused by "nontrachoma" chlamydia, including *C. psittaci*. Anecdotal reports of vasculitis and cerebral vascular disease have been linked to *C. psittaci* but lack convincing clinical or diagnostic criteria.

Physical findings commonly include pulmonary consolidation and an altered mental status. As with other intracellular pathogens, a temperature–pulse dissociation is often reported. Laboratory data are rarely unique to *C. psittaci* infection; however, hepatocellular damage is present in almost 50% of patients. An abnormal chest x-ray film is evident in 80% of infected individuals, almost uniformly a lobar infiltrate as opposed to a diffuse pattern.

DIAGNOSIS

The diagnosis of *C. psittaci* infection is based on serologic confirmation of exposure to the pathogen in the proper clinical setting. As with most cases of atypical pneumonia, a thorough history looking for exposures, systemic symptoms, and atypical features is crucial. Culturing the organism is difficult and hazardous in the laboratory. Two serologic assays are readily available. A complement fixation antibody assay with a 4-fold or greater change in titer between acute and convalescent phase era confirms the diagnosis. A random titer greater than 1:32 with a compatible illness is presumptively diagnostic. The complement fixation assay, however, does cross-react with *Chlamydia trachomatis* and *C. pneumoniae*. The microimmunofluorescence assay has a higher specificity and can demonstrate immunoglobulin M (IgM) or immunoglobulin G (IgG) antibody directed at *C. psittaci*. Evaluation of acute and convalescent sera is still recommended. However, it is important to note that the serologic response can be blunted when therapy is initiated early.

Rapid diagnostic testing has been utilized rarely in the diagnosis of *C. psittaci* infection: Immunohistochemical identification of *C. psittaci* antigen in clinical specimens has been successfully reported, and real-time polymerase chain reaction applied directly to both culture and clinical specimens has shown great specificity and sensitivity. Unfortunately, these techniques are not readily available in the clinical setting. In the acute setting, when therapy is initiated, the diagnosis of *C. psittaci* infection truly rests on clinical grounds, with an exposure history and a compatible clinical presentation.

THERAPY

The therapy of choice for *C. psittaci* infections, both systemic and limited, is a tetracycline. Doxycycline, 100 mg orally twice a day, is the preferred agent. The systemic nature of the infection and reports of relapsing disease require a prolonged course of therapy. The identification of relapsing disease has led most authors to suggest a course of at least 14 days, and most encourage 21 days total. In the seriously ill population requiring intravenous therapy the dosing is the same for doxycycline. In patients with endocarditis, a more prolonged course is necessary, and patients rarely have survived without valve replacement in addition to prolonged doxycycline therapy.

Traditionally, erythromycin, 500 mg orally four times a day, is the second-line drug for *C. psittaci* pneumonia. Because relapses and failures in therapy have been reported, a 21-day course of therapy is indicated. Newer macrolide agents, particularly azithromycin, have been studied in chlamydial infections, specifically *C. psittaci*. Failure of erythromycin has been reported in pregnancy, and some authors suggest tetracyclines or azithromycin in this setting. Azithromycin appears both in vitro and in vivo to be an excellent alternative to doxycycline. A 7-day course at 10 mg/kg of body weight has been effective in experimental models. This reflects the increased intracellular concentration of this agent as well as the prolonged half-life. Both azithromycin and doxycycline are intravenous options in severe disease. There are fewer data to support the use of clarithromycin, although this agent has been shown to be effective in the treatment of infections caused by other *Chlamydia* species. The new glycocyclic agent, tigecycline, although related to the tetracycline family, should not be considered an adequate therapeutic alternative, with no data to support its use for *C. psittaci*.

In the treatment of conjunctivitis where *C. psittaci* is suspected, a 4- to 10-week course of either

doxycycline or erythromycin is appropriate. More traditional agents have also shown efficacy, including chloramphenicol, 500 mg four times a day for 14 days. Patients failing this regimen have done well with the addition of rifampin.

Many reports in the literature demonstrate a prompt clinical response to doxycycline in patients infected with *C. psittaci*. Therefore, a patient's failure to show symptomatic improvement within 48 hours should prompt a re-evaluation of the diagnosis or a suspicion of deep-seated infection such as endocarditis.

There are growing data on the use of quinolones in the management of *C. psittaci* infections. These agents have shown excellent activity against other *Chlamydia* species. In vitro and animal model data have delineated activity of a broad range of quinolones against *C. psittaci*, most notably ofloxacin, ciprofloxacin, moxifloxacin, and sparfloxacin. Ofloxacin in a dose of 200 mg orally twice daily has shown efficacy in a small population of patients with confirmed infection with *C. psittaci*. The use of levofloxacin at 500 mg daily for 21 days would likely be similarly supported. Failure of quinolone therapy in fulminant disease has been described but more likely reflects a delayed diagnosis and the need for high index of suspicion on presentation.

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PART XXI

Specific organisms: *Rickettsia*, *Ehrlichia*, and *Anaplasma*

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170. Rickettsial infections

Paul D. Holtom

The Rickettsiaceae are aerobic, small, gram-negative coccobacilli that are obligate intracellular parasites of eukaryotic cells. There are three groups of rickettsiae based on clinical presentation: the spotted fever group, the typhus group, and scrub typhus. *Coxiella burnetii*, the agent that causes Q fever, is covered in this chapter but is now classified in the γ-proteobacteria group, together with *Legionella* and *Francisella tularensis* (Table 170.1).

The pathogenesis of illness due to the rickettsiae is vasculitis. The rickettsiae proliferate in the endothelial lining cells of the small arteries, capillaries, and veins. In Q fever the organisms are inhaled and proliferate in the lungs, causing inflammation and bacteremic seeding of other organs, particularly the liver. All of the important rickettsial infections are vector-borne, whereas Q fever usually results from inhalation of dust contaminated by the birth fluids of domestic ungulates.

In any discussion of the treatment of rickettsioses it is important to stress that proper treatment cannot be given unless the diagnosis is

Table 170.1 Diseases caused by Rickettsia

Disease	Organism	Geographic distribution	Vector
Spotted fever group			
Rocky Mountain	*Rickettsia rickettsii*	Western Hemisphere	Tick
spotted fever	*Rickettsia parkeri*	United States	Tick
Boutonneuse	*Rickettsia conorii*	Africa, Mediterranean, India	Tick
Queensland tick typhus	*Rickettsia australis*	Australia	Tick
North Asian tick typhus	*Rickettsia sibirica*	Russia, Asia, Africa, France	Tick
Japanese spotted fever	*Rickettsia japonica*	Japan, China	Tick
Flinders Island spotted fever	*Rickettsia honei*	Australia, Thailand	Tick
African tick-bite fever	*Rickettsia africae*	Sub-Saharan Africa, West Indies	Tick
Fleaborne spotted fever	*Rickettsia slovaca*	United States	Tick
Rickettsialpox	*Rickettsia aeschlimannii*	Europe	Tick
	Rickettsia felis	Africa	Flea
	Rickettsia akari	Western Hemisphere, Europe United States, Russia, Korea, Africa	Mite
Typhus group			
Epidemic typhus	*Rickettsia prowazekii*	Western Hemisphere, Africa, Asia	Louse
Murine typhus	*Rickettsia typhi*	Worldwide	Flea
Scrub typhus	*Orientia tsutsugamushi*	Asia, Australia, South Pacific	Mite
Ehrlichia			
Human monocytotropic ehrlichiosis (HME)	*Ehrlichia chaffeensis*	North America, eastern Asia	Tick
Human granulocytotropic anaplasmosis (HGA)	*Anaplasma phagocytophilum*	North America, Europe, Asia	Tick
Other			
Q fever	*Coxiella burnetii*	Worldwide	Airborne

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suspected. Confirmation of the diagnosis is usually serologic and almost always delayed, because antibodies occur no earlier than the second week of illness in any of the rickettsioses. The arthropod-borne rickettsioses are diseases of the spring and summer in temperate climates. Q fever can occur at any season if exposure to aerosols of the organism occurs. Given an appropriate geographic, temporal, and/or occupational history, the triad of fever, headache, and rash should cause the physician to suspect a disease caused by the rickettsiae. As early treatment is important in preventing fatalities, particularly in Rocky Mountain spotted fever (RMSF), therapy should be instituted when the diagnosis is suspected.

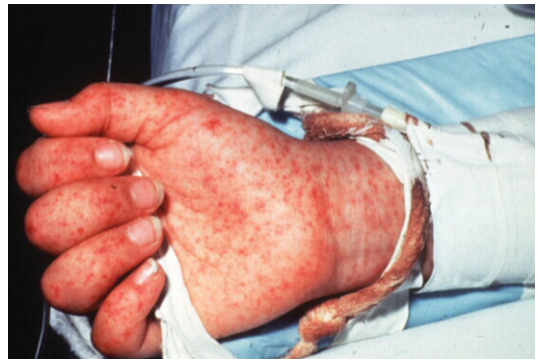

Figure 170.1 Petechial rash in Rocky Mountain spotted fever. (Courtesy of David Schlossberg, MD.)

ROCKY MOUNTAIN SPOTTED FEVER

RMSF was first described in the late 1800s in the Bitterroot Valley of Montana. Although originally recognized in the western United States, it now has a higher documented prevalence in the South Atlantic states and in the south-central region. The causative agent is *Rickettsia rickettsii*, a member of the spotted fever group of rickettsial infections.

Rickettsia rickettsii is transmitted to humans by the bite of an infected tick. Ticks are both the vectors and the main reservoirs of this agent; the specific tick responsible for transmission varies from region to region: In the eastern United States, the dog tick, *Dermacentor variabilis*, is the usual vector, whereas in the western United States it is the wood tick, *Dermacentor andersoni*. The adult tick transmits the disease to humans during feeding, releasing *R. rickettsii* from the salivary glands after feeding for 6 to 10 hours. Humans can also be infected by exposure to infected tick hemolymph, which may occur during the removal of ticks from persons or domestic animals, especially when the tick is crushed between the fingers. Although the incidence of RMSF has increased from less than two per million in 2000 to over eight cases per million persons in 2008, case-fatality rate has declined to 0.5%.

The incubation of RMSF ranges from 2 to 14 days, with a median of 7 days. Virtually all patients have fever, usually above 38.9°C (102°F). The major diagnostic sign is the rash, seen in approximately 90% of the patients, which usually occurs within 3 to 5 days after the onset of fever. Fewer than half of the patients show the rash during the first 3 days of the illness. The rash typically starts around the wrists and ankles, but it may start on the trunk or be diffuse at onset. Although involvement of the palms is considered characteristic, this does not occur in all patients and often occurs late in the course of the disease (Figure 170.1). Other common symptoms include severe headache, myalgias, and gastrointestinal complaints such as nausea, vomiting, and severe abdominal pain.

Complications of RMSF include meningismus, meningitis, renal failure, pulmonary involvement, hepatic dysfunction with development of jaundice, splenomegaly, myocarditis, and thrombocytopenia. Although in the early reports the case-fatality rate was greater than 20% in the absence of early therapy, in recent series of patients death occurs in 4% to 8% of the cases. In those with fulminant RMSF, death occurs 8 to 15 days after the onset of symptoms.

Diagnosis of RMSF is primarily based on a high clinical suspicion in the setting of a patient with fever, headache, and myalgias with exposure to ticks. Rash is found in only 14% of patients on the first day of illness and in 49% of patients during the first 3 days. A skin biopsy of a rash lesion (when present) can show *R. rickettsii* with immunohistochemistry staining or nucleic acid amplification test. This has a specificity of 100% and a sensitivity of 70% but is useful only in patients who have developed a rash. Serologic diagnosis is retrospective. The use of the polymerase chain reaction is not well established for the diagnosis of RMSF.

Treatment of RMSF requires the administration of an effective antibiotic for 7 days, continuing for 2 days after the patient has become afebrile. Early therapy is important, as the risk of death is five times greater in patients treated

after day 5 of illness. The antibiotic of choice for both adults and children is oral doxycycline, 100 mg every 12 hours for 7 days, or at least 2 days after the patient becomes afebrile. Tetracycline, 25 to 50 mg/kg/day in four doses, is also effective. In patients with hypersensitivity to tetracyclines and in pregnant patients, chloramphenicol, 50 to 75 mg/kg/day, is a less effective alternative. Although fluoroquinolones have shown activity against *R. rickettsii*, they are not recommended because of a lack of clinical experience. Glucocorticosteroids have been given to severely ill patients in the past, but there is no documentation of their efficacy. No vaccine is currently available to prevent RMSF.

OTHER SPOTTED FEVER GROUP RICKETTSIA

Five species of spotted fever group rickettsiae (SFGR) – *R. rickettsii, Rickettsia parkeri, Rickettsia felis, Rickettsia akari*, and *Rickettsia* 364D – are causes of infections in humans in the United States. However, standard serologic assays do not differentiate infections caused by SFGR, and all may be lumped into the diagnostic category of RMSF.

Successful treatment for all of them has been reported using doxycycline (200 mg/day); alternates may be tetracycline (25 mg/kg/day), chloramphenicol (2 g/day), or ciprofloxacin (1500 mg/day) for 5 to 7 days.

Rickettsia akari causes the nonfatal disease rickettsialpox, first reported in 1946 in New York but rarely diagnosed. The usual incidence in New York City is five cases per year, and it has been reported in eastern Europe, South Africa, and Korea. The reservoir for this infection is the house mouse, *Mus musculus*, and the vector for transmission to humans is the mouse mite *Allodermanyssus sanguineus*. A painless papule that ulcerates and forms an eschar occurs at the site of the mite bite some 3 to 7 days before the onset of symptoms in most cases. Manifestations include chills, fever, headache, myalgia, backache, and photophobia. Rigors and profuse diaphoresis may be seen. Within 2 to 3 days after onset, a generalized papulovesicular rash occurs. The rash begins as red papules 2 to 10 mm in diameter that vesiculate and heal by crusting. The disease is usually benign; death and complications are very rare.

EPIDEMIC OR LOUSE-BORNE TYPHUS

This classic plague of humanity is caused by *Rickettsia prowazekii* and transmitted by the human body louse *Pediculus humanus corporis*. The bacteria may remain latent in humans for many years after the initial infection and then relapse when persons are stressed by other disease or deprivations. Thus, during war and refugee exodus, when people are stressed and deprived and poor hygiene promotes the spread of lice, a rickettsemic person may initiate the cycle and cause an epidemic. This relapsing disease is generally milder than an initial attack, presumably because it occurs in a person with some established immunity. This recrudescent typhus is called Brill–Zinsser disease. An extrahuman reservoir has been identified in southern flying squirrels, *Glaucomys volans*, which are found throughout the eastern United States. Humans are infected by flying squirrel fleas.

The characteristic incubation period is 8 to 16 days. The onset is usually abrupt, with intense headache, progressive fever, chills, and severe myalgia. Rash begins on about the fifth day of illness, usually on the axillary folds and upper trunk and spreads centrifugally. The rash begins as pink macules that fade on pressure but progresses to become maculopapular, darker, petechial, and nonfading on pressure. The rash may become confluent and involve the entire body, but the face, palms, and soles are spared. In the pre-antibiotic era, mortality was seen in 13%, occurring a median of 12.5 days after onset of the illness; survivors defervesced a median of 14 days after onset. Indigenously acquired typhus related to flying squirrel exposure is a similar but milder illness.

The established therapy for epidemic typhus is doxycycline (100 mg twice daily), tetracycline (25 to 50 mg/kg/day in four doses), or chloramphenicol (60 to 75 mg/kg/day in four doses) given for 7 to 10 days. In epidemic situations where the availability of doxycycline may be limited, a single dose of 200 mg of doxycycline may be effective, but a small proportion of patients may relapse. No vaccine is currently available for the prevention of typhus; the only prevention available is control of body lice by hygiene and insecticides such as permethrin.

MURINE TYPHUS

Murine typhus, caused by *Rickettsia typhi*, has worldwide distribution, especially in tropical and subtropical seaboard regions. Its most important reservoirs are *Rattus* spp., and the classic vector that spreads the organisms from rats to people is the flea *Xenopsylla cheopis*. Although rats are the primary animal reservoir of *R. typhi*, other

mammals (including opossums and domestic dogs and cats) can also serve as reservoirs.

The disease is clinically less severe than epidemic typhus, with reported case-fatality rates of 1% to 4%. Illness begins 1 to 2 weeks after a bite from an infected flea. At first it is nonspecific, with fever, headache, chills, myalgia, and nausea. Rash is seen in about 20% of patients at presentation and in about 50% sometime during the illness. The skin lesions are macular or maculopapular. The trunk is most often involved, but the extremities are involved in about half the patients who develop rash. The rash may also be seen on the palms and soles. The rash is frequently salmon colored and evanescent, but frank hemorrhagic vasculitic rash may develop. Occasionally, patients develop central nervous system (CNS) abnormalities, hepatic or renal failure, respiratory failure, or hematemesis. Diagnosis is suggested by risk factors and clinical findings, and can be confirmed by a 4-fold or greater rise in antibody titer to *R. typhi* antigens between paired serum specimens taken $\geq$3 weeks apart, or by detection of *R. typhi* DNA in a clinical specimen by polymerase chain reaction (PCR).

Rickettsia typhi infection is treated with doxycycline, tetracycline, or chloramphenicol. Antimicrobial therapy should be continued for 2 to 3 days after defervescence.

SCRUB TYPHUS

Scrub typhus occurs when a larval stage trombiculid mite (chigger), infected with *Orientia tsutsugamushi*, bites a susceptible human host. The disease occurs from Korea and Japan to China, Southeast Asia, India, and south to Australia.

Some 6 to 18 days after a chigger bite, the patient develops high fever, severe headache, mental changes, lymphadenopathy, and myalgia. An eschar may be found at the site of the bite. The severity of the signs and symptoms is widely variable, depending on the virulence of the responsible strain and the degree of susceptibility of the host. After about 5 days a macular rash, sometimes evanescent, may occur, beginning on the trunk and spreading to the extremities. Complications include multiple organ system dysfunction and hemorrhage, pneumonia, heart failure, respiratory failure, and renal failure. Case-fatality rates as high as 30% in untreated patients have been reported, but treatment shortens the duration of illness and essentially eliminates fatalities.

Doxycycline and chloramphenicol are the recommended treatments. Doxycycline can be given as a single dose of 200 mg or for a course of 3 to 7 days. Alternative drugs include rifampin (600–900 mg/day) and azithromycin (500 mg initial dose, then 250 mg daily).

Q FEVER

Q fever, an infection caused by *Coxiella burnetii*, can present as an acute infection with an influenza-like illness, including pulmonary and hepatic involvement, or it can develop into a chronic infection with endocarditis and chronic hepatitis.

Coxiella burnetii is an extremely infectious organism. In fact, a single inhaled organism is sufficient to initiate infection. It is endemic worldwide except in New Zealand. *Coxiella burnetii* infects many species of animals, and the infection usually results in long-lasting parasitism. Q fever in humans is usually caused by the inhalation of aerosolized particles from infected domestic animals; these particles can be airborne over long distances.

C. burnetii is asymptomatic in about half of those infected. Those with clinical illness most commonly have a nonspecific febrile illness, which may be associated with pneumonia, hepatitis, or meningoencephalitis. Patients can go on to develop a chronic illness characterized by endocarditis and granulomatous hepatitis.

The incubation period for Q fever can be as short as 4 to 5 days, but it typically ranges from 9 to 39 days. Fever is the most common symptom, occurring in almost all patients, and the temperature often spikes to 40°C to 40.5°C (104°F to 105°F). Pneumonia is the primary clinical manifestation, with a majority of patients showing abnormalities on their chest radiographs. Other signs and symptoms include chills, headache (often severe and debilitating), retrobulbar pain, myalgias and arthralgias, neck pain and stiffness, pleuritic chest pain, cough, nausea and vomiting, diarrhea, jaundice, hepatomegaly, and splenomegaly. Unlike the rickettsial diseases, Q fever does not usually present with a rash, although a transient erythematous macular rash has been noted in about 4% of patients. The manifestations of Q fever usually resolve within 2 to 4 weeks, although some patients have had fever as long as 9 weeks. Case-fatality rates from acute Q fever are very low (none in most series), but in hospitalized patients the case-fatality rate has been reported as 2.4%. Children usually have a milder acute

disease than adults, but are more likely to have a rash (in up to 50%).

Chronic Q fever is uncommon (<5% of patients with acute infections) and usually manifested by endocarditis. Most patients have preexisting valvular heart disease, often a prosthetic valve. Other manifestations include chronic hepatitis, infections of vascular prostheses and aneurysms, osteomyelitis, and interstitial pulmonary fibrosis. The illness evolves slowly, manifesting any time from a few months to 20 years after the acute infection, and presents clinically as a culture-negative endocarditis, although fever is often absent in Q fever endocarditis. Post-Q fever fatigue syndrome, lasting for several years to life, is the most common chronic manifestation after acute infection, occurring in up to 20% of patients.

The diagnosis of Q fever is based on identifying risk factors and clinical suspicion. Culture is not recommended as it is difficult and dangerous, requiring a biosafety level 3 laboratory. Serologic testing of paired acute and convalescent sera, showing a 4-fold increase of IgG to *C. burnetii* phase II antigen by an indirect immunofluorescence antibody assay, is the most commonly used method for diagnosing acute Q fever. PCR testing of blood or tissue is another diagnostic method, but different tests vary in sensitivity and specificity.

Most acute Q fever infections resolve spontaneously, but because of the concern about the development of chronic Q fever specific antimicrobial therapy should be given. The treatment of choice is doxycycline orally for 2 weeks; some success has been reported with trimethoprim–sulfamethoxazole (TMP–SMX), chloramphenicol, rifampin, and (in vitro) telithromycin.

The treatment of chronic Q fever has never been the subject of controlled studies. No antibiotics have been found to be bactericidal for *C. burnetii*, although several (including tetracycline, doxycycline, TMP–SMX, rifampin, ciprofloxacin, and telithromycin) have been shown to be bacteriostatic. Current recommendations are to give doxycycline together with hydroxychloroquine for at least 18 months. A vaccine for people in at-risk professions is available in Australia, but requires testing before vaccination to identify preexisting immunity, as this can lead to a severe local reaction.

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171. Ehrlichiosis and anaplasmosis

Johan S. Bakken and J. Stephen Dumler

Ehrlichiosis is the collective name for infections caused by obligate intracellular gram-negative bacteria in the genera *Ehrlichia*, *Anaplasma*, and *Neoehrlichia*, family Anaplasmataceae. Members of these genera cycle between invertebrate (arthropod) and vertebrate hosts, and some cause human zoonoses. At least seven species cause human tick-borne infection in the United States and Europe, including *Ehrlichia chaffeensis*, the agent of human monocytic ehrlichiosis (HME), *Ehrlichia ewingii*, the agent of human ewingii ehrlichiosis (HEE), *Anaplasma phagocytophilum*, the agent of human granulocytic anaplasmosis (HGA), an *Ehrlichia muris*-like agent (EMLA), the Panola Mountain ehrlichia, an agent phylogenetically similar to *Ehrlichia ruminantium* that has caused fever in humans in the United States, *Ehrlichia canis*, thought limited to canids but identified as an agent of human febrile illness in Venezuela, and *Candidatus* Neoehrlichia mikurensis, which has caused severe sepsis-like conditions in Europe, but mild febrile disease in Asia. While human infection by *Neorickettsia sennetsu* periodically surfaces in Asia, the transmission and disease processes are distinct and it will not be considered here.

Most Anaplasmataceae reside in ixodid (hard-body) ticks, and the bacteria are acquired during the larval stage and passed transstadially with each successive tick stage. *Amblyomma americanum* (the Lone Star tick) is the vector for *E. chaffeensis* and *E. ewingii*, and its range is throughout the south and eastern United States from Maine to Texas. In addition, all documented reports of human infections are limited to North America, although some evidence suggests that they exist in ticks in South America and Asia. In contrast, *A. phagocytophilum* and the *E. muris*-like agent cycle within *Ixodes* species ticks. *Ixodes scapularis* (the black-legged or deer tick) is found in the eastern United States and is a vector for both species. In addition, *Ixodes pacificus* (the western black-legged tick), found in regions of the US Pacific coast (northern California, Oregon, and Washington), and *Ixodes ricinus* and *Ixodes persulcatus*, found in Europe and Asia, respectively, are competent vectors for *A. phagocytophilum*. *Ixodes* species ticks are also vectors for *Borrelia burgdorferi* (the agent of Lyme borreliosis), and most cases of HGA are reported from areas where Lyme borreliosis is endemic.

Thus far, HGA has been reported in 36 US states and in countries in western and central Europe, as well as Russia, China, Korea, and Japan. Active US surveillance in southeastern Missouri identified HME incidence as high as 414 cases per 100 000 population. The incidence for HGA varies from 25 up to 58 cases per 100 000 in endemic regions of Connecticut and Wisconsin. Only a limited number of cases of HEE have been recognized in central US states, but it is anticipated to be common. Clinical cases of infection by the *E. muris*-like agent were recently recognized in up to 48 patients in Wisconsin and Minnesota, and a small fraction of healthy blood donors in Minnesota and Wisconsin have evidence of past exposure. Less than 20 Venezuelan patients with *E. canis* infection, and only a small number of infections by *Candidatus* N. mikurensis, likely transmitted by *I. ricinus* ticks in Europe, have been identified; there is only a single report of Panola Mountain ehrlichia human infection. Most cases of ehrlichiosis present during the period between April and October, and as many as 75% of patients have noted one or more tick bites 1 to 2 weeks prior to the onset of symptoms. Male patients outnumber females by a factor of nearly 3 to 2, and even though HME and HGA affect all age groups, symptomatic infection is less frequent in children. The case-fatality rate is 0.6% and 2.7% for HGA and HME, respectively. Table 171.1 summarizes some of the epidemiologic characteristics associated with HME, HEE, HGA, EMLA-associated illness, and *Candidatus* N. mikurensis infection.

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Table 171.1 Epidemiologic characteristics, incidence rates and reported cases associated with human monocytic ehrlichiosis (HME), human ewingii ehrlichiosis (HEE), human granulocytic anaplasmosis (HGA), *Ehrlichia muris*-like agent (EMLA) infection and *Candidatus* Neoehrlichia mikurensis infection

Bacterial species	*Ehrlichia chaffeensis*	*Ehrlichia ewingii*	*Ehrlichia muris*-like agent	*Anaplasma phagocytophilum*	*Candidatus* Neoehrlichia mikurensis
Tick vector	*Amblyomma americanum*	*A. americanum*	*Ixodes scapularis*	*Ixodes scapularis* (USA) *Ixodes pacificus* (USA) *Ixodes ricinus* (Europe) *Ixodes persulcatus* (Asia) *Haemaphysalis concinna* (Asia)	*Ixodes ricinus* (Europe) *?Ixodes ovatus* (Japan)
Clinical illness	HME	HEE	EMLA infection	HGA	No name
Year first reported	1987	1999	2009	1994	2009
Known geographic distribution	Atlantic USA Southeast USA South Central USA	South Central USA	Upper Midwest (USA)	Upper Atlantic (USA) Upper Midwest (USA) Pacific coast (USA) North and central Europe Asia (China, Korea, Japan, Eastern Russia)	Central Europe Northeast China
Target leukocyte	Monocyte Macrophage	Neutrophilic granulocyte	Monocyte	Neutrophilic granulocyte	?Neutrophilic granulocyte
Incidence rate (cases/100 000)	14	Unknown	Unknown	20	Unknown
Reported cases (*n*)[a]	9411	≤50	44	12 764	15

[a] As of 09/13/2013 per MMWR Weekly Reports, CDC.

When the tick takes a blood meal, bacteria become injected with the tick saliva into the host. Once injected, the bacteria infect specific circulating leukocytes and cause a nonspecific febrile illness. *Ehrlichia chaffeensis* and EMLA typically infect monocytes and macrophages, whereas *E. ewingii* and *A. phagocytophilum* infect neutrophilic granulocytes; *Candidatus* N. mikurensis has been observed only once in human neutrophils but its definitive target is not yet established. The bacteria adhere to leukocyte membrane receptors to enter cells by endocytosis. There are key differences in the vacuoles with *E. chaffeensis* and *A. phagocytophilum*, underscoring that the agents induce distinct pathogenetic pathways. Regardless, the bacteria reside within cytoplasmic vacuoles, where they interact with the host cell to access nutrients, delivering effector proteins to the host cytosol and nucleus that subvert host cell functions, including intracellular signaling, cell cycle regulation, innate immune responses such as respiratory burst or induction of immune activation, delayed induction of apoptosis, and subversion of autophagy, among others. During this interval, the bacteria multiply in the vacuole to form aggregates called morulae. Eventually, each morula fuses with the cell membrane through exocytosis or the cell is mechanically lysed, liberating bacteria to infect other cells. Most recent investigations of disease pathogenesis focus on the induction of innate, inflammatory, and immune-mediated injury as the major consequence of infection. This suggests that an important target for control of disease could include control of inflammatory and immune responses.

Even though they differ with respect to biology, epidemiology, and ecology, HME, HEE, HGA, and infection with EMLA present as clinically similar illnesses with characteristic, albeit nonspecific alterations in hematology and chemistry laboratory tests. The incubation period for HME, HEE, HGA, and EMLA varies between 1 and 2 weeks following tick exposure or tick bite. The symptoms and signs range from asymptomatic to fatal, and clinical severity increases with patient age and comorbid illnesses. Ehrlichiosis presents as a clinical syndrome most commonly manifest by abrupt onset of fever, shaking chills, severe headache, and myalgia (Table 171.2); a specific diagnosis can be difficult because of the undifferentiated nature of the signs and symptoms. Between one-third and one-half of symptomatic patients require hospitalization for 1 week or longer. Infection with *Candidatus* N. mikurensis can result in either a severe febrile illness that lasts for weeks in the absence of therapy, as observed in Europe where most patients

Table 171.2 Mean frequency of symptoms and signs observed in patients with human monocytic ehrlichiosis (HME), human granulocytic anaplasmosis (HGA), human ewingii ehrlichiosis (HEE), *Ehrlichia muris*-like agent (EMLA) infection, and *Candidatus* Neoehrlichia mikurensis infection among published case series

Prevalence of complaint	Symptom or sign	HME (%) $n = 451$	HGA (%) $n = 750$	HEE (%) $n = 8$	EMLA (%) $n=48$	*N. mikurensis* ehrlichiosis $n = 13$
Common	Fever (T >38.0°C)	97	93	100	87	92
	Headache	76	62	63	66	62
	Myalgia/arthralgia	82	66	38	69	38
Less common	Nausea	62	40	25	na	38
	Vomiting	40	28	25	na	38
Uncommon	Pneumonitis or cough	27	25	0	na	31
	Confusion / altered	21	26	0	na	8
	mental status	33[a]	6[b]	0	0	31
	Rash					

[a] Mostly in children.

[b] All erythema migrans in Lyme borreliosis coinfected patients.

Abbreviations: T = temperature; na = data not available.

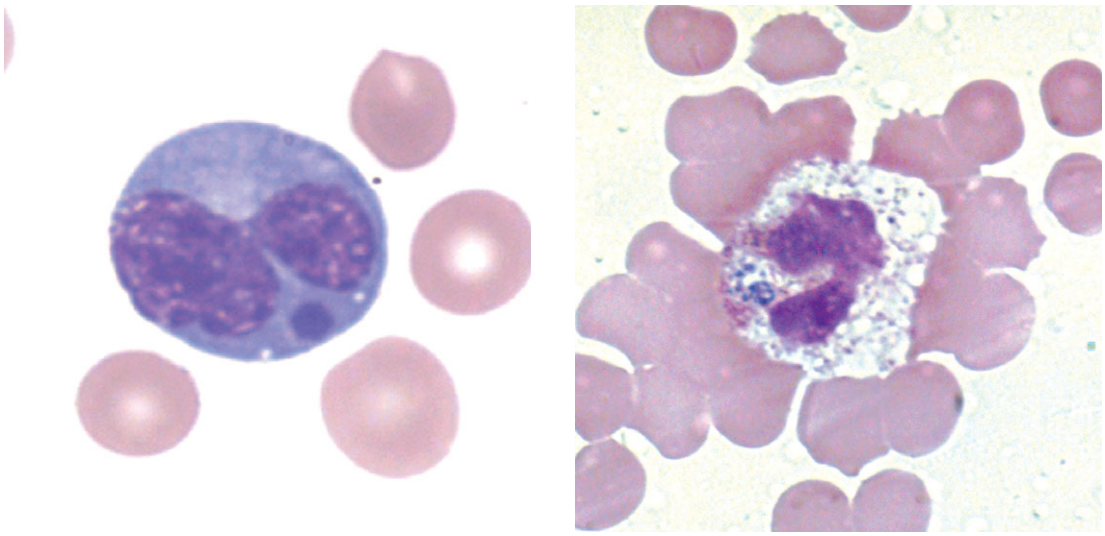

Figure 171.1 *Ehrlichia chaffeensis* morula (**left**) in a peripheral blood monocyte and *Anaplasma phagocytophilum* morula (**right**) in a peripheral blood neutrophil (Wright stain; original magnifications: 360× and 400×, respectively).

had pre-existing immune compromise, or as a mild to moderate and self-limited illness, as observed in Asia where most patients were not immune compromised.

Laboratory abnormalities are nonspecific and include various leukopenia and thrombocytopenia with a differential leukocyte count that reveals increased proportions of band neutrophils and a corresponding decrease in relative and absolute lymphocyte concentrations. In addition, most patients manifest mild to moderate increases in serum transaminase activities reflecting underlying hepatocellular injury. Albeit relatively insensitive, the diagnosis can be confirmed by blood smear examination, because morulae can be observed in peripheral blood leukocytes of 1% to 20% of patients with HME and as many as 60% of patients with HGA during the first week of infection (Figure 171.1). Polymerase chain reaction (PCR) is an excellent tool for diagnosing HME, HEE, HGA, and EMLA during the early stage of infection, and sensitivity >90% and specificity >95% are regularly achieved. However, the availability of these PCR assays is limited to large commercial, academic medical, or public health reference laboratories. More than

95% of patients with HME and HGA form specific antibodies during the course of the infection, and testing of acute and convalescent sera using indirect fluorescent antibody (IFA) tests is currently the most sensitive method for laboratory confirmation of HME and HGA, even though the diagnosis is only retrospective. Antibody titers remain elevated for months to years after convalescence, and no evidence of persistent infection associated with clinical disease has ever been observed. Serologic cross-reactivity between *Ehrlichia* spp. and *Anaplasma phagocytophilum* is frequent, but differential titers can be helpful. No specific serologic tests exist for either HEE or EMLA. Most diagnoses of Panola Mountain ehrlichia and *Candidatus* N. mikurensis infections have been made by specific or broad-range PCR.

Laboratory criteria for *probable* HME and HGA include a compatible exposure history and clinical illness combined with (1) the detection of morulae in peripheral blood, (2) a single high positive IFA titer, or (3) positive PCR of acute phase blood. The criteria for a *confirmed* case of HME or HGA requires (1) demonstration of seroconversion (4-fold or greater change in serum antibody titer) with *E. chaffeensis* or *A. phagocytophilum*, (2) isolation of *E. chaffeensis* or *A. phagocytophilum* in culture from blood, or (3) a single elevated IFA titer combined with either detection of morulae in the peripheral blood smear or a positive PCR. Formal laboratory criteria for probable or confirmed HEE, EMLA or *Candidatus* N. mikurensis infection have yet to be established.

THERAPY

Ehrlichia and *Anaplasma* are susceptible in vitro to tetracycline, tetracycline derivatives, and rifampin. However, no controlled clinical trials of antimicrobial agent efficacy have been conducted and treatment recommendations are therefore based on the experience from empirical antibiotic treatment of infected humans. Even though HME and HGA can manifest as self-limited febrile illnesses that resolve spontaneously without therapy, it is currently recommended that any patient diagnosed with acute infection should receive antibiotic treatment. Doxycycline, 100 mg administered twice daily (oral or intravenous route), is the treatment of choice for adults. Doxycycline, 2 mg/kg, maximum dose 100 mg, given twice daily, is the preferred treatment for children who are seriously ill. The response to doxycycline is rapid; most patients become afebrile and resolve symptoms within 24 to 36 hours. In fact, failure to respond to doxycycline should prompt further clinical evaluation of the patient for an alternative diagnosis. The optimal duration of therapy with doxycycline has not been established. Serologic surveys demonstrate that 15% to 20% of patients with active HGA also are seroreactive with *B. burgdorferi*, the agent of Lyme borreliosis. Doxycycline therapy should therefore be administered for 10 to 14 days to ensure adequate coverage for potential co-incubating Lyme borreliosis.

Treatment with rifampin can be considered for pregnant women, known hypersensitivity to tetracycline class drugs, and children younger than 8 years with mild to moderate illness suitable for outpatient management. The dose of rifampin is 300 mg given twice daily for adults and 10 mg/kg (maximum dose 300 mg) twice daily for children for 5 to 7 days. Chloramphenicol is not recommended for treatment of ehrlichiosis, since in vitro susceptibility assays with chloramphenicol demonstrate poor activity against *E. chaffeensis* and *A. phagocytophilum*, and treatment failures with fatal outcome have been noted. Fluoroquinolones have in vitro activity against *A. phagocytophilum*, but not *E. chaffeensis*; however, limited experience has shown that levofloxacin is apparently not bactericidal and should not be used to treat HGA.

Human ehrlichioses are for the most part self-limited clinical illnesses that resolve spontaneously, even without active antibiotic therapy. Unlike Lyme borreliosis and babesiosis, HME, HEE, HGA, and EMLA have not been reported to be associated with persistent infection, but several patients with *Candidatus* N. mikurensis infection had severe febrile illnesses that lasted as long as several weeks before treatment or death. The long-term prognosis after resolved HME, HEE, HGA, and EMLA appears favorable, and patients should expect to make a complete recovery.

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PART XXII

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172. Candidiasis

Christopher F. Carpenter and Nicholas Gilpin

Candida species are small unicellular yeasts that are found in a number of environments, including soil, hospital surroundings, food, and other inanimate objects. Most species are commensal organisms, colonizing the skin, gastrointestinal tract, and vagina. They become opportunistic pathogens when the host has compromised immunologic or mechanical defenses or when there are changes in the host's normal flora, such as those triggered by broad-spectrum antibiotic use and chemotherapy. *Candida* species are common causes of disease ranging from superficial cutaneous and mucocutaneous infections to invasive infections such as candidemia and disseminated candidiasis. There are more than 150 species of *Candida*, with *Candida albicans* (Figure 172.1) being the most frequently implicated in human disease processes. Over the past two decades, however, there has been a noticeable increase in disease due to non-*albicans* species. Important non-*albicans* pathogens include *Candida tropicalis* (Figure 172.2), *Candida parapsilosis*, *Candida glabrata* (Figure 172.3), *Candida krusei* (Figure 172.4), *Candida kefyr*, *Candida lusitaniae*, *Candida dubliniensis*, and *Candida gulliermondii*. Less commonly isolated species with medical significance include *Candida lipolytica*, *Candida famata*, *Candida rugosa*, *Candida viswanathii*, *Candida haemulonii*, *Candida norvegensis*, *Candida catenulate*, *Candida ciferri*, *Candida intermedia*, *Candida utilis*, *Candida lambica*, *Candida pulcherrima*, and *Candida zeylanoides*.

Diagnosis of *Candida* infections continues to be primarily via culture, although a number of faster

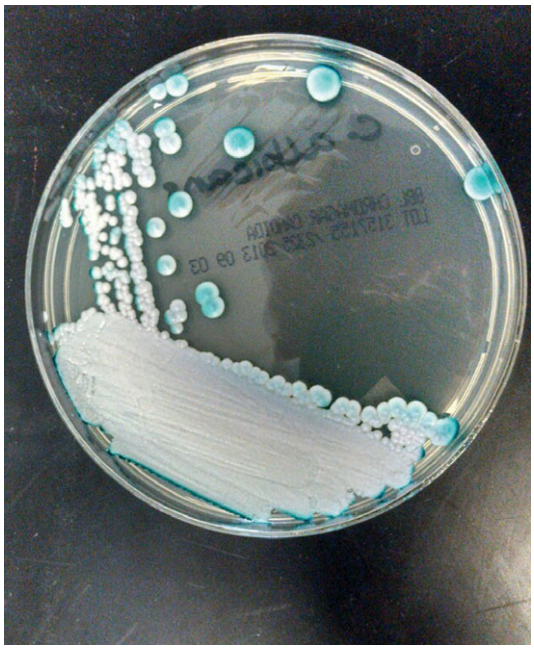

Figure 172.1 *Candida albicans*. CHROMagar. (Courtesy of Dr. Barbara Robinson-Dunn and Ms. Mrudula Nandwana, Beaumont Health System.)

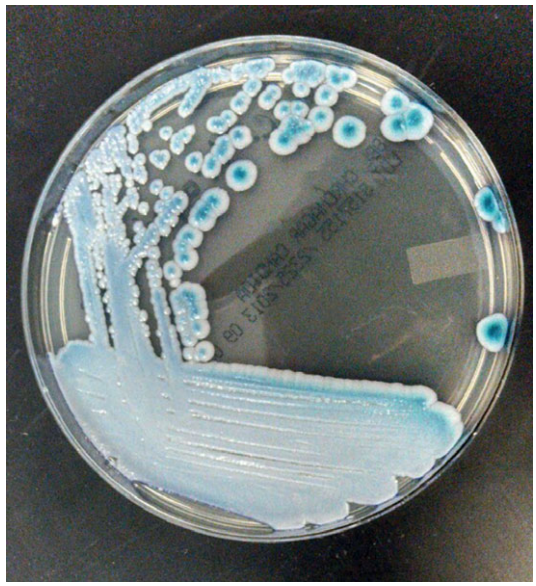

Figure 172.2 *Candida tropicalis*. CHROMagar. (Courtesy of Dr. Barbara Robinson-Dunn and Ms. Mrudula Nandwana, Beaumont Health System.)

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Figure 172.3 *Candida glabrata*. CHROMagar. (Courtesy of Dr. Barbara Robinson-Dunn and Ms. Mrudula Nandwana, Beaumont Health System.)

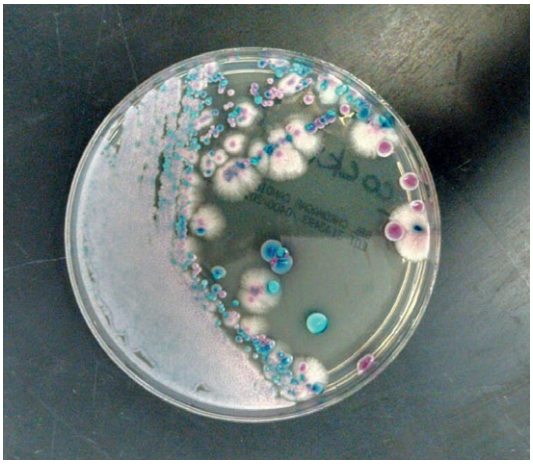

Figure 172.5 Mixture of *Candida* species (*C. albicans*, *C. tropicalis*, *C. glabrata*, and *C. krusei*). CHROMagar. (Courtesy of Dr. Barbara Robinson-Dunn and Ms. Mrudula Nandwana, Beaumont Health System.)

and more sensitive contemporary diagnostic methods have become available, including polymerase chain reaction (PCR), CHROMagar (Figure 172.5), and fluorescent *in situ* hybridization (FISH). Indirect diagnostic methods have also become more widely used in clinical practice, such as the serum or plasma (1→3)-β-D-glucan (BDG) assay, which is specific for a unique component of the cell wall in many fungi that is

Figure 172.4 *Candida krusei*. CHROMagar. (Courtesy of Dr. Barbara Robinson-Dunn and Ms. Mrudula Nandwana, Beaumont Health System.)

detectable during invasive candidiasis. Given that several *Candida* species have intrinsic or acquired resistance to antifungal agents (Table 172.1), these tests may prove to be cost-effective approaches for guiding early appropriate antifungal therapy in certain clinical settings. Newer antifungal agents have become available for the treatment of *Candida* infections, including advanced-generation triazoles and the echinocandins (Table 172.2), which are particularly useful when antifungal resistance is suspected or proven.

INFECTIOUS SYNDROMES AND TREATMENT/PROPHYLAXIS

Mucocutaneous *Candida* syndromes

CUTANEOUS CANDIDIASIS

Primary cutaneous candidiasis is commonly seen in normal hosts manifesting as diaper dermatitis and intertriginous infections. Other manifestations include balanitis, folliculitis, paronychia, and onychomycosis. Cutaneous candidiasis most commonly presents in skin areas that are moist and/or occluded, or in areas of impaired skin integrity, such as burns or chronic wounds. Immunocompromised patients, including patients with diabetes mellitus, are also at increased risk. Cutaneous candidiasis is generally a clinical diagnosis, demonstrated by the presence of a confluent erythematous rash with satellite lesions in a typical warm, moist environment such as the perineum or axilla. Microscopic

Table 172.1 *Candida* species and susceptibility patterns

	Triazoles		Extended-spectrum triazoles	Polyenes	Echinocandins	
SPECIES	FLUCONAZOLE	ITRACONAZOLE	VORICONAZOLE POSACONAZOLE	AMPHOTERICIN B	CASPOFUNGIN, ANIDULAFUNGIN, AND MICAFUNGIN	RISK FACTORS
C. albicans	S	S	S	S	S	HIV/AIDS, surgery
C. glabrata	S-DD to R	R	S-I	S-I	S	Hematologic malignancies, azole prophylaxis
C. parapsilosis	S	S-DD	S	S	S-I	Foreign bodies, azole prophylaxis, neonates
C. tropicalis	S	S	S	S	S	Neutropenia
C. krusei	R	R	S	S-I	S	Hematologic malignancies, azole prophylaxis
C. guillermondii	S	S	S	R	S	Azole prophylaxis, previous amphotericin treatment
C. lusitaniae	S	S	S	R	S	Previous amphotericin treatment

Abbreviations: HIV = human immunodeficiency virus; AIDS = acquired immunodeficiency syndrome; S = susceptible; S-DD = susceptible-dose dependent; S-I = intermediate; R = resistant.

Table 172.2 Antifungal agents

Class	Antifungal
Polyene	Conventional amphotericin B Lipid formulations of amphotericin B (liposomal amphotericin B, amphotericin B lipid complex, and amphotericin B colloid dispersion)
Triazole	Fluconazole Itraconazole Voriconazole (extended spectrum) Posaconazole (extended spectrum)
Echinocandin	Caspofungin Anidulafungin Micafungin

examination of skin scrapings revealing budding yeast cells and hyphae may be useful to confirm the diagnosis. Positive cultures for *Candida* species may also assist with diagnosis; however, positive results may occur because of colonization or contamination, and thus culture is generally not recommended. Bacterial superinfection may also coexist with cutaneous candidiasis, and sometimes necessitates antimicrobial therapy. Nonantimicrobial methods are important in both prevention and treatment of cutaneous candidiasis, such as keeping skin surfaces clean and dry, frequent diaper changes, and control of hyperglycemia in diabetics. Topical antifungals such as nystatin cream or an imidazole cream are the mainstay of treatment. Systemic therapy with fluconazole, itraconazole, or terbinafine is rarely required for severe or refractory cases.

CHRONIC MUCOCUTANEOUS CANDIDIASIS

Individuals with chronic mucocutaneous candidiasis suffer from persistent and recurrent *Candida* infections of the skin, nails, and mucous membranes. It most commonly occurs within the first two decades of life. T-cell dysfunction is the primary immunologic abnormality associated with chronic mucocutaneous candidiasis, although other immune abnormalities such as immunoglobulin deficiency and cutaneous anergy have been described. Several endocrine disorders have been associated with chronic mucocutaneous candidiasis, such as hypoparathyroidism, Addison's disease, hypothyroidism, and diabetes. The disease is a complex disorder that may manifest as one of many different syndromes with variable severity, although associated invasive disease is quite rare.

Therapy for mucosal infections is typically accomplished with topical or systemic triazole antifungal agents. A significant problem with mucosal disease is its propensity for repeated relapses, particularly among immunocompromised hosts and persons with human

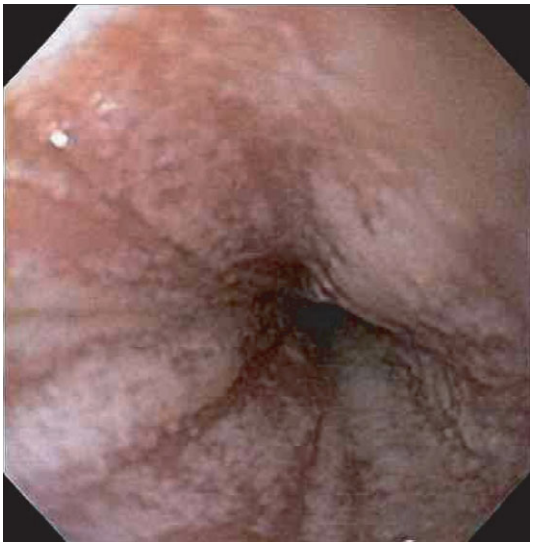

Figure 172.6 Endoscopic view, *Candida* esophagitis.

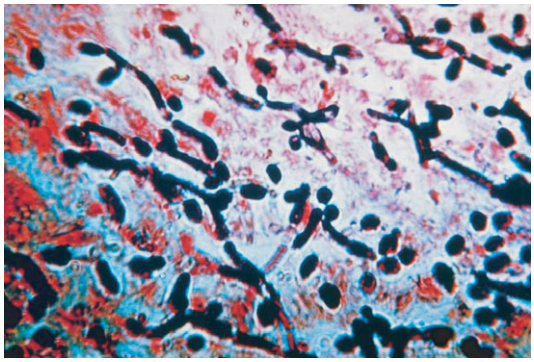

Figure 172.7 Photomicrograph of esophageal candidiasis (silver stain, ×100). (Courtesy of Sherry Brinkman, CDC Public Health Image Library.)

immunodeficiency virus (HIV) infection. Chronic suppressive therapy is usually unnecessary, but occasionally employed in select cases, with the associated risk of emerging resistance.

OROPHARYNGEAL AND ESOPHAGEAL CANDIDIASIS

As normal members of the gastrointestinal tract flora, *Candida* species become pathogenic in the oropharynx and esophagus in patients with various risk factors, including impaired cell-mediated immunity (e.g., HIV infection, chronic mucocutaneous candidiasis, stem cell and solid organ transplant recipients), diabetes mellitus, extremes of age, or esophageal motility disorders. The use of certain medications, including progesterone, broad-spectrum antibiotics, or immunosuppressive agents is also a contributing factor in many cases.

Oral candidiasis most commonly presents as creamy white plaque-like lesions on the oropharyngeal mucosa or tongue surface. Candidiasis lesions are typically painless, but atypical and more symptomatic forms may exist, such as erythematous or pseudomembranous plaques (erythematous candidiasis), *Candida* leukoplakia, or hyperplastic candidiasis. Angular chelitis, a painful condition with associated cracking and erythema at the oral commissure, can also be a result of *Candida* infection. As with cutaneous candidiasis, oropharyngeal candidiasis is usually a clinical diagnosis. Cultures are not usually recommended because of the potential for positive results due to colonization. For treatment of mild disease, clotrimazole troches or nystatin suspension for about 7 to 14 days are recommended first-line agents. For more moderate-to-severe oropharyngeal candidiasis, including patients with HIV infection, systemic therapy with low-dose oral fluconazole for 7 to 14 days is generally recommended. Infections that are refractory to fluconazole should be managed with another systemic antifungal agent, such as an extended-spectrum triazole or echinocandin.

Esophageal candidiasis often presents as dysphagia or odynophagia, usually with retrosternal pain. Clinically, it can be difficult to distinguish *Candida* esophagitis from other causes of esophagitis, such as cytomegalovirus esophagitis, herpes simplex virus esophagitis, esophageal ulcers, eosinophilic esophagitis, or pill esophagitis. The presence of oral thrush coupled with dysphagia or odynophagia has relatively good predictive value for esophageal candidiasis, and a therapeutic trial is a reasonable alternative to endoscopy in such patients. Empirical therapy should include a systemic antifungal for about 14 to 21 days; typically fluconazole in oral or parenteral form is prescribed. In rare circumstances, an alternative antifungal agent such as an echinocandin, extended-spectrum triazole, or low-dose amphotericin B may be required. In refractory cases, endoscopy with mucosal brushings or biopsy may be necessary to confirm the diagnosis, test for antifungal resistance, and evaluate for other potential concomitant pathogens or disorders (Figures 172.6 and 172.7).

VULVOVAGINAL CANDIDIASIS

Vulvovaginal candidiasis (VVC) is common in women of childbearing age and is the most common form of mucosal candidiasis. Several

Table 172.3 Classification of vulvovaginal candidiasis (VVC)

Uncomplicated VVC	Complicated VVC
All of the following: • Sporadic and infrequent VVC • Mild to moderate VVC • Likely to be *Candida albicans* • Nonimmunocompromised women	At least one of the following: • Recurrent VVC • Severe VVC • Non-*albicans* VVC • Women with uncontrolled diabetes mellitus, debilitation, or immunosuppression, or women who are pregnant

Source: Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep.* 2010;59(RR-12):1–110.

host risk factors can predispose to VVC, including pregnancy, oral contraceptive use, antibiotic use, diabetes mellitus, HIV infection, and the presence of an intrauterine device or a diaphragm. Many times no precipitating factor can be found. The mechanism by which asymptomatic colonization transforms into symptomatic VVC remains unclear. For clinical purposes, VVC may be classified as complicated or uncomplicated (Table 172.3). About 90% of cases are classified as uncomplicated. The clinical manifestations of VVC are primarily vulvar pruritus, vaginal discharge, dyspareunia, dysuria, and vaginal irritation, although none of these symptoms are particularly sensitive or specific. Signs include erythema and edema of the vulva with erythema of the vagina and vaginal discharge of variable consistency, often described as thick and curd-like. As with other forms of mucocutaneous candidiasis, the diagnosis is typically made clinically, but confirmation is easily obtained by observing budding yeast, with or without pseudohyphae, on a wet mount or 10% potassium hydroxide preparation of vaginal secretions. Evaluation for concomitant pathogens or sexually transmitted infections is also prudent.

Uncomplicated VVC can be managed successfully with a number of topical antifungal agents, with courses typically ranging from about 3 to 7 days. Alternatively, fluconazole as a single dose of 150 mg is also quite effective. Treatment with azoles results in symptomatic relief in about 80% to 90% of patients who complete therapy, and no agent is considered clearly superior.

Complicated VVC, including recurrent VVC (RVVC, usually defined as four or more episodes of symptomatic VVC in 1 year), affects a small percentage of women (≤5%). Vaginal cultures should be obtained to confirm the clinical diagnosis of RVVC and to identify unusual species, including non-*albicans* species such as *C. glabrata*, for which conventional antifungal therapies may not be as effective. Each individual episode of RVVC caused by *C. albicans* usually responds well to short-duration oral or topical azole therapy, but in some situations a course of induction therapy followed by a maintenance dose of suppressive antifungal therapy for several months is necessary for control of symptoms. Unfortunately, 30% to 50% of women will have recurrent disease after suppressive therapy is discontinued. For pregnant patients with VVC, topical therapy is recommended.

Candidemia and disseminated candidiasis

CANDIDEMIA

Candida species are a significant cause of nosocomial bloodstream infections in the United States. Crude mortality rates of candidemia range from 30% to 61% with attributable mortality ranging as high as 49%. *Candida* species, like some bacterial pathogens, are capable of forming biofilms on catheters and other surfaces, leading to infections that are difficult to eradicate. Certain risk factors are known to predispose to candidemia, but it remains very difficult to clinically predict which patients will develop infection. For example, colonization with yeast remains a leading risk factor for infection in the intensive care unit (ICU). However, the prevalence of colonization in the ICU is high (50%–70% or more), which corresponds to a low predictive value given the relatively low rate of invasive infection. Nevertheless, colonization in ICU patients with unexplained fever, leukocytosis, and hypotension merits strong consideration of invasive candidiasis and candidemia as a potential cause of sepsis. Delay of antifungal treatment portends significantly high mortality. In all cases, candidemia requires antifungal treatment and removal of potential sources, such as vascular devices. Search for additional foci of infection is also critical, as dissemination to areas such as the eye, liver, spleen, kidney, heart, soft tissues, bone, central nervous system (CNS), and gastrointestinal tract may occur. This is of particular concern in patients who are immunocompromised.

Empiric therapy for suspected invasive candidiasis should include a triazole or echinocandin. *Candida albicans* is usually susceptible to most antifungals, including fluconazole, whereas other species are more likely to demonstrate reduced

susceptibility or resistance to select antifungals. For example, *C. krusei* is intrinsically resistant to fluconazole and itraconazole but is usually susceptible to the extended-spectrum triazoles, echinocandins (nearly 100% susceptible), and amphotericin B formulations (though higher doses may be required). *Candida glabrata* has variable dose-dependent susceptibility to fluconazole and itraconazole, and it may be frankly resistant to these antifungals. It also typically shows some degree of cross-resistance to the newer triazoles, although both voriconazole and posaconazole are usually effective. The echinocandins have activity against most *Candida* species, although *C. parapsilosis* typically has relatively higher minimum inhibitory concentrations to these antifungals. The clinical relevance of these in vitro data is not clear.

For non-neutropenic patients, potential antifungal choices include fluconazole (800 mg [12 mg/kg] loading dose, followed by 400 mg [6 mg/kg] per day), caspofungin (70 mg loading dose followed by 50 mg/day), micafungin (100 mg/day), or anidulafungin (200 mg loading dose followed by 100 mg/day). Amphotericin B or a lipid-based amphotericin B formulation is an alternative that is much less commonly used for this indication today, generally only if there is intolerance to the other antifungal agents. For stable patients or those without prior azole exposure, fluconazole is reasonable for empiric therapy. Critically ill or hemodynamically unstable patients should be started on an echinocandin rather than fluconazole. Most neutropenic patients should initially be managed with an echinocandin. Select circumstances may lead to use of a lipid-based amphotericin B formulation, fluconazole, or voriconazole. Fluconazole and amphotericin B are considered alternatives due to concerns for potential resistance and toxicity, respectively. All candidemia treatment should be extended for at least 2 weeks after clearance of candidemia and resolution of sepsis. For neutropenic patients, recovery of neutrophil counts is another important factor, and antifungal treatment should generally be continued until this occurs.

CHRONIC DISSEMINATED CANDIDIASIS

Chronic disseminated candidiasis (CDC, formerly hepatosplenic candidiasis) is an indolent process most commonly found in patients with severe persistent neutropenia (e.g., in patients with acute leukemia or stem cell transplant recipients) that frequently becomes apparent when the neutrophil count begins to recover. It typically involves the liver and/or spleen, although other organs may be involved. Computed tomography (CT) or magnetic resonance imaging (MRI) studies are helpful in confirming the diagnosis (>90% sensitive), often by identifying small discrete lesions within the liver or spleen. Unfortunately, such lesions may be absent early in the course of disease. Signs and symptoms of CDC are neither sensitive nor specific, and may include right upper quadrant tenderness, elevated transaminases and alkaline phosphatase concentrations, and hepatosplenomegaly. Blood cultures are often negative, and biopsy may be required to confirm the diagnosis. Much of what is known about treatment of CDC has been gathered from case-series data. Amphotericin B, fluconazole, and echinocandins have been shown successful. Therapy should be continued until lesions appear calcified or cleared, a process which may take several months. Notably, in patients who receive repeated courses of antineoplastic therapy or who persistently remain immunosuppressed, prolonged treatment or suppression may be necessary.

Other forms of invasive candidiasis

ENDOCARDITIS AND CARDIAC DEVICE INFECTIONS

Patients with *Candida* endocarditis and patients with bacterial endocarditis share both risk factors (intravenous drug use, cardiac surgery, prosthetic heart valves, abnormal native heart valves, and central venous catheters) and clinical presentation (fever, nonspecific signs and symptoms, cardiac murmur, and congestive heart failure). Mycotic emboli to major arteries are more common in *Candida* endocarditis, and blood cultures are often negative initially. The diagnosis should be considered in all patients with candidemia. Evidence of a valvular vegetation by transthoracic or the more sensitive transesophageal echocardiogram establishes the diagnosis. Definitive treatment for native or prosthetic valve *Candida* endocarditis involves valve replacement in conjunction with a prolonged course of antifungal therapy, typically lipid-based amphotericin B formulation (3–5 mg/kg/day with or without flucytosine 25 mg/kg four times daily) for at least 6 weeks. Alternatives include amphotericin B or higher doses of an echinocandin. Chronic suppression with fluconazole is recommended if valve replacement cannot be performed and the yeast is susceptible. Following treatment, patients should be monitored

closely for a minimum of 1 year due to the propensity for relapse.

Infections due to *Candida* species involving cardiac devices such as pacemaker and implantable cardiac defibrillator infections are fortunately uncommon. Therapy should include removal of the entire device as well as systemic antifungal therapy as recommended for endocarditis. If the infection is limited to the generator or pocket, 4 weeks of therapy is recommended. If the infection involves wires or leads, at least 6 weeks of therapy is recommended. Failure to remove the device completely should warrant long-term suppressive azole therapy.

CENTRAL NERVOUS SYSTEM INFECTIONS

Meningitis is the most common form of CNS candidiasis, but numerous other forms of infection such as cerebral or epidural abscesses may occur. Low-birth-weight infants and immunosuppressed hosts are at particularly increased risk for meningitis. Nosocomial risk factors such as recent neurosurgery and the presence of ventricular shunts and drains are also significant in the development of *Candida* CNS infections. Signs and symptoms are similar to, but often less severe than, bacterial meningitis. Typically there is a more indolent and chronic course. Cerebrospinal fluid (CSF) analysis usually reveals a neutrophilic predominance, elevated protein, and either normal or depressed glucose. The diagnosis can be difficult because the organism is present in low numbers in the CSF and the yield of standard CSF cultures is poor; thus repeated CSF cultures may be required. Combination therapy with lipid-based amphotericin B (3–5 mg/kg/day) plus flucytosine (25 mg/kg four times daily) is recommended initially. After there is clinical response to initial therapy (usually several weeks later), treatment may be adjusted to fluconazole (400–800 mg/day) until all signs and symptoms have resolved. Removal of any ventricular shunt or drain is highly recommended to achieve eradication.

OCULAR INFECTIONS

Up to 15% of patients with candidemia have retinal lesions, often visible within 1 week of the onset of illness. The mortality rate in ICU patients with *Candida* endophthalmitis is considerably higher than the mortality rate in patients with candidemia alone. Symptoms may include bulbar pain, scotomas, and blurred vision. Diagnosis requires a high degree of clinical suspicion, and thus all patients with candidemia should be screened at least once for endophthalmitis by an ophthalmologist. Additional screening is discretionary, and may be required in cases of persistent candidemia or in patients who are unable to communicate regarding visual disturbances. Lesions may be sight-threatening; diagnosis relies on characteristic ocular findings such as white lesions on the retina with ill-defined borders with possible vitreal extension. A diagnostic vitreal aspiration is often necessary if endophthalmitis is suspected and the etiology is unknown. The sensitivity of vitreous humor cultures remains low, ranging from 33% to 50%. Recommended systemic therapy for endophthalmitis includes an amphotericin B formulation with or without flucytosine at doses used for candidemia, particularly for sight-threatening lesions. Fluconazole or voriconazole are other treatment options. Both have good vitreal penetration and less toxicity compared with amphotericin B. Caution is advised with the use of echinocandins because of poor ocular tissue penetration. Typically, about 4 to 6 weeks of therapy is anticipated for endophthalmitis in conjunction with close ophthalmology follow-up. Vitrectomy with intravitreal amphotericin B should be considered for severe endophthalmitis, vitritis, or evidence of progression or an absence of response.

GASTROINTESTINAL CANDIDIASIS

Candida peritonitis may develop in patients on peritoneal dialysis, after gastrointestinal surgery, as a complication of candidemia, or as an extension of local organ or tissue infection. In addition, gastric and duodenal mucosal infections may develop in patients with peptic ulcer disease or mucosal neoplasm. Other rare intra-abdominal manifestations of *Candida* infection include isolated pancreatic abscess, gangrenous cholecystitis, and obstruction of the common bile duct with a *Candida* fungus ball. *Candida albicans* is the predominant species isolated in intra-abdominal infections, but *C. glabrata* plays a significant role. Diagnosis is made by paracentesis or by endoscopic, percutaneous, or open biopsy. Antifungal therapy targeting *Candida* is not recommended for all patients with community-acquired intra-abdominal infection, but antifungal therapy is recommended in patients with severe infection or healthcare-associated intra-abdominal infection. An echinocandin or fluconazole is most commonly recommended for empiric therapy. Amphotericin B formulations are not usually recommended due to significant toxicity. As with all intra-abdominal infections, appropriate source

control measures (e.g., drainage of abscesses, removal of infected material, etc.) are also crucial in management.

BONE AND SOFT-TISSUE INFECTION

Bone and soft-tissue infections are rare complications of *Candida* dissemination or direct extension of a local *Candida* infection and are diagnosed by needle aspiration or via surgical debridement. They also may result from exogenous inoculation during trauma, intra-articular injection, a surgical procedure, or injection drug use. Treatment usually requires a combination of surgical debridement and often prolonged systemic antifungals, and high-dose fluconazole or a lipid-based amphotericin B formulation should be considered for initial therapy; extended-spectrum triazoles and echinocandins may have a role as well, but few data are available. Treatment is recommended for at least 6 to 12 months in cases of osteomyelitis, and about 6 weeks in cases of septic arthritis and bursitis. If prosthetic joint hardware or other devices are involved, removal is highly recommended to achieve cure.

RESPIRATORY TRACT CANDIDIASIS

Pneumonia due to *Candida* spp. is exceedingly rare as an isolated *Candida* infection. It is also poorly defined as a clinical entity because positive cultures cannot distinguish between true infection and either colonization or contamination of samples with oropharyngeal contents. Confirming a diagnosis of *Candida* pneumonia requires histopathologic confirmation, which is rarely performed. Growth of *Candida* from respiratory secretions alone is insufficient to warrant therapy and perhaps best serves to document colonization.

Patients with empyema due to *Candida* generally have an underlying predisposing condition such as malignancy, and esophageal perforation should be considered in patients at risk. Most cases are nosocomially acquired, occurring frequently with concomitant bacterial infection. Diagnosis is made with isolation of a fungal species from an exudative pleural effusion in association with clinical signs of infection. Treatment via drainage and systemic antifungals with an amphotericin B formulation or fluconazole is appropriate. The newer triazoles and echinocandins also may be considered, but data are limited.

GENITOURINARY *CANDIDA* INFECTIONS

The isolation of *Candida* in the urine is common in hospitalized or nursing home patients, especially in those with indwelling urinary catheters. Most often catheter-related candiduria is asymptomatic, and although it generally does not require antifungal treatment, it may occasionally be difficult to distinguish patients with asymptomatic candiduria from those with true *Candida* urinary tract infections. Infections are more common and potentially more serious in patients who are taking broad-spectrum antibiotics or immunosuppressive agents, in patients with diabetes mellitus or who are otherwise immunosuppressed, and in patients with genitourinary abnormalities (including obstructive uropathy and renal transplant recipients). The diagnosis is problematic, as high colony count is not a strong indicator of infection, and pyuria in this setting is not always helpful. Frequently, the clinical suspicion combined with signs and symptoms of infection and culture results post removal of the catheter may be all that is available for the clinician. In most episodes of candiduria, catheter removal is often all that is required. *Candida* infection of the bladder also must be distinguished from infection of the kidney, although the two entities can coexist. Invasive infection of the kidney is unusual and is more difficult to treat. Other genitourinary syndromes (e.g., epididymo-orchitis) often require percutaneous culture for diagnosis.

Antifungal treatment for candiduria is recommended if symptoms of urinary tract infection are present, for patients with neutropenia, for low-birth-weight infants, for renal transplant recipients, or for patients undergoing urologic procedures. Fluconazole is appropriate initial therapy, because it is well tolerated and achieves good levels in the urinary tract. If fluconazole resistance is suspected, systemic amphotericin B is an appropriate treatment alternative. Amphotericin B bladder irrigations are not routinely recommended due to high relapse rates, and other systemic antifungals (e.g., the echinocandins, posaconazole, and voriconazole) do not achieve adequate urine levels to be considered optimal for treatment.

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173. Aspergillosis

Sanjay Ram and Stuart M. Levitz

Aspergillus is readily isolated from environmental samples of soil, water, and air worldwide. *Aspergillus fumigatus*, followed by *Aspergillus flavus*, *Aspergillus niger*, and *Aspergillus terreus*, are the most common species that cause human disease. Aspergillosis follows exposure of a susceptible host to the ubiquitous conidia (spores). Germinating conidia form hyphae, the invasive form of the fungus. *Aspergillus* hyphae average 2 to 4 μm in diameter and are septate, with dichotomous (Y-shaped) branching (Figure 173.1). The spectrum of diseases caused by the aspergilli is wide and profoundly influenced by the underlying immune status of the host.

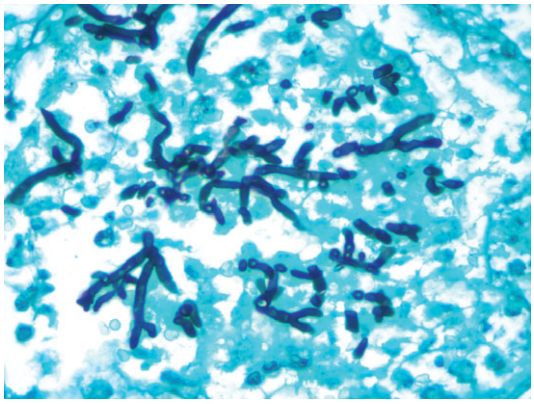

Figure 173.1 Photomicrograph demonstrating *Aspergillus* hyphae in a lung at autopsy in a liver transplant patient who died of systemic aspergillosis. The hyphae are stained with methenamine silver. (Courtesy of Dr. Barbara Banner, University of Massachusetts Medical School.)

CLINICAL MANIFESTATIONS AND DIAGNOSIS OF INVASIVE ASPERGILLOSIS

Although inhalation of conidia is common, invasive disease is relatively rare. The vast majority of affected patients are severely immunosuppressed. Major risk factors include prolonged neutropenia and macrophage dysfunction secondary to cytotoxic chemotherapy and high doses of corticosteroids, respectively. In patients who have undergone hematopoietic stem cell transplantation, additional risk factors are graft-versus-host disease and cytomegalovirus infection. Invasive aspergillosis also is particularly common in individuals with chronic granulomatous disease, a rare genetic disorder characterized by a defective phagocyte respiratory burst. Finally, critically ill patients appear to be at risk for invasive aspergillosis, even without aforementioned risk factors.

Invasive pulmonary aspergillosis, with or without dissemination, is the most common form of disease. Signs and symptoms of invasive aspergillosis are nonspecific. Fever is generally present. Radiographic features include patchy densities or well-defined nodules that may be single or multifocal and can progress to cavitation or consolidation. High-resolution computed tomography (CT) scanning has greater sensitivity than plain films. Macronodules (nodules greater than 1 cm in diameter) are present in the vast majority of patients with invasive pulmonary aspergillosis. Nodules may be surrounded by a perimeter of ground-glass opacity, the so-called halo sign (Figure 173.2). Cavitation ("air-crescent sign") is less common and tends to occur as a later manifestation of disease. Tracheobronchitis without alveolar invasion may be seen, particularly in lung transplant recipients and those with advanced acquired immunodeficiency syndrome (AIDS). Invasive *Aspergillus* sinusitis is the second most common manifestation and must be distinguished from saprophytic colonization. Its clinical features include fever, localized pain, proptosis, and visual problems. Fungal keratitis due to direct inoculation of *Aspergillus* has been increasingly recognized as an important cause of visual loss, particularly among agrarian workers in developing countries. Less common manifestations include cutaneous aspergillosis, which may be seen at intravenous catheter insertion sites in neutropenic patients or at sites of burn

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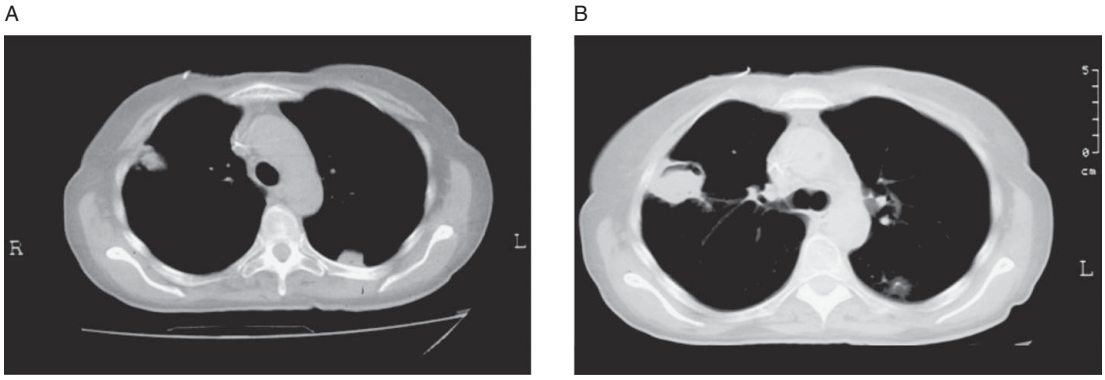

Figure 173.2 High-resolution computed tomography scans from patients with invasive pulmonary aspergillosis. A: Two pleural-based nodules can be seen. The one on the right is surrounded by a gray area of low-attenuation (halo sign). B: Air-crescent sign in a patient recovering from neutropenia. (Courtesy of the *Aspergillus*/Aspergillosis website: www.aspergillus.org.uk. Copyright by the Fungal Research Trust. Used with permission.)

wounds. While disseminated aspergillosis can involve any organ, cerebral involvement is a particularly common manifestation. Endocarditis due to *Aspergillus* is relatively rare and can be difficult to diagnose as blood cultures are often negative.

Invasive aspergillosis must be strongly suspected in any high-risk patient with fever unresponsive to broad-spectrum antibiotics, and empiric antifungal therapy should be considered. Although *Aspergillus* can be a laboratory contaminant or a colonizer, a positive culture for *Aspergillus* in an at-risk patient is predictive of invasive disease and should not be ignored. However, in patients with established disease, cultures and even biopsies are often negative.

In an effort to improve prognosis with earlier detection, nonculture methods to detect *Aspergillus* antigens and nucleic acids in specimens from high-risk patients have been studied. Tests to detect two cell wall antigens released by growing aspergilli, galactomannan and β-glucan, are clinically available. Serum galactomannan levels have excellent specificity but only moderate sensitivity. Sensitivity is higher in patients with hematologic malignancies, where positive results may precede clinical or radiologic manifestations, than in those with solid organ transplants. False positives have been noted in patients receiving piperacillin–tazobactam and amoxicillin–clavulanate due to contamination of some lots with galactomannan. False negatives are considerably more common in patients receiving antimold prophylaxis. Assays to detect β-glucans in clinical specimens appear to perform comparably to those for galactomannan, with the caveat that elevated β-glucans may be seen in fungal infections besides aspergillosis. Tests to detect *Aspergillus* DNA and RNA in clinical samples remain investigational. It should be emphasized that the aforementioned surrogate detection markers cannot definitively establish or exclude a diagnosis of aspergillosis and clinical correlation is required. Moreover, testing for antibodies, while useful for other forms of aspergillosis (see below), is not helpful in invasive aspergillosis.

TREATMENT OF INVASIVE ASPERGILLOSIS

Licensed drugs with activity against *Aspergillus* include amphotericin B (a polyene); the triazoles, itraconazole, voriconazole, and posaconazole; and the echinocandins, caspofungin, micafungin, and anidulafungin. Fluconazole and ketoconazole do not inhibit *Aspergillus* at clinically obtainable concentrations and should not be used to treat aspergillosis. It is somewhat difficult to rank the active drugs in terms of relative efficacy because few randomized comparative trials have been performed. Studies based on comparisons to historical controls are problematic due to significant differences in the patient populations. A multicenter, randomized trial compared voriconazole with amphotericin B in 277 patients with definite or probable acute invasive aspergillosis. The voriconazole regimen demonstrated superior efficacy and a 22% relative survival benefit. Moreover, there were fewer treatment-related adverse events in the voriconazole group. This study was criticized for its unblinded design, the use of conventional (rather than lipid-based) amphotericin B preparations, and the allowance

of a switch to other licensed antifungal medications. Nevertheless, the large survival benefit observed established voriconazole as the drug of choice for initial treatment of invasive aspergillosis. An important caveat though is voriconazole is not effective therapy against zygomycosis, which can present in a similar manner to aspergillosis.

In the above study, two doses of 6 mg/kg of intravenous voriconazole were administered on day 1, followed by 4 mg/kg/day. A switch to oral voriconazole at a dose of 200 mg twice a day was allowed after 1 week. Transient visual disturbances, including blurred vision, altered color perception, and photophobia, are common with voriconazole and tend to resolve without incident. Other side effects that have been observed include rash and liver function test abnormalities. Voriconazole is a substrate and an inhibitor of CYP2C19, CYP2C9, and CYP3A4. Thus, drug interactions are common and dose adjustments of voriconazole and coadministered drugs may be needed. The authors recommend obtaining steady-state trough levels and adjusting the dosing if necessary to achieve levels between 1.0 and 5.5 μg/mL. In patients with an estimated creatinine clearance <50 mL/min, accumulation of the intravenous vehicle occurs; these patients should be given oral voriconazole whenever possible.

In addition to voriconazole, other licensed triazoles with activity against *Aspergillus* are itraconazole and posaconazole. Itraconazole appears to be least potent and is mainly used for the treatment of aspergillomas and allergic bronchopulmonary aspergillosis (see below). Posaconazole appears more promising and has the added advantage of having useful activity against zygomycetes, but clinical experience with its use for primary treatment of invasive aspergillosis is limited. Delayed-release tablets and an IV formulation of the drug recently became available. Resistance of *Aspergillus* to voriconazole and other triazole drugs can emerge during therapy although the extent to which this leads to clinical failure is not clear. Ominously, primary resistance has been increasingly reported in both environmental and initial clinical isolates of *Aspergillus*, perhaps as a consequence of the agricultural use of azoles.

Amphotericin B is generally used for the treatment of invasive aspergillosis in patients who cannot take voriconazole because of contraindications or intolerance. (Amphotericin B should not be used to treat *Aspergillus terreus* or *Aspergillus nidulans* due to decreased susceptibilities.) However, controversy exists regarding the optimal daily dosage and formulation. For the conventional amphotericin B desoxycholate formulation, following a test dose of 1 mg, dosages ranging from 0.6 to 1.5 mg/kg/day have been recommended, with higher dosages reserved for severely ill and/or profoundly immunosuppressed patients. Fevers, chills, and rigors, observed in a significant number of patients treated with amphotericin B, may be alleviated by premedication with acetaminophen, meperidine, 25 to 50 mg given intravenously, or the addition of 25 to 50 mg of hydrocortisone sodium succinate to the infusion solution. Amphotericin nephrotoxicity has been associated with sodium-depleted states and may be reduced by giving 1 L of normal saline a day to patients with no contraindications to volume expansion. As amphotericin B causes renal tubular losses of potassium and magnesium, their levels should be monitored closely and supplementation provided as needed. The dosage of amphotericin B must be individualized depending on factors such as the expected duration and degree of immunosuppression, and the extent of the disease.

In an effort to reduce the toxicity associated with the conventional amphotericin B preparation, lipid-associated formulations have been developed. Currently available formulations include amphotericin B lipid complex, amphotericin B colloidal dispersion, and a liposomal preparation. Comparisons between the different formulations of amphotericin B are difficult to make due to the lack of well-designed randomized trials. However, at the usual daily dosages recommended for the treatment of invasive aspergillosis (3 to 5 mg/kg/day), the lipid formulations appear to be at least as efficacious as amphotericin B deoxycholate. The lipid formulations are less nephrotoxic than the conventional preparation but cost considerably more. A clinical trial comparing 3 and 10 mg/kg/day of liposomal amphotericin B as primary therapy for invasive aspergillosis found the lower dose was equally effective but less toxic.

Three members of the echinocandin class of antifungal drugs, caspofungin, micafungin, and anidulafungin, are licensed for use. All have modest activity against *Aspergillus* in vitro and in animal models, although none has been adequately studied in comparative clinical trials for primary treatment of invasive aspergillosis. In an open-label study of 83 patients with invasive aspergillosis who were refractory or intolerant to amphotericin B, a favorable response to

caspofungin therapy was observed in 37 (45%) of the subjects. Due to poor oral absorption, the echinocandins must be administered intravenously. Although infusion-related reactions and liver function test elevations are relatively common, serious side effects of this class of drugs are rare.

Due to the high failure rate associated with monotherapy for invasive aspergillosis, combination regimens as initial and salvage therapy have been tried. A randomized, double-blind study comparing voriconazole and anidulafungin combination therapy with voriconazole monotherapy in the treatment of invasive aspergillosis was recently completed. As of this writing, the results had not yet been published in a peer-reviewed journal. However, an analysis of the data revealed a trend, which did not reach statistical significance, towards improved overall survival in the group that received combination therapy. It is the authors' practice to treat most cases of invasive aspergillosis with voriconazole monotherapy, but to add an echinocandin if progression results.

Regardless of whether monotherapy or combination therapy is utilized, the duration of treatment should be individualized depending on the extent of disease and degree of immunosuppression. Most patients will require several months of treatment. Surgery should be considered as an adjunct to treatment in instances where there is localized disease, particularly in cases where there is progression despite antifungal therapy or further courses of neutropenia-inducing chemotherapy are anticipated. Whenever possible, immunosuppression should be withdrawn or decreased. In neutropenic patients, recombinant granulocyte colony-stimulating factor (G-CSF) may improve outcome by decreasing the duration of neutropenia and increasing the functional activity of neutrophils. Finally, patients with filamentous fungal keratitis should be treated with 5% natamycin eyedrops initially applied every hour. Surgical intervention by ophthalmology is often required.

PROPHYLAXIS AND PRE-EMPTIVE TREATMENT OF INVASIVE ASPERGILLOSIS

Given the high mortality associated with established disease, strategies for the prevention of invasive aspergillosis have been advocated and are summarized in Table 173.1. Numerous studies have examined empiric antifungal therapy in neutropenic patients with persistent or recurrent fevers despite empiric antibacterial therapy. This group is at high risk for invasive fungal infections, particularly aspergillosis and candidiasis, but also other opportunistic mycoses, including zygomycosis and fusariosis. Thus, ideal agents will have activity against a broad spectrum of opportunistic fungi. However, for those for whom the duration of neutropenia is expected to be short, candidiasis is the main concern, with aspergillosis and other mold infections being less common.

The earlier studies, published in the 1980s, established that amphotericin B deoxycholate could decrease the incidence of invasive fungal infections in patients with persistent neutropenic

Table 173.1 Prevention of invasive aspergillosis

Preventive strategy	Comments
1. Avoidance of exposure to *Aspergillus* conidia a. Avoidance of environmental exposure b. High-efficiency particulate air (HEPA) filters or laminar air flow (LAF)	Heavily contaminated areas include compost heaps, grain silos, moldy hay, and marijuana Although expensive, HEPA and LAF may be considered for hospitalized patients at very high risk of invasive aspergillosis, particularly if mold counts are high
2. Prophylaxis of high-risk patients	Posaconazole or other mold-active antifungals should be considered in very high-risk groups[a]
3. Administration of colony-stimulating factors to neutropenic patients	Expensive. May be considered as part of an overall strategy to reduce infections in selected patients
4. Pre-emptive, empirical administration of antifungals to neutropenic patients with fevers despite broad-spectrum antibacterial agents	Strongly recommended[a]
5. Secondary prophylaxis (antifungal treatment to prevent recrudescence of invasive aspergillosis in patients who will become immunosuppressed)	Due to high relapse rates, voriconazole or amphotericin B should be given at the onset of chemotherapy or neutropenia. Consider surgical resection of localized disease[a]

[a] See text for details.

fevers. Subsequent noninferiority studies compared amphotericin B (either deoxycholate or lipid-based formulations) with fluconazole, itraconazole, voriconazole, and caspofungin. An important caveat in interpreting these studies is the variability in inclusion criteria and end points defining success. Fluconazole has been successfully used in patient populations at low risk of invasive aspergillosis. Itraconazole and caspofungin have demonstrated noninferiority compared with amphotericin B. In a large study comparing voriconazole with liposomal amphotericin B, there were fewer breakthrough fungal infections in the voriconazole group, though the study design has been criticized.

A study compared posaconazole (200 mg three times daily) with either fluconazole (400 mg/day) or itraconazole (200 mg/day) in 602 patients undergoing intensive chemotherapy for acute myelogenous leukemia or myelodysplastic syndrome. Patients received antifungal medications with each cycle of chemotherapy until complete remission or for up to 12 weeks. Remarkably, during the treatment phase of the study, only 2 cases of aspergillosis were seen in the posaconazole arm compared with 20 in the fluconazole–itraconazole arm. Moreover, there was a significant overall survival benefit in favor of posaconazole. Similarly, a significant reduction in cases of aspergillosis and in mortality was seen in a study comparing posaconazole with fluconazole for allogeneic hematopoietic stem cell transplant recipients with graft-versus-host disease.

ASPERGILLOMAS

Pulmonary aspergillomas are the result of saprophytic colonization of *Aspergillus*, usually within pre-existing lung cavities such as might result from sarcoidosis or tuberculosis. The diagnosis is most often made by chest radiography, where a round to oval intracavitary mass partially surrounded by a radiolucent crescent of air is seen. Serum precipitins and sputum cultures for *Aspergillus* are positive in about 90% and 50% of cases, respectively. Hemoptysis is the most common symptom, and in most cases is mild and self-limited. Rarely, extrapulmonary aspergillomas can form, particularly in the sinuses.

Therapy for aspergillomas must be individualized according to the pulmonary and immunologic status of the host, but in most cases a conservative approach with close clinical follow-up is recommended. Resection generally is reserved for those with life-threatening hemoptysis. However, many patients are not surgical candidates due to poor baseline lung function. Bronchial artery embolization can be tried as a temporizing measure for massive hemoptysis in patients with a high operative risk. Other measures, including intracavitary instillation of amphotericin B, oral itraconazole, and oral voriconazole, have been associated with reduction in cavity size and severity of hemoptysis in case reports. In one series of 40 patients, all patients had short-term resolution of hemoptysis following instillation of a locally formulated paste consisting of amphotericin B, fatty acids, and emulsifying wax.

A subset of patients with aspergillomas tends to be chronically ill, with fever, weight loss, pulmonary symptoms, and leukocytosis. This entity, termed "chronic necrotizing pulmonary aspergillosis," is seen in patients with chronic pulmonary disorders and mild systemic immunocompromise such as in diabetes mellitus, alcoholism, low-dose corticosteroids, or malnutrition. Whenever possible, host defenses should be strengthened by diminishing factors responsible for immunosuppression. Other patients have "chronic cavitary pulmonary aspergillosis" characterized by progressive expansion of *Aspergillus*-infected pulmonary cavities in the absence of known immunocompromise. With both entities, dramatic clinical responses have been observed in some patients following a course of antifungal therapy as is given for invasive aspergillosis. Resection may be considered in the small subset of patients with focal disease whose pulmonary function and underlying disease do not preclude surgery.

ALLERGIC MANIFESTATIONS OF *ASPERGILLUS*

Extrinsic allergic alveolitis occurs in nonatopic individuals who are exposed to *Aspergillus* conidia, as in "malt-worker's lung" or "farmer's lung," following their exposure to moldy grain or hay. Spontaneous recovery usually occurs over several weeks, without the need for corticosteroids. Exposure to *Aspergillus* in individuals with asthma can result in an exacerbation of their disease (extrinsic asthma).

Allergic bronchopulmonary aspergillosis (ABPA) is a syndrome characterized by asthma, proximal bronchiectasis, immediate cutaneous reactivity to *Aspergillus*, elevated serum immunoglobulin E (IgE) concentrations, and elevated

serum immunoglobulin G (IgG) and IgE antibodies specific to *A. fumigatus*. An increase in T_H2 CD4+ cells that respond to *Aspergillus* antigens and generate interleukin (IL)-4, -5, and -13 may contribute to the eosinophilia and high IgE levels seen in ABPA. Pulmonary infiltrates, peripheral eosinophilia, serum precipitins against *Aspergillus* antigens, and expectoration of fungus-laden mucus plugs may also be seen. Major predisposing factors are asthma and cystic fibrosis.

The goals of therapy are to reduce acute inflammation and minimize long-term lung damage. For patients with ABPA and pulmonary infiltrates, the primary treatment is prednisone in doses of 0.5 to 1.0 mg/kg/day for 1 to 2 weeks, followed by an alternate-day regimen and then a gradual taper over a 3- to 6-month period. Total IgE levels in the serum directly correlate with disease activity and response to corticosteroids. In clinical trials, itraconazole in doses of 200 mg twice daily was associated with fewer exacerbations, improved immunologic parameters, and a reduced requirement for corticosteroids. The salutary effects of itraconazole are likely to be primarily due to its antifungal activity. However, some of the responses could be due to inhibition of corticosteroid metabolism by itraconazole. Although it has not been well studied in randomized trials, based on its superiority in invasive aspergillosis voriconazole is increasingly being used in the treatment of ABPA.

Currently, two oral formulations of itraconazole are available: capsules and an oral aqueous acidified solution in 5% hydroxypropyl-β-cyclodextrin. Absorption of the capsular form is best in an acidic environment, and in the presence of a meal. Histamine-2 blockers and antacids may interfere with absorption. In contrast, the oral aqueous hydroxypropyl-β-cyclodextrin solution should be taken without food. This preparation achieves peak serum concentrations about 60% higher than the capsules but is more expensive and is associated with a higher incidence of gastrointestinal side effects. Drugs that induce hepatic microsomal enzymes (e.g., rifampin, isoniazid, phenytoin, phenobarbital, and carbamazepine) may significantly reduce serum itraconazole levels. Itraconazole itself slows hepatic drug metabolism and may increase the toxicity of phenytoin, oral hypoglycemics, digoxin, warfarin, and cyclosporine. Plasma concentrations of itraconazole can be measured in patients for whom absorption or drug metabolism problems are suspected, although therapeutic levels have not been established.

Allergic *Aspergillus* sinusitis often responds to endoscopic surgical debridement and drainage, particularly when there are obstructive symptoms. Intranasal corticosteroids may provide symptomatic relief but long-term use should be avoided as it can be detrimental to the nasal mucosa. There are anecdotal reports that itraconazole may be of benefit in refractory cases.

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174. Mucormycosis (and entomophthoramycosis)

Scott F. Davies

The term mucormycosis refers to a group of highly lethal angioinvasive fungal infections, mostly in immunocompromised hosts, caused by members of the order Mucorales, which include various species of the genera *Rhizopus*, *Lichtheimia* (formerly *Absidia*), *Mucor*, and *Saksenaea*. Other genera of Mucorales have also been implicated in human disease including *Cunninghamella*, *Apophysomyces*, and *Rhizomucor*. Most infections (50%–65% of total) are caused by *Rhizopus* species.

Classification is in flux because of extensive molecular phylogenetic analysis that has been ongoing for more than 10 years. Note that it is incorrect to use the term mucormycosis to refer only to infections caused by species of the genus *Mucor*, which are only a small minority of the total number of cases. Rather, mucormycosis refers to infection by any of the organisms within the seven genera of the order Mucorales as noted.

The term entomophthoramycosis refers to infections by members of the separate genera *Conidiobolus* and *Basidiobolus*. These organisms generally occur in tropics and cause chronic subcutaneous infection mostly in immunocompetent hosts. Only rarely (less than 15 reported cases) have they ever caused clinical syndromes overlapping with mucormycosis.

For the remainder of this chapter the term mucormycosis will be used to refer to the range of clinical infections caused by organisms in the seven genera of the order Mucorales. In recent usage this term is generally preferred over the term zygomycosis, because of elimination of Zycomycetes from the taxonomic structure and the very different clinical syndrome as compared to entomophthoramycosis with virtually no clinical overlap.

PATHOGENESIS

The causative agents of mucormycosis are found throughout the world, associated with decaying organic matter. They grow as a mycelium (broad nonseptate hyphae with short stubby right-angle branches) in nature and in infected mammalian tissue.

Airborne spores of the fungi settle on the skin or are inhaled into the nose, the pharynx, and the lung. The organism has little chance of invading healthy tissue defended by neutrophils. *Rhizopus* organisms grow best at acid pH in a high-glucose environment. A specific enzyme, ketone reductase, plays an important role. Thus diabetic ketoacidosis provides a favorable opportunity for the fungus to locally invade tissues of the upper airway, resulting in the fulminant rhinocerebral form of mucormycosis. Once established, the fungus is angioinvasive, leading to infarction of tissues and wider areas of necrosis, in which the fungus thrives. The tissue response to the fungus includes pyogenic inflammation, but there is little tendency for granuloma formation. A second form of disease is pulmonary mucormycosis, in which infection occurs in the lung or, less commonly, in proximal airways. The disease resembles invasive pulmonary aspergillosis and occurs, although much less commonly, in the same substrate: patients with profound neutropenia and patients in whom phagocyte function is depressed by high-dose glucocorticoid therapy. Like *Aspergillus* species, agents of mucormycosis are angioinvasive in the lung, leading to tissue necrosis and eventually to pyemic spread to distant sites, including the skin, kidney, and brain. Rare forms of mucormycosis include a direct cutaneous infection that can complicate severe burns and contaminated wounds and the gastrointestinal form of the illness, associated with profound protein malnutrition (usually in infants), in which organisms directly invade the bowel wall, causing hemorrhage, bowel infarction, peritonitis, and death.

When uncontrolled diabetes is the main predisposing factor, rhinocerebral mucormycosis is more common. When hematologic malignancy and organ transplantation are the predisposing

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factors, pulmonary mucormycosis is more common. Patients being treated for leukemia and bone marrow transplantation recipients appear to have an increasing risk of pulmonary mucormycosis. Early use of fluconazole for these indications reduced *Candida* infections but likely shifted what was once a reasonably even split between disseminated candidiasis and invasive aspergillosis more heavily toward aspergillosis. More recently, other triazoles, including itraconazole and now voriconazole, that are highly active against *Aspergillus* species have been used for prophylaxis, reducing *Aspergillus* infections but likely resulting in higher relative frequency of mucormycosis. There are several studies implicating itraconazole and voriconazole prophylaxis as independent risk factors for development of invasive mucormycosis.

CLINICAL MANIFESTATIONS

Rhinocerebral mucormycosis is an extremely fulminant infection. Infection begins in the nose, sometimes manifested by dark, blood-tinged discharge from one or both nostrils. Necrosis of the nasal septum and turbinates then follows, with spread to the paranasal sinuses. In sequence, the disease accelerates with ulceration and necrosis of sinus walls, periorbital cellulitis, and direct invasion of the orbit, eye, cavernous sinuses, and brain. Arterial thrombosis adds to the extent of tissue destruction. Early clinical findings include eye pain, decreased visual acuity, and cranial nerve palsies. A black eschar from ischemic necrosis, either in the nose or on the palate, is a strong signal of disease presence. Early symptoms and signs may be followed by seizures and progressive decrease in level of consciousness. Death may occur in 1 week.

Pulmonary mucormycosis is acquired by inhalation or possibly by microaspiration from colonized sinuses. The disease presents as an acute or subacute pneumonia, with fever, cough, and purulent sputum. Some patients have pleuritic pain and hemoptysis from superimposed pulmonary infarction caused by invasion of pulmonary vessels. The most characteristic finding on chest radiograph is an area of consolidation, often peripheral and sometimes wedge-shaped. Focal areas of consolidation often cavitate as the infection progresses. The spectrum of radiographic abnormalities also includes large masses (even to 6 to 10 cm in size), multiple nodules, and multiple peripheral infiltrates. The computed tomography (CT) halo sign (ground-glass changes surrounding a dense central nodule) was first reported in invasive pulmonary aspergillosis (the most common cause of this finding in immunosuppressed patients), but also occurs in mucormycosis (with similar frequency as in aspergillosis) and in other infections and conditions, including bronchoalveolar carcinoma (the most common cause in immunocompetent patients). The CT reverse halo sign (central ground-glass area surrounded by denser consolidation) seems to be relatively more common in mucormycosis (the most common cause in immunosuppressed patients) than in aspergillosis, but also occurs in other infections and conditions, including cryptogenic organizing pneumonia (the most common cause in immunocompetent patients). The CT halo signs may be helpful in individual patients, but lack great sensitivity and specificity.

Metastatic abscesses may develop in the brain, liver, spleen, kidney, and skin. Metastatic skin lesions often show extensive necrosis (ecthyma gangrenosum) and offer easy diagnosis with a simple punch biopsy. Clinically, pulmonary mucormycosis with or without pyemic dissemination cannot easily be distinguished from invasive aspergillosis. Most cases occur in patients with hematologic malignancy with prolonged neutropenia. Cases of pulmonary mucormycosis also occur in organ transplant recipients, in patients receiving prolonged courses of high-dose glucocorticoid therapy for malignant or nonmalignant disorders, and even in diabetic patients.

Deferoxamine therapy, used for chelation in some patients receiving long-term dialysis and in other iron-overloaded states, is also a risk factor for mucormycosis because it is a siderophore, mobilizing iron from peripheral storage sites and making it more available to the fungus as a growth factor.

Endobronchial mucormycosis is a rare form of pulmonary mucormycosis that has been reported mainly in patients with advanced acquired immunodeficiency syndrome (AIDS). Patients have cough, purulent sputum, and often hemoptysis. Physical findings may include a localized wheeze. The chest radiograph may be normal or may show segmental or even lobar infiltrates with significant volume loss distal to the obstructed airway. Several other unusual forms of mucormycosis have also been reported in this population. Isolated renal mucormycosis has been described in AIDS patients who abuse drugs intravenously or have long-term intravascular access catheters for various therapeutics. Nodular skin lesions

have also been reported in AIDS patients who abuse drugs intravenously. Cerebral mucormycosis of the basal ganglia has also been reported in similar patients.

Cutaneous mucormycosis can also complicate contaminated wounds via direct inoculation, rather than pyemic spread. This has been reported from war theaters including those in Afghanistan. It can also complicate civilian trauma; a total of 13 cases were reported following a tornado in Joplin, Missouri, in 2011. The causative organism in all cases was an *Apophysomyces* species. There was an association between fungal infection and penetrating wounds containing wood, soil, gravel, and other foreign material. The patients developed a cutaneous necrotizing infection within a few days of the trauma; 5 of the 13 patients died.

DIAGNOSIS

The diagnosis of rhinocerebral mucormycosis can often be strongly suspected based on the setting of diabetic ketoacidosis and the clinical features of the illness. Specific diagnosis usually depends on demonstration of characteristic broad nonseptate hyphae in biopsies of diseased tissue (Figure 174.1). Positive cultures are confirmatory and also serve to define the exact species causing the infection. PCR may play an increasing role in the future for species identification. Positive cultures for causative organisms of mucormycosis must be interpreted cautiously and in clinical context because the organisms are ubiquitous in the environment and occasionally can be recovered from the skin, pharynx, and sputum of patients without disease. No useful skin tests or serologic tests are available.

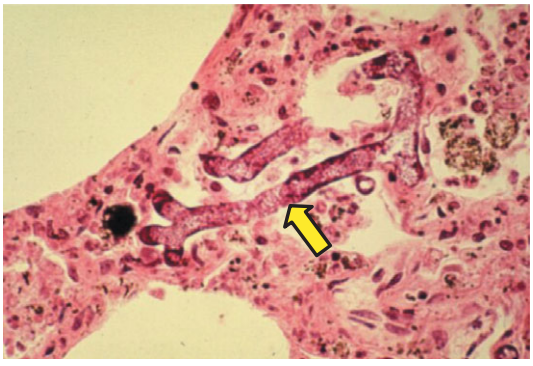

Figure 174.1 Mucormycosis: Hyphae (*arrow*) vary from 6 to 50 μm in diameter, are nonseptated, and typically branch at 90° angles. (Courtesy of www.doctorfungus.org © 2007.)

The diagnosis of pulmonary mucormycosis is also highly dependent on clinical awareness in high-risk clinical settings, with leukemia and bone marrow transplantation most important predispositions, followed by organ transplantation. Prior use of itraconazole or voriconazole for prophylaxis or empiric antifungal therapy may also be a risk factor. The disease resembles invasive aspergillosis in similar hosts and can be distinguished only by histopathology or by culture.

TREATMENT

Rhinocerebral mucormycosis has a very high mortality, beyond 50% of cases in many series. Successful therapy is most likely if the diagnosis is made early and initiation of therapy is based entirely on clinical findings, before confirmation by histopathology or culture. There are three aspects to the treatment. First, the diabetic ketoacidosis must be controlled. Second, and most importantly, aggressive surgical debridement of all necrotic tissue must be done. Sometimes several procedures are needed as the limits of the diseased tissue become more apparent. Finally, full doses of amphotericin B (AMB) must be given quickly. Use of lipid-based formulations of AMB (AMB-L) have become standard because of lower toxicity and likely superior efficacy. Usual dose of AMB-L is 5 mg/kg/day – higher dosing to 7.5 or 10 (or even higher) mg/kg/day has been used in select cases, but has higher toxicity.

Pulmonary mucormycosis is also highly lethal. Once there is spread to distant sites and particularly to the brain, fatal outcome is nearly certain. Localized pulmonary disease can sometimes be managed successfully. Again, a three-pronged approach is necessary. First, the predisposing causes must be reversed. This means return of neutrophils (either spontaneously or aided by marrow-stimulating biologicals) and/or rapid taper of glucocorticoid therapy to the extent it is possible. Second, AMB-L should be started and escalated quickly to full dosages. Third, if the patient stabilizes, strong consideration should be given to surgical resection of necrotic lung tissue, if the lung disease is localized and the risk of thoracotomy is reasonably low. There are anecdotal reports of successful treatment of pulmonary mucormycosis by surgical resection alone. In those rare cases, the preoperative diagnosis was uncertain, total excision of all involved lung was

accomplished, the diagnosis was established by histopathology of the resected tissue, and the patient recovered fully without other therapy.

When possible, isolated renal mucormycosis in patients with AIDS should be treated with nephrectomy combined with AMB-L. When nephrectomy is either not possible or is not a reasonable option given the overall condition of the patient, AMB-L alone should be used. There are some anecdotal successes using AMB-L without surgery.

Cutaneous mucormycosis is treated with aggressive surgical debridement and aggressive antifungal therapy, with AMB-L the first-line therapy.

As mentioned above, itraconazole and voriconazole are triazoles with activity against *Aspergillus* but no activity against Mucorales species. Wide use of these agents for prophylaxis and empiric antifungal therapy in patients with hematologic malignancy likely has increased the incidence of mucormycosis.

A possible advance in treatment of mucormycosis is posaconazole, the first triazole compound with activity against Mucorales species. Compassionate use in a large series of 91 patients with mucormycosis (69 proven disease, 22 probable) who had failed or were intolerant to prior antifungal treatment (usually a form of AMB) showed a success rate of 60% at 12 weeks. That exceeds historical success rates with prior standard therapy. Although posaconazole is not yet approved for use in mucormycoses, one approach pending further data might be to start patients with proven disease on AMB-L plus posaconazole until clinical response, and then extending posaconazole to 12 or more weeks. However, posaconazole is available only in oral formulation, limiting its use in critically ill patients. For now, AMB-L remains standard treatment with posaconazole used as an adjunctive, salvage, or continuation therapy on an individual case basis.

Echinocandins are another possible candidate for combination therapy. *Rhizopus oryzae* (the most common *Rhizopus* species causing infection) expresses the enzyme 1,3 β-glucan synthetase, which is the target enzyme for the echinocandins. Use of echinocandins in animal models has shown additional benefit when combined with AMB-L. There are anecdotal reports of successful use in selected cases, usually in combination with AMB-L. At present there is more experience and a larger number of positive clinical reports with posaconazole as a second agent or for salvage, and for now echinocandins should not be used as an alternate therapy versus AMB-L.

As mentioned, iron availability is an important promoter of growth for Mucorales species and deferoxamine, which mobilizes iron and also increases availability of iron to the organisms, is a risk factor for mucormycosis. However, newer iron chelators such as desferasirox bind iron but are not used as siderophores by Mucorales and thus deprive the fungus of iron availability. In models of mucormycosis in mice, desferasirox was as effective as AMB-L and it also had additive effects when used together with AMB-L. Anecdotal reports have suggested some benefit in patients, but a very small (20 patients) randomized prospective trial showed poorer outcome (more frequent death at 30 and 90 days and lower global success) when desferasirox was used in combination with AMB-L for initial therapy of mucormycosis. At present desferasirox should not be used as combination therapy with AMB-L or other agents.

Finally, hyperbaric oxygen therapy has been proposed, based on limited and anecdotal reports, as an adjunctive therapy for some patients with mucormycosis. As for other unproven therapies, hyperbaric oxygen can be considered for selected patients.

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175. *Sporotrichum*

Ronald A. Greenfield

Sporotrichosis is a subacute or chronic fungal infection caused by *Sporothrix schenckii* and related species. It occurs most commonly in cutaneous or lymphocutaneous forms resulting from direct inoculation of the pathogen but also occurs in a variety of extracutaneous forms. Among the extracutaneous forms, a primary sporotrichotic pneumonia, presumably acquired by inhalation, occurs rarely. More commonly, musculoskeletal or osteoarticular sporotrichosis occurs, either as a result of direct inoculation into tendons, bursae, and joints or as a result of hematogenous dissemination. Hematogenous dissemination may result in disseminated cutaneous sporotrichosis and/or infection of a variety of unusual sites, including the meninges.

EPIDEMIOLOGY

Sporothrix schenckii is widely distributed in nature; it grows on plant debris in soil, and on the bark of trees, shrubs, and garden plants. The fungus and the disease occur in much of the world, primarily in the tropical and temperate zones. The abundance of the organism and the reported incidence of the disease show great geographic variation, perhaps related to genotypic differences between organisms in different locales. The penetrating trauma that introduces the fungal conidia into the human host is most commonly accomplished by splinters, thorns, or woody fragments of plants, but any contact with plants or plant products (e.g., sphagnum peat moss, mulch, hay, timber) accompanying minor skin trauma may initiate infection. Activities most frequently associated with acquisition of sporotrichosis include gardening (particularly rose gardening), landscaping, farming, berry-picking, horticulture, and carpentry. Skin test and serologic surveys demonstrate that most *S. schenckii* inoculations promote the development of immunity without clinically apparent infection. Zoonotic transmission also occurs from infected animals, particularly cats with extensive skin lesions, but may result from the scratch of any digging animal. Both pulmonary and disseminated sporotrichosis appear to occur more commonly in patients with a history of alcoholism.

Patients with immunosuppression due to human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) appear to more frequently develop disseminated cutaneous sporotrichosis and hematogenously disseminated sporotrichosis, including sporotrichotic meningitis, than immunocompetent hosts. Although the incidence of HIV/AIDS-associated sporotrichosis is not precisely known, it is less than that of other endemic mycoses. Patients treated with immunosuppressive agents, including tumor necrosis factor-α antagonists, have also developed disseminated sporotrichosis.

LABORATORY DIAGNOSIS

Definitive diagnosis of sporotrichosis requires the isolation of *Sporothrix* spp. in culture specimens from a normally sterile body site. Occasionally, the organism can be visualized in biopsied tissue specimens stained with periodic acid–Schiff, Gomori methenamine silver, or immunochemical stains (Figure 175.1). The organism can be recovered by fungal culture from sputum, pus, synovial fluid, bone drainage, and surgical specimens. Concentrations of organisms in joint fluid and particularly cerebrospinal fluid may be relatively low. Therefore, repetitive large-volume cultures may be required for diagnosis. Serologic techniques for measurement of antibody are available but exhibit significant interlaboratory variability in sensitivity and specificity; they are best used to suggest the need for more aggressive attempts at definitive diagnosis.

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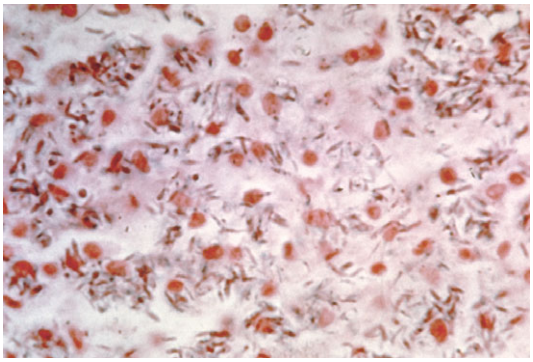

Figure 175.1 Histopathologic demonstration of the cigar-shaped yeasts of *Sporothrix schenckii*. (CDC/Dr. Lucille K. Georg, CDC Public Health Image Library.)

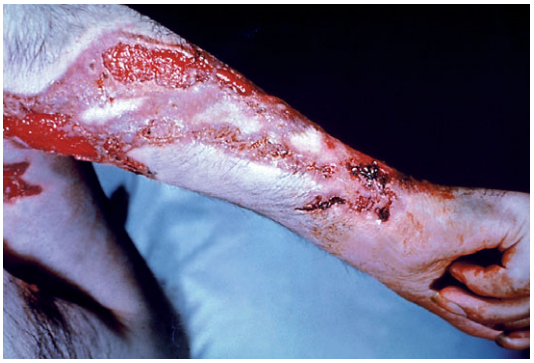

Figure 175.2 Lymphocutaneous sporotrichosis. (CDC/Dr. Lucille K. Georg, CDC Public Health Image Library.)

CLINICAL MANIFESTATIONS

Cutaneous sporotrichosis

The primary lesion develops at the site in the skin, 20 to 90 days after inoculation, most typically distally in the upper extremities. Over a few weeks, the initial small nodule enlarges, reddens, becomes pustular, and ulcerates, releasing purulent material from which the organism is readily cultured. Patients are typically afebrile and not systemically ill. In the lymphocutaneous form of the disease, an ascending chain of nodules develops along lymphatic channels of the skin, with the older distal lesions ulcerating and draining and the younger, more proximal lesions forming subcutaneous nodules that attach to the skin as they age and begin to ulcerate (Figure 175.2). The lesions are usually minimally painful, but extensive disease may result in functional impairment. Some patients exhibit no lymphangitic spread, and the disease presents as an indolent ulcerating plaque that persists for years if untreated (fixed cutaneous sporotrichosis). Patients often have received courses of antibacterial therapy without benefit before the process is recognized as sporotrichosis. The lymphocutaneous form of sporotrichosis can be mimicked by infection with *Nocardia*, *Mycobacterium marinum* and other mycobacteria other than tuberculosis, *Leishmania*, and *Francisella tularensis*.

Pulmonary sporotrichosis

Pulmonary sporotrichosis is a subacute or chronic pneumonitis with cavitation, usually in the upper lobes, clinically indistinguishable from mycobacterial infection or chronic pulmonary histoplasmosis. Almost all patients have underlying chronic obstructive pulmonary disease. They present with productive cough, sometimes with weight loss and increasing dyspnea, but rarely with fever, chills, or sweats. Diagnosis requires isolation of *S. schenckii* from sputum cultures or its histopathologic recognition in biopsy specimens.

Osteoarticular sporotrichosis

Lesions of deeper tissues may occur in almost any organ, but there is a distinct predilection for the joints, particularly of the extremities, and the long bones adjacent to these joints. The resulting chronic arthritis is often confused with rheumatoid or other chronic inflammatory arthritis, not infrequently for 10 or more years, until destruction of adjacent bone or development of draining fistulas encourage efforts to establish the microbial etiology of the chronic osteomyelitis. Cutaneous or lymphocutaneous lesions are unusual in these patients. The process generally begins in a single joint, but additional joints may be involved successively. The patient usually has pain on motion, and the involved areas may be warm and red. Functional impairment resulting from osteoarticular sporotrichosis can become very severe.

Disseminated sporotrichosis

Sporotrichotic lesions occur infrequently in many other organs such as the eye, the prostate, the oral mucosa, and the larynx, and the clinical manifestations in these patients depend on the organ

Table 175.1 Treatment of sporotrichosis

Form of sporotrichosis	Preferred treatment	Alternative agents
Cutaneous or lymphocutaneous	SSKI, itraconazole, terbinafine	Fluconazole, posaconazole, amphotericin B
Pulmonary	Itraconazole	Amphotericin B
Osteoarticular or musculoskeletal	Itraconazole	Amphotericin B
Disseminated	Amphotericin B	Amphotericin B plus flucytosine, itraconazole step-down therapy

Abbreviation: SSKI = saturated solution of potassium iodide.

involved. Involvement of the central nervous system (CNS) and meninges, which was distinctly rare in the pre-AIDS era, has become more common but is still rare in persons living with AIDS. Patients may present with subtle changes in mental status as the only symptom and are found to have chronic lymphocytic meningitis. Recovery of the fungus from extracutaneous lesions may be difficult, particularly in meningitis.

THERAPY

Spontaneous healing of the cutaneous forms of sporotrichosis has been reported, but without treatment, the lesions usually progress slowly with draining and scarring. In immunocompetent patients, the infection is not life threatening. Treatment options are presented in Table 175.1. Historically, cutaneous and lymphocutaneous sporotrichosis have been treated with saturated solution of potassium iodide (SSKI), although the mechanism of action has not been determined. An initial dose of 5 to 10 drops diluted in liquid, preferably fruit juice, is given three times daily after meals, and increased dropwise to 120 drops per day or the maximum tolerated by the individual patient (frequently <60 drops per day). Although relatively inexpensive, this form of therapy is poorly accepted by many patients due to adverse effects, including increased lacrimation, increased salivation, metallic taste perversion, salivary gland swelling, gastrointestinal upset, and frequent rash.

Itraconazole is the treatment of choice for lymphocutaneous sporotrichosis; 100 mg orally daily for 3 to 12 months, determined by continuing treatment for 2 to 4 weeks beyond resolution of all lesions. Itraconazole can be given either as capsules that must be taken with food and must not be coadministered with therapies that suppress gastric acidity and that have somewhat erratic absorption or as an itraconazole oral solution, which is less palatable and generally more expensive but avoids these drawbacks. In patients who do not respond to itraconazole initially, one can consider increasing the dosage of itraconazole to 400 mg/day. Therapy with terbinafine, 250 mg orally daily, appears to be as effective as itraconazole therapy. By historical comparison, treatment with fluconazole, 200 to 400 mg orally daily, was less effective than itraconazole. The effectiveness of higher doses of fluconazole is subject to speculation. Amphotericin B preparations should only be necessary as a treatment of last resort for patients with cutaneous or lymphocutaneous sporotrichosis. Because many strains of *S. schenckii* that cause fixed cutaneous sporotrichosis grow poorly in the laboratory at 37°C, local application of heat may be an effective adjunct to antifungal therapy.

Pulmonary sporotrichosis should be treated with either itraconazole, 200 mg orally twice daily, for patients with non-life-threatening infection or with an amphotericin B preparation (preferably a liposomal amphotericin B preparation because of better tolerability) in patients with life-threatening or extensive pulmonary infection. For the latter patients who have the lung capacity to tolerate such a procedure, treatment with an amphotericin B preparation with subsequent surgical resection of involved lung areas may be the best therapy.

Itraconazole, 200 mg orally twice daily, should be initial therapy for patients with osteoarticular sporotrichosis. As with other joint and bone infections, drainage and debridement may be important surgical adjuncts to antimicrobial therapy. Conventional amphotericin B therapy appears to be approximately as effective as itraconazole but is less convenient and associated generally with more frequent adverse reactions; therefore, it is generally used only after failed itraconazole therapy. The role of liposomal amphotericin B preparations in osteoarticular sporotrichosis has not been defined. Fluconazole has been used with only modest success in osteoarticular sporotrichosis. Itraconazole treatment should generally be continued for

12 months, therapy with amphotericin B preparations for 6 to 10 weeks. Voriconazole has poor activity in vitro against sporotrichosis and should not be used. Posaconazole has in vitro activity, but its role in vivo is undefined.

Sporotrichotic meningitis should be treated with amphotericin B, based on limited numbers of anecdotally reported cases; liposomal amphotericin B is preferred because of increased penetration into the cerebrospinal fluid. Based on possible in vitro synergy and anecdotal reports, the addition of flucytosine may be beneficial for patients with recalcitrant meningitis. Itraconazole may offer effective step-down therapy after clinical improvement.

An amphotericin B preparation should be considered initial therapy for patients with disseminated sporotrichosis with or without AIDS. Itraconazole might be used for non-life-threatening infection and in cases in which meningitis has been actively excluded. Itraconazole may also play a role in lifelong suppressive therapy for patients with disseminated sporotrichosis and AIDS after initial induction therapy with an amphotericin B preparation.

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176. *Cryptococcus*

William G. Powderly

Cryptococcus neoformans, which is found worldwide as a soil organism and thought to be transmitted by inhalation, most often causes disease in patients with abnormal cell-mediated immunity, notably patients with human immunodeficiency virus (HIV) infection and solid organ transplant recipients, but the infection also occurs rarely in apparently immunocompetent persons. It is the most common systemic fungal infection in patients infected with HIV. It is estimated that over 1 million cases of invasive cryptococcal infection occur annually in patients with acquired immunodeficiency syndrome (AIDS) worldwide with more than 600 000 deaths each year. Most of these cases occur in resource-poor settings, especially in sub-Saharan Africa. With the advent of effective antiretroviral therapy (ART), cryptococcal infections have become much less common in the United States.

Two varieties of *C. neoformans* exist, distinguishable by serology: *C. neoformans var. neoformans* (serotypes A and D) and *C. neoformans var. gattii* (serotypes B and C). Virtually all HIV-associated infection is caused by *C. neoformans var. neoformans*. *C. neoformans var. gattii* is endemic in Australia and recent outbreaks of *C. neoformans var. gattii* infection have occurred in the Pacific northwestern parts of North America.

PRESENTATION AND DIAGNOSIS

The most common manifestation of cryptococcal infection is meningitis. Most patients develop insidious features of a subacute meningitis or meningoencephalitis, with fever, malaise, and headache, and are generally symptomatic for at least 2 to 4 weeks before presentation. In patients with a more subacute or chronic course, mental status changes such as forgetfulness and coma can also be seen. Classic meningeal symptoms and signs such as stiff neck and photophobia occur in only about one-quarter to one-third of all patients and generally are less likely to occur in HIV-positive patients. The typical pattern in the cerebrospinal fluid (CSF) is chronic meningitis with a lymphocytic pleocytosis. However, the CSF may appear normal in HIV-positive patients with cryptococcal meningitis because the usual response to infection is usually markedly blunted. In fact, fewer than half of HIV-positive patients with cryptococcal meningitis have an elevated protein level, only about one-third have hypoglycorrhachia, and only about 20% have more than 20 white blood cells per cubic millimeter of CSF. The opening pressure is usually elevated in patients with cryptococcal meningitis (up to 70% of patients present with pressures greater than 20 cm H_2O) and is an important issue associated with therapy. India ink stain of the CSF is positive, showing encapsulated yeast, in about 75% of cases and the cryptococcal antigen titer in the CSF is almost invariably positive with sensitivity of 93% to 100% and specificity of 93% to 98%. Serum cryptococcal antigen (sCRAG) is elevated in 95% of patients with meningitis. A positive sCRAG with titer above 1:8 suggests disseminated cryptococcosis. Such patients should be evaluated for possible meningeal involvement. False-positive sCRAG can happen secondary to infection with *Trichosporon beigelii* and secondary to residual disinfectant on laboratory test slides. Culture of *C. neoformans* from any body site should also be regarded as an indication for further evaluation and initiation of therapy. However, colonization of *Cryptococcus* can be found in the respiratory system. Patients with isolated positive respiratory cultures for *C. neoformans* should be carefully evaluated for disseminated infection; therapy might not be necessary in immunocompetent patients with no symptoms and negative sCRAG.

Cryptococcus neoformans can invade sites other than the meninges. Isolated pulmonary disease has been well described. It usually presents as a solitary nodule in the absence of other symptoms. Cryptococcus pneumonia has also been described. In immunocompromised patients, especially

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Table 176.1 Drugs used in the treatment of cryptococcal infection

Drugs	Dosage	Side effects	Drug interactions	Comments
Amphotericin B	0.7–1.0 mg/kg/d 3–6 mg/kg/d (liposomal) 5 mg/kg/d (lipid complex)	Immediate hypersensitivity reaction, fever, hypotension, nausea and vomiting during administration, hypokalemia, and nephrotoxicity	Nephrotoxic drugs (e.g., aminoglycosides, pentamidine, foscarnet, cidofovir)	Liposomal or lipid complex formulation should be considered in patients with renal dysfunction
Flucytosine (5-FC)	25 mg/kg q6h	Gastrointestinal, bone marrow suppression	Nephrotoxic drugs	Dosage must be reduced in patients with renal dysfunction; drug level should be monitored
Fluconazole	400 mg/d (acute therapy), 200 mg/d (suppressive therapy)	Nausea, rash, and hepatitis	Rifabutin (increased rifabutin levels); rifampin (decreased fluconazole levels)	Dosage may need to be adjusted in renal dysfunction
Itraconazole	200–400 mg BID	Nausea, abdominal pain, rash, headache, edema, and hypokalemia	Rifamycins, ritonavir, phenobarbitol, phenytoin all decrease itraconazole levels The effect of nevirapine is unknown; the drug should not be used concomitantly with terfenadine or astemizole Antacids, histamine blockers decrease itraconazole absorption Itraconazole itself acts as a moderate inhibitor of cytochrome P450 system and can increase levels of indinavir, cyclosporin, digoxin, and phenytoin	Absorption of itraconazole is dependent on food and gastric acid and may be erratic; the newer solution is better absorbed

those with AIDS, disseminated disease is common. About half of HIV-positive patients with cryptococcal meningitis have evidence of pulmonary involvement at presentation, with clinical symptoms such as cough or dyspnea and abnormal chest radiographs. The chest radiographic finding is usually diffuse interstitial infiltrates in immunocompromised patients or focal lesions in immunocompetent patients. Concomitant opportunistic infections, especially with *Pneumocystis jirovecii* (*carinii*), occur in about 15% to 35% of patients. Cutaneous involvement is common and with this presentation suggests disseminated disease. The most common skin involvement resembles that of molluscum contagiosum. As many as three-quarters of patients with cryptococcal meningitis have positive blood cultures. Infection of bone, eye, adrenal glands, prostate, and urinary tract has also been described. The prostate gland represents a reservoir of infection and potential source of reinfection after completion of therapy.

THERAPY

Management of cryptococcal infection depends on the extent of disease and the patient's immune status. A solitary pulmonary nodule in a normal host may not need treatment, provided the patient has careful follow-up. The advent of relatively safe antifungals such as fluconazole permits a short course of therapy for most patients with localized disease. Extrapulmonary disease is generally managed in the same way as meningitis. A search for potential underlying problems should be initiated in patients who are not known to be immunosuppressed, including an HIV antibody test and CD4 lymphocyte count, because cryptococcal infections have been described as one of the manifestations of so-called isolated CD4 T-cell lymphocytopenia. Drugs generally used in the treatment of cryptococcal infection are summarized in Table 176.1.

Cryptococcal infection in normal hosts

Untreated cryptococcal meningitis is uniformly fatal, so all patients with meningitis must be treated. Most of the available evidence suggests that amphotericin B-based therapy remains the gold standard and the combination of an amphotericin B preparation plus flucytosine (5-FC) should be regarded as the best initial treatment. Recent studies indicate that this combination is most likely to lead to more effective and more

Table 176.2 Factors predicting relapse of cryptococcal meningitis

Immunosuppression
Presentation with neurologic abnormalities
CSF leukocyte count $\leq$20 cells/mm^3
CSF antigen titer >1:32
Positive India ink stain after 4 wk of treatment
CSF antigen titer greater than 1:8 after 4 wk of treatment

Abbreviation: CSF = cerebrospinal fluid.

rapid clearance of the fungus from the CSF, which is probably the best surrogate marker for ultimate successful therapy. This conceptual approach is consistent with clinical trial data in AIDS that amphotericin B-based therapy is superior to initial therapy with azoles. The different amphotericin B preparations have not been shown to have important differences in response rates of cryptococcal meningitis, although clearly the lipid-based formulations are less toxic than amphotericin B deoxycholate. Because some degree of nephrotoxicity is inevitable if amphotericin B deoxycholate is given for 4 to 6 weeks, current recommendations suggest that liposomal amphotericin at a dose of 5 mg/kg is the preferred treatment for cryptococcal meningitis in normal hosts. Although it is unclear whether 5-FC is necessary in normal hosts, extrapolation from trials in patients with AIDS would suggest that it accelerates clearance of the fungus and improves mortality. The recommended dosage is 37.5 mg/kg four times daily. Levels must be measured to minimize toxicity (especially bone marrow suppression), and dosages must be adjusted for renal insufficiency.

The duration of therapy is not well defined for patients with cryptococcal infection. Normal subjects with no evident risk factors for a poor outcome respond well to 4 weeks of combination therapy, and this is often curative. Prolonged therapy should be considered for patients at risk of relapse (Table 176.2). Pulmonary cryptococcosis without meningeal involvement can be treated initially with fluconazole. However, for meningitis, there is no controlled trial of fluconazole, especially comparing initial azole therapy with an amphotericin B-based regimen. With current data, amphotericin B plus 5-FC is still recommended as standard therapy for cryptococcal meningitis. Fluconazole can be used to treat patients (or to complete a course of treatment in patients) who cannot tolerate amphotericin B or patients without neurological involvement. In many circumstances (need for intravenous access, difficulties with outpatient parenteral therapy, toxicity) a full course of parenteral amphotericin B is impractical or undesirable, and a switch to fluconazole is preferred. Timing of such a switch is uncertain. There is insufficient evidence to advocate using changes in cryptococcal antigen as a guide to making treatment decisions, but it is probably reasonable to consider using the clearance of yeast from CSF as an indicator for switching treatment from polyene to oral azole therapy. In most patients, this is likely to take 2 to 3 weeks to achieve, suggesting this is probably the minimum amount of amphotericin B therapy that should be used.

Once patients have been switched to fluconazole, the next question becomes how long to treat? Unfortunately, there are absolutely no well-controlled studies to answer this question. Given the potential severity of cryptococcal infection, the most prudent recommendation would be to treat with fluconazole for 6 to 12 months after clearance of CSF has been documented.

Cryptococcal infection in AIDS

In patients with AIDS, the acute mortality with cryptococcal meningitis ranges from 10% to 25%. Multiple clinical factors have been identified in studies as predictors of a poor outcome, as summarized in Table 176.3. The current recommendations for the treatment of cryptococcal meningitis in AIDS are to use a combination of amphotericin B (either deoxycholate or a liposomal preparation) plus 5-FC (25 mg/kg every 6 hours) for at least 2 weeks followed by at least 8 weeks of fluconazole, 400 mg PO daily. This strategy was first evaluated in a large randomized trial conducted by the National Institutes of Allergy and Infectious Diseases Mycosis Study Group (MSG) and AIDS Clinical Trials Group (ACTG). Patients with cryptococcal meningitis were randomized to receive 2 weeks of amphotericin B (0.7 mg/kg/day) with either 5-FC (25 mg/kg every 6 hours) or matching placebo. The study was designed to address two questions: (1) Does adding 5-FC to amphotericin B as induction therapy for cryptococcal meningitis improve 2- or 10-week survival compared with induction with amphotericin B alone and (2) is itraconazole as effective as fluconazole in suppressing relapse of cryptococcal meningitis during the maintenance phase of treatment? At the end of 2 weeks, patients who were stable or improved were again randomized to receive either fluconazole, 400 mg/day, or

Table 176.3 Factors at baseline predictive of a poor outcome in AIDS patients with cryptococcal meningitis

Decreased mental status at diagnosis
CSF leukocyte count $\leq$20 cells/mm^3
High titer of CSF cryptococcal antigen
Positive blood culture for *C. neoformans*
Age $\leq$35 yr
Hyponatremia

Abbreviations: AIDS = acquired immunodeficiency syndrome; CSF = cerebrospinal fluid.

itraconazole, 200 mg twice daily. The acute mortality with this regimen was 6%. The addition of 5-FC to amphotericin B did not improve the mortality and clinical course. However, 5-FC was well tolerated. Furthermore, the use of 5-FC as initial therapy has been associated with a decreased risk of later relapse of cryptococcal meningitis. There was no significant difference in clinical symptoms, response rate, or mortality among patients randomized to either fluconazole or itraconazole. This approach has recently been validated by a large randomized trial comparing amphotericin B plus 5-FC to amphotericin B plus fluconazole and to amphotericin B alone. There were fewer deaths among patients receiving amphotericin B and 5-FC compared with those receiving amphotericin B alone, whereas combination therapy with fluconazole had no significant effect on survival, as compared with amphotericin B alone.

There have been a number of controlled comparative trials of the orally active antifungal triazoles, fluconazole and itraconazole. In each trial, the azole antifungals were effective in about 50% of patients. Similarly, in a study directly comparing fluconazole and itraconazole, fewer than 50% of patients responded to either drug. Thus at least 50% of patients treated initially with azole antifungals will fail to respond. Most studies of amphotericin B report response rates of 70% to 80% or more.

The availability of the alternative formulations of amphotericin B raises the issue of their use in cryptococcal meningitis. Several studies have shown that both liposomal amphotericin B and amphotericin B lipid complex are effective in AIDS-associated cryptococcal meningitis. None show superiority to amphotericin B deoxycholate, and most patients tolerate a short course of amphotericin B deoxycholate (10–14 days) without significant nephrotoxicity. Thus the role of lipid preparations of amphotericin B in AIDS-associated cryptococcal meningitis remains uncertain, although they may be useful in patients with impaired renal function. There have been some studies looking at high doses of fluconazole and at fluconazole–5-FC combinations, but none are robust enough to allow any recommendations. Voriconazole and posiconazole are active against *C. neoformans*, but clinical experience is limited.

An important aspect of management of acute cryptococcal meningitis in AIDS is the recognition that clinical deterioration may be caused by increased intracranial pressure (ICP), which may not respond rapidly to antifungal therapy. Analyses have shown a relationship between baseline opening pressure and long-term outcome, with the median survival in patients with the highest pressures being significantly less than that in patients whose pressures were normal. I believe that all patients with cryptococcal meningitis should have opening pressure measured when a lumbar puncture is performed, and strong consideration should be given to reducing such pressure if the opening pressure is high (>25 cm H_2O). Lumbar puncture with removal of 30 mL of spinal fluid daily is often effective. If elevated opening pressure persists with neurologic symptoms despite serial lumbar puncture, lumbar drainage should be considered. Some patients have required placement of lumbar peritoneal shunts for persistently elevated ICP despite successful antifungal therapy. Neither acetazolamide nor corticosteroids are effective in this situation, and may be detrimental, so they should not be used.

The advent of effective ART has changed the natural history of AIDS-related cryptococcal infection. Prior to effective HIV therapy, lifelong maintenance therapy was required in AIDS patients with cryptococcal infection to prevent relapse of infection. Relapse rates of 50% to 60% and a shorter life expectancy were reported in patients who did not receive long-term suppressive therapy. Fluconazole, 200 mg daily, is the drug of choice. Routine monitoring by measurement of sCRAG has not been shown to predict relapse, although elevations of antigen in the CSF may predict recurrence. However, it is now clear that long-term suppressive treatment can be stopped after at least 12 months of antifungal therapy if the patient's immune system recovers with ART (usually defined as the CD4+ T-cell count increasing to >200 cells/mm^3).

All HIV-positive patients with cryptococcal meningitis should receive ART. Recent studies

evaluating the timing of ART in AIDS patients with cryptococcal meningitis suggest a higher mortality if given during the acute treatment for cryptococcal infection. Consequently ART initiation should be deferred for 6 to 8 weeks after initiation of antifungal therapy. Efavirenz-based therapy has been shown to be well tolerated in patients receiving fluconazole for cryptococcal meningitis.

It is thought that a likely mechanism for increased mortality with early initiation of ART is immune reconstitution inflammatory syndrome (IRIS), which is a more vigorous inflammatory response to the underlying infection associated with restoration of the immune system. The pathogenesis of IRIS is unclear but is thought to represent an overexuberant immunologic response to a high antigen load in the context of an immune response that is recovering but not yet fully normal. Clinically there can be considerable morbidity and even mortality. In the case of cryptococcal meningitis, IRIS may manifest as an apparent recurrence of meningitis, with all the features of the initial meningitis presentation. Lumbar puncture will typically show inflammation but, by definition, will remain culture negative. Rarely, the syndrome may present outside the central nervous system (CNS) as pulmonary infiltrates or hilar/mediastinal lymphadenitis due to extra-CNS *Cryptococcus*. Typically IRIS presents following an initial clinical improvement. The majority of cases of IRIS occur within 30 days of starting ART, and the frequency of IRIS following initiation of ART in cryptococcal meningitis has varied from 10% to 50% in different series. IRIS has been found more frequently in patients who are antiretroviral naïve before ART. It is also more commonly seen in those with a higher CSF cryptococcal antigen, probably due to increased antigen producing a greater inflammatory response. Starting ART within 30 days of diagnosis of cryptococcal meningitis is also associated with a higher likelihood of IRIS, presumably due to a greater antigenic burden. If an immune reconstitution syndrome develops in a patient receiving ART, the patient should remain on antiviral therapy and continue antifungal treatment. Anti-inflammatory treatment may be needed for symptom management, and in some cases, immunosuppressive therapy such as corticosteroids has been used.

Fluconazole, 200 mg PO daily, has been shown to be effective as primary prophylaxis in patients with advanced HIV disease. However, this has not been regarded as cost-effective in developed countries such as the United States. However, a strategy of primary prophylaxis may be appropriate in patients with advanced HIV disease (CD4+ T-cell count <100 cells/mm^3) in resource-poor settings; alternatively, screening patients using cryptococcal antigen testing and treating asymptomatic patients with positive serum antigen tests may also be effective.

Cryptococcal infection in other immunocompromised hosts

Management of cryptococcal meningitis in the setting of organ transplantation or lymphoma is also uncertain. The MSG found patients with underlying immunosuppression to have poor outcomes when treated with amphotericin B and 5-FC and to be likely to relapse. Furthermore, amphotericin B nephrotoxicity complicates the use of immunosuppressives such as cyclosporine in such patients. However, there is very little published experience with the use of fluconazole, itraconazole, voriconazole, or fluconazole plus 5-FC in this setting, and these agents are also associated with significant drug interactions. An approach similar to that used with AIDS patients (i.e., an initial period of treatment with amphotericin B plus 5-FC followed by fluconazole) is recommended. Because nephrotoxicity is an issue in many of these patients, liposomal amphotericin B is generally preferred, again for at least 2 to 3 weeks. An area of considerable uncertainty is the duration of fluconazole therapy after acute therapy. Suppressive antifungal therapy for at least 1 year after the completion of acute treatment is recommended. In some patients with persistent immunosuppression, such as solid organ transplant recipients, it may be necessary to continue treatment even further, although again there are very limited data on which to base a recommendation.

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177. Histoplasmosis

Mitchell Goldman and Alvaro Lapitz

INTRODUCTION

Histoplasma capsulatum is a thermal dimorphic fungus found most frequently in soil in the midwestern United States. Bird and bat excreta rich in organic nitrogen support the growth of the fungus. Sites associated with blackbird roosts are the most common sources of outbreaks currently, whereas domestic chicken coops were a common source in the past. Recent outbreaks have occurred after cleaning a campsite contaminated by bat excreta, rototilling soil in a schoolyard below a bird roost, and digging for buried treasure. When sites are disturbed the spores become airborne, producing an infective aerosol. The lung is the portal of entry in almost every case of histoplasmosis. Spores of *H. capsulatum* are inhaled, and in the alveoli they convert to a yeast, the tissue-invasive form. The now multiplying yeasts are phagocytosed by alveolar macrophages that are initially incapable of killing the fungus. Ingested yeasts multiply inside macrophages and spread throughout the body via the lymphatics during the preimmune phase of the illness to organs rich in reticuloendothelial cells. Once adequate cell-mediated immunity (CMI) develops, the now "armed" macrophages can either kill or wall off the infecting organisms. Following a strong immune response, as is seen in immunocompetent individuals, necrosis occurs, which in time becomes calcified. These calcified granulomas are seen in the lung, hilar lymph nodes, liver, and spleen of individuals who successfully limited the infection.

Most individuals infected with *H. capsulatum* develop adequate CMI. If CMI fails to develop, progressive dissemination will occur.

CLINICAL MANIFESTATIONS

Localized pulmonary and self-limited infections

Most *H. capsulatum* infections are asymptomatic. After low-level exposure, some patients develop a localized form of infection with fever, chills, headaches, myalgia, anorexia, cough, and chest pain. Erythema multiforme or erythema nodosum may develop. The incubation time following low-level, outdoor exposure is approximately 14 days. This form of acute localized pulmonary infection is self-limited; after 2 to 4 weeks, most immunocompetent patients will have recovered completely, and treatment is usually not necessary. Chest radiographs usually demonstrate localized pneumonitis but may be normal. Ipsilateral hilar lymph nodes are usually enlarged. Healing may be complete with normalization of the radiograph but frequently multiple cycles of central necrosis and peripheral calcification occur, leaving the characteristic "coin" lesion as a proof of prior infection.

When the infective aerosol is unusually large, fulminant infection may occur, with severe hypoxemia and respiratory failure, requiring prompt and aggressive treatment. Patients who inhale large inocula may develop multiple nodular lesions of variable size. The radiologic appearance of an overwhelming infective dose is diffuse micronodular infiltrates.

Patients with emphysema may develop upper lobe infiltrates after exposure. The resultant infection may result in cavitation. The radiographic appearance of this infection mimics reactivation tuberculosis. Low-grade fever and anorexia with weight loss are common. Without treatment, most of these patients develop progressive destructive disease. The clinical and radiologic similarities to tuberculosis make the diagnosis challenging.

Late complications of healed and calcified histoplasmosis are related to the location of the calcified lymph nodes, which may involve and compress various mediastinal structures. A rare late complication is the development of mediastinal fibrosis, which can lead to crippling complications, such as the superior vena cava syndrome.

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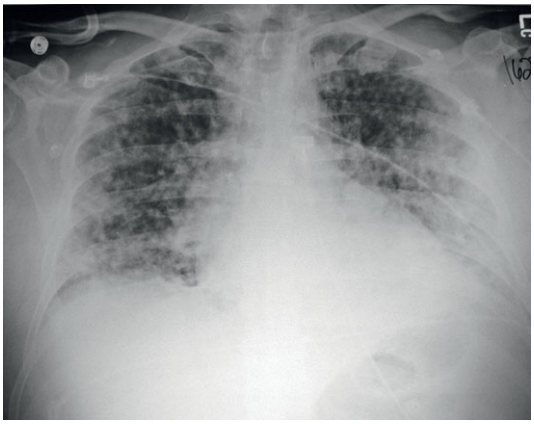

Figure 177.1 Chest radiograph demonstrating diffuse infiltrates in a patient with rheumatoid arthritis with progressive disseminated histoplasmosis following initiation of treatment with a TNF-α inhibitor.

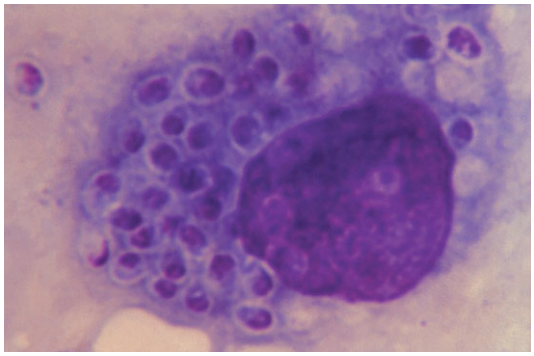

Figure 177.2 Histiocyte containing numerous yeast cells of *Histoplasma capsulatum*. Giemsa stain. (Public Health Image Library, Centers for Disease Control and Prevention [CDC], Dr. D. T. McClenan.)

Progressive disseminated histoplasmosis

During the preimmune phase of the infection the fungus disseminates widely. With the development of adequate CMI, the cells of the reticuloendothelium are responsible for limiting spread of the disease.

In the immunosuppressed patient or at extremes of age this dissemination becomes progressive. This form of the disease is known as progressive disseminated histoplasmosis (PDH), and prognosis is poor without treatment. Fever and weight loss are the most common symptoms, and hepatosplenomegaly is frequent.

Dissemination to the oropharyngeal or gastrointestinal mucosa, skin, and adrenal glands may occur. Patients may develop respiratory distress and hepatic or renal failure, and coagulopathy and shock may complicate severe cases. Central nervous system (CNS) involvement may occur either as chronic meningitis or focal lesions. In PDH the mortality is close to 100% without treatment. In severely ill patients, mortality may still be high despite treatment.

Prior to the widespread use of cytotoxic agents and glucocorticoids, most patients with PDH had underlying lymphoreticular malignancies, most commonly Hodgkin's disease. Currently, the most common underlying disease of patients with PDH is the acquired immunodeficiency syndrome (AIDS). Through the growing use of organ transplantation and newer immune-modulating treatments such as the tumor necrosis factor (TNF) blocking agents, an increasing number of individuals remain at risk for PDH (Figure 177.1).

DIAGNOSIS

The gold standard is the recovery of the organism, but this is time-consuming, requiring up to 30 days for identification of the organism.

Sputum cultures are not very useful in the cases of suspected acute pulmonary infection because the inoculum is not high enough and only rarely do patients have productive cough. In patients with acute disseminated histoplasmosis and in those with chronic pulmonary or cavitary infections, sputum cultures are frequently positive. When bronchoscopy and bronchoalveolar lavage are employed with appropriate stains, the sensitivity of respiratory secretions increases. Biopsy of accessible lesions (Figure 177.2) and bone marrow can be used in cases of disseminated infection.

Detection of histoplasma polysaccharide antigen in urine or serum offers high sensitivity and rapid diagnosis for patients with large inoculum acute pulmonary disease and those with PDH. Sensitivity for antigen detection is higher in disseminated infections than isolated pulmonary disease. The highest sensitivity of histoplasma antigen testing is in patients with AIDS and PDH when compared to other immunosuppressed or immunocompetent individuals with PDH. Earlier generation tests were characterized by a significantly higher sensitivity of the urine test when compared to serum testing. This does not appear to be the case with the newest generation of testing. As the levels of antigen are highest in the urine for most patients, urine testing is a helpful initial strategy. Antigenemia testing may be particularly useful in anuric

patients. Antigenuria levels have correlated with disease severity and have been useful when monitoring treatment, since the levels decrease with successful therapy and increase with relapse.

Serologic complement fixation and immunodiffusion are also helpful in some cases and may be the only means by which an infection can be diagnosed in immunocompetent individuals. In immunocompetent patients, it frequently takes 2 to 6 weeks for the development of detectable antibodies. The use of antibodies for diagnosis of histoplasmosis is most helpful in chronic pulmonary histoplasmosis and for those with persistent symptoms following recent infection.

As in the case of antigen detection there is also clinical correlation between the severity of the disease and the antibody response. In immunosuppressed patients antibody responses may be weaker and in some cases undetectable.

TREATMENT

The vast majorities of patients with acute histoplasmosis are asymptomatic or have a mild self-limited disease and do not require antifungal treatment. In the few patients where treatment is required, therapy (Table 177.1) depends on the clinical scenario.

Acute localized pulmonary infection resolves without therapy in the majority of cases, and treatment is indicated only when symptoms persist for more than 4 weeks. In these patients oral itraconazole, 200 mg three times daily for 3 days, followed by oral itraconazole, 200 to 400 mg daily for 6 to 12 weeks, is recommended. In more severe cases of acute diffuse pulmonary histoplasmosis in the immunocompetent host that require hospitalization, lipid formulations of amphotericin B in doses of 3 to 5 mg/kg/day are recommended for up to 2 weeks, followed by oral itraconazole, 200 mg three times daily for 3 days, followed by oral itraconazole, 200 mg twice daily for an additional 12 weeks. The parent compound, amphotericin B deoxycholate, is also effective, but the potential for nephrotoxicity limits its use. The usual dose is 0.7 mg/kg infused daily. Methylprednisolone, 0.5 to 1.0 mg/kg/day intravenously, may be used in severely ill, hypoxemic, or ventilated patients for up to 2 weeks.

The treatment of chronic pulmonary histoplasmosis is oral itraconazole, 200 mg three times daily for 3 days, followed by 200 to 400 mg daily for at least a year. Therapy may be extended if resolution is slow. Itraconazole levels should be monitored, especially in patients where the resolution is slow. Amphotericin B is also effective when used for 12 to 16 weeks. Relapses after apparently successful treatment may occur, and close follow-up is indicated.

The treatment of severe PDH is liposomal amphotericin B at the dose of 3 mg/kg/day for 1 to 2 weeks or until clear-cut clinical improvement occurs. This is followed by oral itraconazole, 200 mg three times daily for 3 days, followed by oral itraconazole, 200 mg twice daily for at least 12 months. Other lipid preparations may be substituted in appropriate doses. Amphotericin B deoxycholate is also effective in patients at

Table 177.1 Recommendations for treatment of patients with histoplasmosis

Manifestation	Treatment
Acute pulmonary: moderately severe or severe when symptoms persist for 4 weeks or longer	Itraconazole, 200 mg 3× daily for 3 d, followed by itraconazole, 200–400 mg daily for 6–12 wk
Acute pulmonary with severe manifestations	Liposomal amphotericin, 3–5 mg/kg/d for up to 2 wk, followed by itraconazole, 200 mg 3× daily for 3 d, then itraconazole, 200 mg 2× daily for 12 additional wk Amphotericin deoxycholate, 0.7 mg/kg/d, is also effective and may be substituted for liposomal amphotericin in patient at low risk for renal damage
Chronic cavitary pulmonary	Itraconazole, 200 mg 3× daily for 3 d, followed by itraconazole, 200 mg 2× daily for at least a year. Itraconazole levels should be measured in patients where resolution is slow Amphotericin B deoxycholate may also be used at the dose of 0.7 mg/kg/d for 12–16 wk
Progressive disseminated: moderately severe/severe, with or without HIV/AIDS	Liposomal amphotericin B, 3 mg/kg/d for 1–2 wk or until stability, followed by itraconazole, 200 mg 3× daily and then 200 mg 2× daily for at least 1 yr; other lipid formulations may be used as well as the deoxycholate preparation if needed
Progressive disseminated mild to moderate	Oral itraconazole, 200 mg daily for 3 d followed by 200 mg 2× daily for at least 1 yr
Central nervous system	Liposomal amphotericin B, 5 mg/kg/d for a total of 175 mg/kg, followed by itraconazole, 200 mg 2–3× daily for at least 1 yr

low risk for renal failure. Mildly ill patients with PDH may be treated with itraconazole alone for at least 12 months. PDH in AIDS patients is treated in a similar fashion. Chronic suppressive therapy with itraconazole is recommended for patients who do not recover immune function. CNS histoplasmosis is treated with liposomal amphotericin B, 5 mg/kg/day, for a total of 175 mg/kg over 4 to 6 weeks, followed by oral itraconazole, 200 mg two to three times daily for at least 1 year.

In areas endemic for histoplasmosis, particularly when high rates of histoplasmosis are observed, prophylaxis with oral itraconazole, 200 mg daily may be considered for patients with AIDS if the CD4 count is <150 cells/mm^3.

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178. Blastomycosis

Peter G. Pappas

Blastomycosis is a systemic pyogranulomatous disease caused by the thermally dimorphic fungus *Blastomyces dermatitidis*. The disease is endemic to parts of the midwestern and south-central United States and Canada, although blastomycosis has been reported worldwide, including isolated reports from Africa, Asia, and Central and South America. Within the United States and Canada, the disease is concentrated in areas along the Mississippi and Ohio River basins and the Great Lakes. In endemic areas, small point-source outbreaks of blastomycosis have been associated with recreational and occupational activities occurring in wooded areas along waterways. Current evidence indicates that *B. dermatitidis* exists in warm moist soil enriched by organic debris, including decaying vegetation and wood.

Most infections with *B. dermatitidis* occur through inhalation of aerosolized spores, although infection through direct inoculation has been reported rarely. Primary infections are usually asymptomatic or may result in a self-limited flu-like illness. Hematogenous dissemination of organisms from the lung can result in extrapulmonary manifestations.

Blastomycosis is usually recognized as a chronic, indolent systemic fungal infection associated with various pulmonary and extrapulmonary manifestations. Pulmonary blastomycosis usually manifests as a chronic pneumonia syndrome characterized by productive cough, chest pain, hemoptysis, weight loss, and low-grade fever. There are no distinguishing radiologic features of pulmonary blastomycosis, although nodular and mass lesions, with or without cavitation, often mimicking other granulomatous diseases or bronchogenic carcinoma are common. Hilar adenopathy and pleural effusions are uncommon. Rarely, diffuse interstitial infiltrates consistent with adult respiratory distress syndrome can occur secondary to blastomycosis.

Clinical manifestations of blastomycosis are highly variable. The lungs are involved in up to 90% of cases, and the skin is involved in 40% to 60% of cases. Multiple organ involvement is common, occurring in approximately 50% to 60% of cases. Osteoarticular disease is the next most common manifestation, followed by male genitourinary tract (especially the prostate and epididymis) involvement. Central nervous system (CNS) involvement occurs in fewer than 5% of patients, and can present as either granulomatous meningitis or an intracerebral mass lesion. *Blastomyces dermatitidis* is an uncommon opportunistic pathogen, but may cause overwhelming disease in the immunocompromised host. Among patients with predisposing factors, chronic glucocorticosteroid use, solid organ transplant, and advanced human immunodeficiency virus (HIV) disease are the most common underlying conditions.

DIAGNOSIS

The definitive diagnosis of blastomycosis requires a positive culture for *B. dermatitidis* from clinical specimens. A presumptive diagnosis is based on the finding of classic-appearing broad-based budding yeasts with doubly refractile cell walls compatible with *B. dermatitidis* on histopathologic examination of clinical specimens (Figure 178.1). Ten percent potassium hydroxide (KOH) is used to prepare wet specimens for examination, whereas fixed specimens are usually stained with hematoxylin and eosin, periodic acid–Schiff (PAS), or Gomori's methenamine silver (GMS) reagents. Serologic assays are of limited value in the diagnosis of blastomycosis. The complement fixation assay for serum antibody is highly cross-reactive and of little diagnostic value. Recent studies suggest that immunodiffusion or enzyme immunoassay (EIA) tests for A antigen of *B. dermatitidis* or antibody to more purified antigens have potential as serologic markers of disease. The *Blastomyces* EIA urine antigen assay is sensitive but nonspecific and gives false-positive

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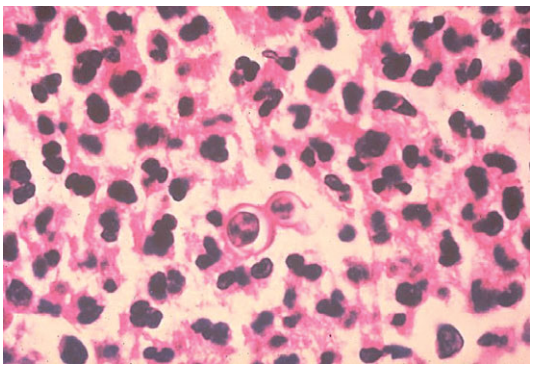

Figure 178.1 Histopathology of blastomycosis of skin. Cell of *Blastomyces dermatitidis* undergoing characteristic broad-based budding, surrounded by neutrophils. Multiple nuclei are visible. (Public Health Image Library, Centers for Disease Control and Prevention [CDC].)

results among patients with active histoplasmosis, paracoccidioidomycosis, and penicilliosis. The blastomycin skin test antigen lacks sufficient sensitivity and specificity and should not be used as a diagnostic test.

TREATMENT

Presently, three drugs are approved for the treatment of blastomycosis: amphotericin B, itraconazole, and ketoconazole. Traditionally, amphotericin B has been the mainstay of therapy for all forms of blastomycosis, but studies and experience gained since the early 1990s indicate that ketoconazole, itraconazole, and fluconazole are highly effective alternative oral therapies. It was recently recommended that ketoconazole no longer be manufactured for systemic use because of hepatotoxicity concerns, so it is unclear if this compound will remain available to clinicians. More recently, voriconazole has emerged as an effective alternative to the older azoles, especially for patients with complicated disease involving the CNS. Although no comparative trials have been performed, itraconazole appears to have greater efficacy and less toxicity than either fluconazole or ketoconazole, and therefore is the oral agent of choice. In a recently published trial, 95% of patients with non-life-threatening, non-CNS blastomycosis were treated successfully with itraconazole, 200 to 400 mg daily for 2 to 6 months. This approximates the observed efficacy seen with amphotericin B. Clinical data regarding the use of fluconazole suggest similar efficacy of this agent, with at least 80% of patients responding to 400 to 800 mg daily for 6 months. Most patients with blastomycosis can be started on oral itraconazole, 200 mg daily and advanced by 100-mg increments at monthly intervals to a maximum of 400 mg daily in patients with persistent or progressive disease. In patients with more aggressive disease, an initial dose of 400 mg is appropriate. Therapy with any of the azoles should be given for a minimum of 6 months. Clinical experience with posaconazole is very limited in all forms of blastomycosis; however, based on in vitro susceptibility data, one would anticipate excellent clinical activity of this compound.

A formulation of amphotericin B is generally reserved for patients with overwhelming life-threatening and/or CNS disease, patients who are severely immunocompromised, and for those in whom oral therapy has failed. In selected patients, an induction dose of amphotericin B for a rapid fungicidal effect to gain control of the disease may be useful, followed by oral therapy with itraconazole for at least 6 months. For patients with CNS involvement, several reports suggest that fluconazole and voriconazole, two azoles with significant CNS penetration, are effective therapeutic agents among individuals who have had an initial favorable response to amphotericin B. There is substantial clinical experience but few published data concerning the use of the lipid formulations of amphotericin B in the treatment of blastomycosis. There are no data to suggest superior efficacy of these agents compared with conventional (deoxycholate) amphotericin B. However, the use of the lipid formulations of amphotericin B, at doses ranging from 3 to 6 mg/kg daily, to treat blastomycosis has become a standard approach in many developed countries where there is broad access to these compounds. Despite their greater expense, the lipid formulations are associated with significantly less nephrotoxicity than deoxycholate amphotericin B.

The treatment of acute pulmonary blastomycosis remains controversial. Many investigators suggest close observation without therapy in patients who are not immunocompromised; however, this approach has become less acceptable to many clinicians given the extensive safety and efficacy profile of the azole compounds. Available data suggest that most cases of acute pulmonary blastomycosis resolve spontaneously without therapy, although careful long-term evaluation of these untreated patients is important to monitor for evidence of active disease.

All patients with chronic blastomycosis should receive antifungal therapy. Cure rates of at least 90% should be expected, with relapse rates of less than 10%. Mortality is uncommon, and is usually seen among patients with extensive pulmonary involvement and acute respiratory distress syndrome (ARDS). A few patients, especially chronically immunocompromised individuals such as organ transplant recipients, patients receiving chronic glucocorticosteroid treatment, and patients with acquired immunodeficiency syndrome require long-term suppressive therapy to prevent relapse.

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179. Coccidioidomycosis

Laurence F. Mirels and Stan Deresinski

BACKGROUND

Coccidioidomycosis, first described more than a century ago by Alejandro Posadas, is a disease of protean manifestations primarily endemic within ecologic zones of the Western Hemisphere characterized as the Lower Sonoran Life Zone with hot summers, few winter freezes, and annual rainfall of 10 to 50 cm. This includes areas in the southwestern United States (California, Arizona, western Texas, and highly localized areas of New Mexico, Nevada, and Utah), northern Mexico, and possibly Washington State, as well as scattered foci in Central and South America. Within these areas the incidence of coccidioidomycosis may vary significantly due to soil and climatic conditions that affect fungal and airborne dispersal, together with human behavior that increases exposure. There has been a marked increase in incidence in Arizona and California in recent years. *Coccidioides*, the etiologic agent of the infection, is a dimorphic fungus that grows in its soil reservoir in the mycelial (mold) phase. Under appropriate conditions, arthroconidia, the infectious spore form, disarticulate from mycelia and are carried airborne and inhaled, reaching the alveoli of the host. There the organism converts to the spherule phase, which reproduces by endosporulation with the subsequent rupture of the spherule releasing as many as 100 endospores, which subsequently, in turn, mature into spherules. Local control of the infection within the lung is the rule, but in some cases a chronic pulmonary infection may result or infection may spread within the thorax and/or distantly, via the lymphatics and bloodstream. Disseminated infection, especially when it involves the meninges, carries with it considerable potential for morbidity and mortality.

Coccidioides consists of two individual species, each with its own geographic distribution: *Coccidioides immitis* (found primarily in California) and *Coccidioides posadasii* (Arizona, Texas, and Mexico and areas of Central and South America). There are no substantive phenotypic differences between the species and the differentiation of one from the other is not routinely performed in the clinical laboratory. Similarly, no specific diagnostic, therapeutic, or prognostic ramifications have been attributed to the individual species.

PRIMARY INFECTION

Infection generally provides protection from subsequent exposure to the fungus. Approximately 60% of people acutely infected with *Coccidioides* spp. develop either no or minimal symptoms. After a usual incubation period of 7 to 21 days, the other approximately 40% of acutely infected people develop "flu-like" symptoms that may last weeks, including fever, sweats, myalgia, arthralgia, anorexia, weight loss, and fatigue. These constitutional symptoms are usually accompanied by a spectrum of respiratory complaints ranging from dry cough to symptoms such as pleuritic chest pain, tachypnea, and dyspnea. Reflecting this spectrum, the chest radiograph may be normal or may reveal scattered, patchy segmental infiltrates or dense lobar infiltrate(s) (Figure 179.1). Pleural effusion, usually minimal in volume, is noted in about 20%. In more severe cases, as may be seen following particularly heavy exposures or in infections of the immunocompromised, the chest radiograph may demonstrate diffuse reticulonodular infiltrates, a miliary pattern, or a pattern consistent with acute respiratory distress syndrome (ARDS). In fulminant cases, hemodynamic changes, including septic shock, may be present. In the acute phase, some patients develop a transient diffuse erythematous macular skin eruption, erythema nodosum, or, less commonly, erythema multiforme. These lesions are not the result of fungal dissemination but rather appear to represent immune reactions to the fungal infection, as does a self-limited arthritis ("desert rheumatism"), which may also occur. Development of erythema nodosum trad-

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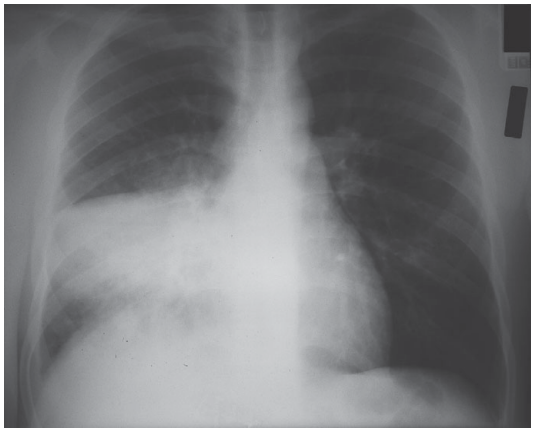

Figure 179.1 Primary pulmonary coccidioidomycosis. This 18-year-old male Pacific Islander presented with community-acquired pneumonia, and this chest radiograph shows a dense right middle lobe infiltrate. Coccidioidomycosis was suspected as the patient had recently moved to California's Central Valley to attend college, demonstrating the importance of the travel history in such settings. He was treated with fluconazole for 6 months and recovered uneventfully.

itionally has been associated with subsequent successful resolution of disease.

Because the presentation of acute coccidioidomycosis resembles that of many other respiratory infections, obtaining a travel history placing the patient in an endemic area in the weeks prior to onset of illness can greatly expedite the diagnosis and emphasizes the importance of a detailed exposure history for all such patients, not only for consideration of coccidioidomycosis but for other endemic mycoses or even more exotic infections. Although no findings are unique to acute coccidioidomycosis, those that tend to suggest this diagnosis include unexpectedly pronounced fever, fatigue, and weight loss and immune phenomena such as erythema nodosum. Eosinophilia may occur. Radiographic hints, when present, include a thin-walled cavity, nodule formation at sites of infiltrates, and pronounced hilar adenopathy, but these findings are nonspecific. Usually the clinical picture is indistinguishable from other causes of community-acquired pneumonia; patients are frequently prescribed one or more courses of antibacterial antibiotics and the absence of a response may be an important diagnostic clue. Some cases are serendipitously discovered when a routine sputum culture yields growth of the fungus.

The infection resolves spontaneously without treatment in the vast majority of patients. Some symptoms, particularly fatigue, may take weeks and in some cases, months to completely resolve. Persisting radiographic residua in the form of pulmonary nodules or cavities develop in approximately 5% of all infected individuals. Viable organisms may persist and remain inactive for decades after resolution of the primary infection. Reactivation may, however, occur, particularly in patients who subsequently become immunosuppressed.

Table 179.1 Risk factors for dissemination

Ethnicity: Filipino > African American
Pregnancy and the postpartum period
Immunodeficiency states, including acquired immunodeficiency syndrome
Diabetes

CHRONIC PULMONARY AND DISSEMINATED COCCIDIOIDOMYCOSIS

The development of chronic active pulmonary infection or clinically important dissemination following primary infection is fortunately uncommon, occurring in just several percent of cases. Certain characteristics define individuals or groups with a greatly increased risk of dissemination or progressive pulmonary infection (Table 179.1) and in whom these complications tend to be more refractory to treatment. Included are those who are overtly immunocompromised due to underlying illness (e.g., human immunodeficiency virus/acquired immunodeficiency virus [HIV/AIDS], lymphoma) or due to receipt of immunosuppressants (e.g., patients who have undergone transplantation or are receiving treatment for rheumatologic disorders). Recently, several patients with disseminated coccidioidomycosis and abnormalities in their interferon (IFN)-γ–interleukin (IL)-23–IL-12 axis, as well as at least one patient with hyper-IgE syndrome have been described. For reasons that remain unexplained, Filipinos and African Americans are at increased risk of dissemination of their infection. Pregnant women (especially in the third trimester) and women in the immediate postpartum state often have great difficulty controlling their infections, although it has been suggested that flares of disease after delivery may represent a form of immune reconstitution inflammatory syndrome. It is not certain that transplacental infection of the fetus occurs and the very rarely

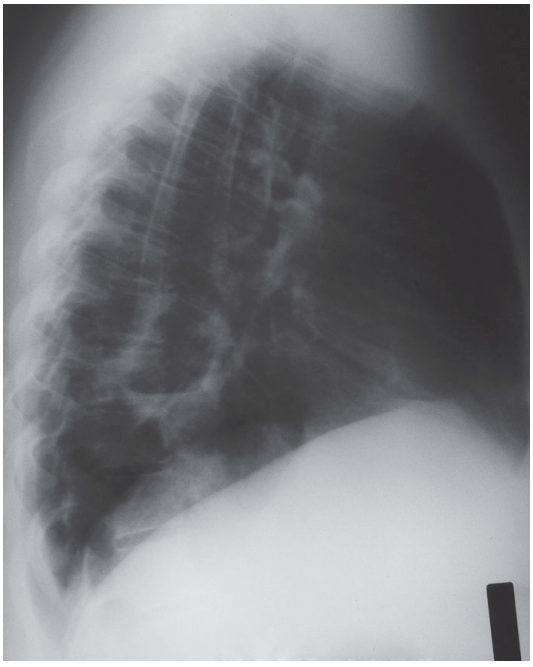

Figure 179.2 Chronic cavitary pulmonary coccidioidomycosis. Chest radiograph of a 21-year-old Hispanic woman with type II diabetes and known chronic cavitary coccidioidomycosis. She presented with 1 week of low-grade fever and increasing productive cough. Her lateral chest radiograph shows a chronic cavity with thickened walls and an air–fluid level consistent with bacterial superinfection. She responded to a 14-day course of amoxicillin–clavulanate and remained on fluconazole.

observed neonatal infections are likely the result of aspiration of amniotic fluid or vaginal secretions. Diabetes mellitus, particularly if poorly controlled, has been associated with the development of chronic cavitary pulmonary disease and possibly also carries an increased risk of dissemination. It is also likely that exposure to very large inocula of arthroconidia may result in severe disease, including dissemination, even in previously healthy individuals without known risk factors.

Following primary infection, a small proportion of individuals go on to develop persistent infections confined to the lung. Such patients may display pulmonary cavities with walls that appear thicker than that seen in classical coccidioidal cavities (Figure 179.2) and chronic symptoms of dry or productive cough, chest pain, shortness of breath, and hemoptysis, each of which may wax and wane. A distinct subgroup will develop a destructive, progressive fibrocavitary pulmonary infection with fibrotic changes in the lung parenchyma and bronchiectasis. In addition to the symptoms mentioned earlier, these patients are often plagued by constitutional symptoms such as fever and weight loss, which may progress to cachexia. Complement-fixing antibody (CFA) titers in this group tend to be somewhat high. Complications associated with cavities include bacterial superinfection (recurrent), fungus ball formation (due to *Coccidioides* spp. or other fungi), and rupture into the pleura with (hydro-)pneumothorax, empyema, and/or bronchopleural fistula. In the absence of profound immunocompromise, chronic pulmonary disease is infrequently associated with extrapulmonary foci of infection.

Disseminated disease usually becomes clinically evident within 6 months of the initial infection. Evaluation of the patient may reveal involvement of only a single anatomic site or of multiple organ systems. Dissemination may occur in patients who were asymptomatic with their primary infection and, in those with symptomatic primary infections it is common for pulmonary symptoms and findings on chest radiograph to have resolved completely at the time of presentation with extrathoracic disease. Both of these circumstances tend to obscure the diagnosis of coccidioidomycosis.

Skin lesions are the most frequently recognized manifestation of extrapulmonary dissemination. Lesions may be single or numerous, range in size from several millimeters to many centimeters in diameter, and, even in the same patient, may take on a variety of forms, including smooth to verrucous papules, plaques, ulcers, or pustules (Figure 179.3A). Bone is a frequent site of dissemination with vertebrae, often numerous, being particularly favored. The cranial vault, pelvis, ribs, tibia, feet, metacarpals, and metatarsals are other common targets. Bone lesions may be asymptomatic or associated with pain that may be described by the patient as constant and gnawing. These lesions are usually lytic, may be highly destructive, and may be accompanied by extensive adjacent soft-tissue involvement. Bone scans and magnetic resonance imaging (MRI) are particularly useful modalities for identifying bone lesions and for evaluating the extent of bone and neighboring soft-tissue involvement, respectively (Figure 179.4). Dissemination to joints is not infrequent and may be heralded by rapid or more insidious development of findings typical of septic arthritis. The knee is affected most frequently followed by joints of the ankle and foot, wrist, hands, and the elbow. The resultant

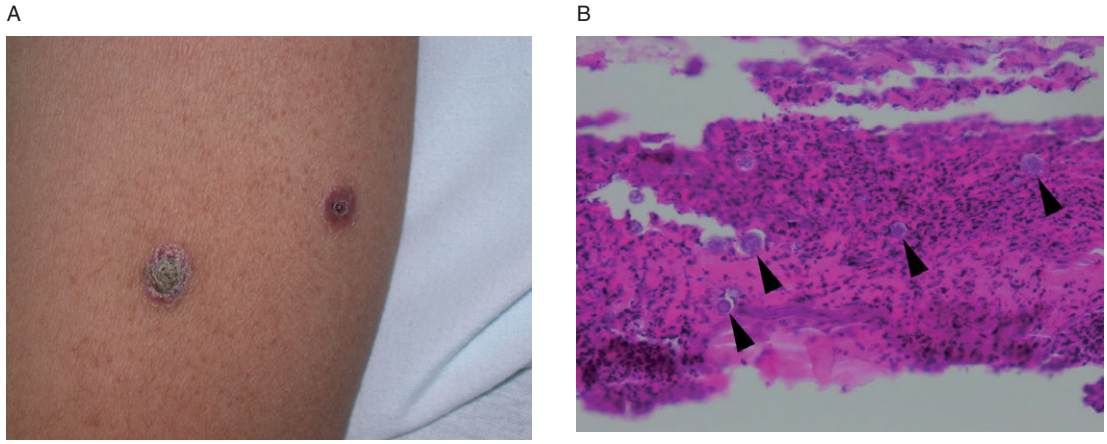

Figure 179.3 Disseminated coccidioidomycosis, skin lesions. (**A**) This 26-year-old previously healthy Filipino man presented with coccidioidomycosis featuring numerous skin lesions of varying size and appearance. This photograph shows two suspicious lesions on the arm, each measuring ~5 mm in diameter. (**B**) Photomicrograph of a punch biopsy of the skin which was taken from the margin of the verrucous lesion shown in the adjacent photograph. There is significant lymphocytic infiltration, and numerous spherules are evident (several of which are highlighted by arrowheads) thus making the diagnosis of disseminated coccidioidomycosis. (Original magnification, 400×, tissue stained with hematoxylin and eosin.) This patient made a full recovery and continues on itraconazole.

synovial proliferation may be mistaken for rheumatoid arthritis by the arthroscopist. Pelvic joints may be involved, intervertebral disks are usually spared. Arthrocentesis may lead to the diagnosis; synovial biopsy, however, offers a higher yield. Subcutaneous abscesses may represent primary sites of dissemination but often prove to have resulted from suppuration of a lymph node or extension of pus from a deeper (sometimes surprisingly distant) focus by formation of a sinus tract.

The central nervous system is a major site of dissemination and infection at this site is most likely to result in permanent disability or death. *Coccidioides* spp. typically cause a chronic granulomatous meningitis, most often involving the basilar meninges of the brain and those of the upper spinal cord (Figure 179.5). Central nervous system involvement generally occurs within months of the primary infection but occasionally is seen after much longer intervals. Symptoms may be abrupt or insidious in onset and progress inexorably at a tempo that varies from patient to patient. If the underlying disease remains untreated it virtually always will lead to death within 2 years. Patients complain primarily of headache with anorexia, nausea, vomiting, visual changes, generalized weakness, and ataxia as possible associated symptoms (often being secondary to the development of hydrocephalus). Progressive lassitude and altered mentation often are the dominant findings. Furthermore, patients may have only very mild symptoms even in the face of impressive cerebrospinal fluid (CSF) findings and meningeal signs are often subtle or absent. Nonetheless, routine lumbar puncture is not indicated in the absence of potentially suspicious signs or symptoms. Hydrocephalus is a frequent complication of coccidioidal meningitis and may even develop late and in the face of appropriate, otherwise effective therapy. Abscess formation, cranial nerve involvement, myelitis, arachnoiditis, and syrinx formation, as well as cerebral vasculitis are also occasionally seen.

Other anatomic sites involved with some regularity in disseminated disease include lymph nodes, liver, spleen, male and female genitourinary tracts, peritoneum, pericardium, thyroid, and the eye.

DIAGNOSIS

The diagnosis of coccidioidomycosis is best made by direct examination of tissues or secretions for the presence of characteristic fungal forms (Figure 179.3B) and by culture, which usually requires 2 to 6 days for recovery of the organism. Amplification with subsequent sequencing of DNA encoding 18S rRNA has successfully identifed fungal pathogens in tissue and may prove useful in coccidioidomycosis. Blood cultures may rarely be positive and only in individuals, usually

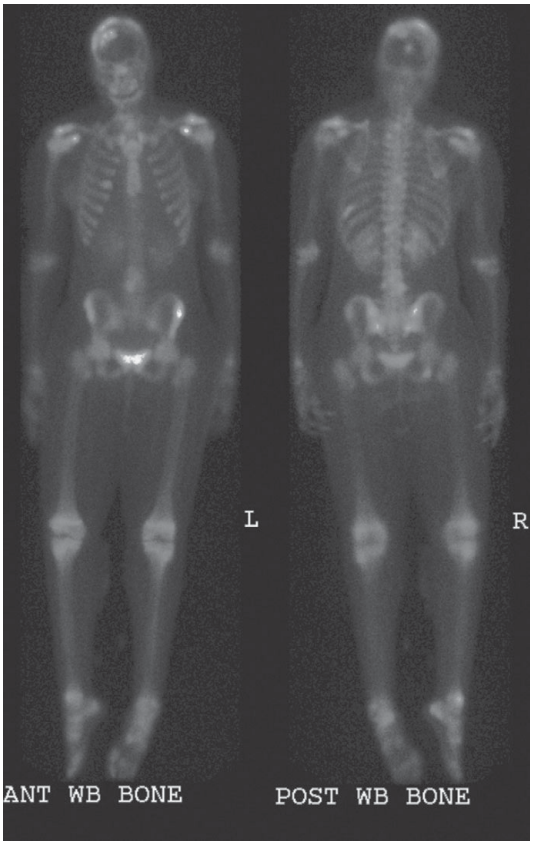

Figure 179.4 Disseminated coccidioidomycosis, bone lesions. This 14-year-old healthy African-American adolescent presented with widely disseminated coccidioidomycosis. These delayed whole-body three-phase bone scan images demonstrate abnormal uptake indicative of a multitude of bone lesions that were subsequently verified by magnetic resonance imaging, computed tomography, or plain film: vertebral lesions are seen throughout the length of the spine; there are multiple lesions of the calvaria; lesions affecting the right sixth rib, the left tenth rib, both shoulders, the right ankle, and the right ischium are readily appreciated. Of note, only her shoulder and lower spine lesions were symptomatic. She was successfully treated medically with 1 month of intravenous amphotericin B, which was transitioned to itraconazole. She continues on itraconazole.

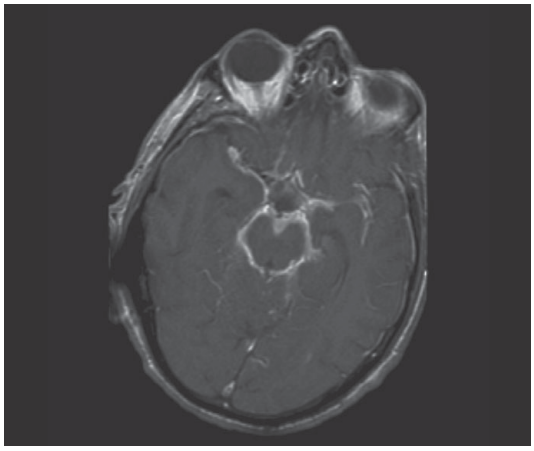

Figure 179.5 Coccidioidal meningitis. This 48-year-old Hispanic man with type II diabetes presented with headache and obtundation. This axial T1-weighted magnetic resonance image taken after the administration of contrast shows abnormal enhancement of the leptomeninges at the base of the brain. Hydrocephalus was treated by placement of a ventriculoperitoneal shunt, and a lumbar reservoir was placed to facilitate delivery of intrathecal amphotericin, which was given along with fluconazole. He made a full recovery and now continues on fluconazole alone.

severely immunocompromised, with severe acute dissemination of infection. Urine cultures may very rarely be positive. When culture samples are submitted in a case of suspected coccidioidomycosis, laboratory personnel should be notified in order to reduce the risk of transmission in that setting. Serologic tests, such as immunodiffusion and enzyme-linked immunosorbent assays, that identify anticoccidioidal immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies in serum and IgG in CSF are useful. The magnitude of the CFA titer, which is a measure of the amount of anticoccidioidal IgG antibody, has the valuable property of correlating with the extent of disease so that 80% or more of patients with dissemination to more than one site will have serum titers $\geq$1:16. Furthermore, changes in the CFA titer are useful in guiding therapeutic decisions – a falling titer is an indication of response to antifungal administration.

Antibody testing may be negative during the first weeks of infection and, if coccidioidomycosis is still suspected, repeat testing is indicated. Positive tests may revert to negative with successful control of infection. A positive IgM anticoccidioidal antibody test together with a negative IgG test may reflect very recent infection and, once again, repeat testing will clarify the diagnosis. If repeated and the pattern persists, the IgM test is likely falsely positive, although early initiation of fluconazole therapy may produce the same result. False-negative antibody results occur in immunocompromised patients, such as immunosuppressed transplant recipients and patients with immunodeficiency syndrome (among whom the incidence of coccidioidomycosis has dramatically decreased with the widespread use of effective

antiretroviral therapy). A coccidioidal antigen test is available in a commercial laboratory, but its characteristics remain to be fully defined.

In patients with meningitis, analysis of CSF demonstrates a predominantly mononuclear pleocytosis (usually 50 to 500 cells/mm^3, with the percentage of polymorphonuclear leukocytes present tending to decrease over time), elevated protein (usually 100 to 500 g/dL), and low glucose – a picture that is compatible with other etiologies, including tuberculosis. A marked increase in protein concentration may indicate the development of an impairment of CSF flow and reabsorption. Eosinophils may be present (usually in a range of 1% to 10% of CSF white blood cells) and, in patients with an appropriate travel history (including one that does not suggest the possibility of cysticercosis or of *Angiostrongylus* infection), coccidioidomycosis should be considered. Culture of CSF yields the organism in only a minority of cases, but IgG antibodies directed at coccidioidal antigens may be detected in the fluid in >90% of cases. Nucleic acid amplification-based tests for the detection of *Coccidioides* spp. in body fluids or tissue specimens may ultimately prove to be an important advance in the diagnosis of coccidioidomycosis, but they are not yet available for general use.

Human-to-humn transmission of *Cocccidioides* spp. does not occur and patient isolation is not indicated. Infection has, however, been transmitted to solid organ transplant recipients via the transplanted organ. Objects such as linens, bandages, and casting materials contaminated with body fluids containing the organism (e.g., pus or sputum) are capable of supporting its conversion to the infectious mycelial form over a period of several days at room temperature. All such fomites should therefore be collected daily and sterilized using standard hospital practices for handling biologic waste.

TREATMENT

General considerations

Table 179.2 summarizes treatment recommendations.

Azole antifungal agents have, in most instances, supplanted the use of amphotericin B in the treatment of coccidioidomycosis. Amphotericin B is, however, often preferred as initial therapy when rapid control of the disease is imperative, such as in life-threatening, fulminant, or rapidly progressive infections. Once control of the infection is achieved, therapy may be transitioned to use of an azole, usually fluconazole. Amphotericin B is also preferred during the first trimester of pregnancy due to the teratogenicity of prolonged high-dose fluconazole (and presumably other members of the class) administration during this period. While there is no evidence that a lipid formulation of the polyene is more effective, one is preferred because of lesser associated toxicity than seen with the deoxycholate preparation. Whether an azole is used from the outset or for later replacement of amphotericin B, either fluconazole or itraconazole may be safely chosen, but the former has the distinct advantages of reliable bioavailability and fewer pharmacokinetic interactions with other medications, making it the preferred agent. Voriconazole and posaconazole are each active in vitro against *Coccidioides* spp. and, while their role in initial therapy has not been systematically evaluated, published clinical experience indicates that they have a place in salvage therapy. While there is no value in therapeutic drug monitoring in patients receiving fluconazole in the absence of changing renal function, the erratic bioavailabilities of itraconazole, voriconazole and posaconazole make such testing potentially useful. The echinocandins, which have in vitro activity when evaluated by a nonstandard method, have been used as part of salvage therapy in combination with other antifungals and it is not possible to judge their efficacy in coccidioidomycosis. IFN-γ, when administered in conjunction with antifungals, has a role in some patients with genetic mutations affecting the IFN-γ–IL-23–IL-12 axis. It has also been administered to a small number of patients with progressive therapy-resistant infection in the absence of defects in that axis with clinical improvement in some, but its use remains experimental (and very expensive).

Uncomplicated primary pulmonary infection

In the majority of cases, primary infection with *Coccidioides* is self-limited and, given the continued absence of contrary evidence, antifungal therapy is not routinely warranted. Patients considered at increased risk of complications are, however, potential treatment candidates. In addition to those listed in Table 179.1, risk factors in this setting may also include pre-existing cardiopulmonary disease, chronic renal insufficiency, and severe manifestations of infection such as extensive pulmonary involvement, intense night sweats lasting >3 weeks, loss of >10% of body

Table 179.2 Summary of treatment recommendations

Primary pulmonary
No dissemination risk: No treatment or fluconazole, 400 mg daily, or itraconazole, 200 mg BID, for approximately 3–6 mo or for 3 mo after complete resolution of clinical infection. All patients should be followed closely
Dissemination risk or severe disease: fluconazole, ≥400 mg daily, or itraconazole, ≥200 mg BID, for approximately 3–6 mo, including ≥3 mo after resolution of clinical infection
Pulmonary cavity (uncomplicated) or fibrocavitary disease
Observation or fluconazole, 400 mg daily for ≥6–12 mo, and assess for response. Individualized management of complications. Surgical resection in selected cases
Progressive pulmonary or disseminated (nonmeningeal)
Immediately life threatening: amphotericin B lipid formulation, 3.0–5.0 mg/kg/d; consideration given to transition to fluconazole or itraconazole when disease is controlled. Alternatively, fluconazole, ≥400 mg daily, or itraconazole, ≥200 mg BID. The duration of therapy is usually at least 2 yr; some patients may require lifelong therapy. Individualized management depending on site(s) of involvement
Slowly progressive or stable: fluconazole, ≥400 mg daily, or itraconazole, ≥200 mg BID. The duration of therapy is usually at least 2 years; some patients may require lifelong therapy. Individualized management depending on site(s) of involvement
Meningitis
Fluconazole, ≥400 mg daily (many advocate starting dose of ≥800 mg), or itraconazole ≥200 mg BID (doses as high as 600 mg BID have been used, recommend checking serum levels)
or
Amphotericin B directly into cerebrospinal fluid (usually with an oral triazole dosed as above) transitioned to oral azole alone (usually dosed at no lower than 400 mg total daily)
Patients must be evaluated frequently for the emergence of complications and serial CSF analyses must be performed to document response to therapy, particularly early in the course
Due to the high relapse rate, patients with coccidioidal meningitis usually continue on antifungal therapy for life
HIV-infected patients
All HIV infected patients with CD4+ lymphocyte count ≤250 cells/mm^3 with any form of coccidioidomycosis should receive antifungal therapy. If the infection is immediately life threatening, initial treatment with amphotericin B is preferred. With stabilization, fluconazole or itraconazole may be used, with careful attention to drug interactions with some antiretrovirals. Consider discontinuation if nonmeningeal disease, therapy has been prolonged and the CD4+ count is stably >250 for at least 6 mo. For meningeal disease, lifelong antifungal treatment regardless of CD4+ count achieved
Pregnant patients in first trimester
Amphotericin B lipid formulation, 3.0–5.0 mg/kg/d

Abbreviations: HIV = human immunodeficiency virus; CSF = cerebrospinal fluid.

weight, persistent hilar adenopathy (although a recent study found only a nonstatistically significant trend risk for patients with mediastinal lymphadenopathy), and CFA ≥16. Thus, each patient requires individualized assessment.

If it is elected to treat, fluconazole, 400 mg once daily, is the preferred choice (except in those in the first trimester of pregnancy who should receive amphotericin B). Itraconazole, 200 mg twice daily, is an alternative but bioavailability is variable and drug interactions are many. The optimal duration of therapy is unknown but a minimum of 3 months is often recommended. Longer durations may be indicated in others, including those with significant ongoing immunocompromise and those whose high CFA titers fail to fall during therapy.

Whether treated or not, it is imperative that patients be evaluated at intervals for as long as 2 years to assure that infection has successfully resolved and to detect complications as early as possible. Evaluations should include a complete review of systems, physical examination, serum CFA titer, and, as appropriate, repeat radiographic studies or cultures. For those receiving an azole antifungal, monitoring for side effects and periodically obtaining routine bloodwork (e.g., liver function tests, electrolytes, complete blood count) are advisable.

Progressive pulmonary or nonmeningeal disseminated infection

Amphotericin B is often recommended for initial treatment of patients with rapidly progressive pulmonary or disseminated infection that is immediately life threatening. Nonmeningeal coccidioidomycosis that is progressing at a more indolent pace, however, is generally treated with

an orally administered azole. In the United States ketoconazole, despite having demonstrated efficacy in the treatment of coccidioidomycosis, has been supplanted by other agents, with fluconazole being the preferred choice. In patients who fail fluconazole therapy, other triazoles may still prove effective.

In general, treatment of nonmeningeal disseminated or progressive pulmonary coccidioidomycosis should continue for at least 2 years or for 1 year after the infection appears to have resolved completely, whichever is longer. As many as one-third of patients may relapse after discontinuation of even such prolonged courses. For this reason, there is a critical need for continued, long-term, careful observation of patients who are no longer receiving antifungal therapy. Patients with AIDS should continue to receive an antifungal agent until their CD4+ T-cell count remains >250 cells/mm^3 for at least 6 months.

Meningitis

A multicenter study demonstrated a response (defined as resolution of ≥40% of baseline abnormalities) rate of 79% with a daily dose of fluconazole of 400 mg given for a median duration of 37 months in the treatment of coccidioidal meningitis. Daily doses of fluconazole of 800 mg or greater may possibly be associated with an improved early response to therapy but also with a greater incidence of adverse reactions. While the available data are more limited, itraconazole, at total dosages of 400 mg daily or higher, may possibly have similar efficacy. Although apparent cures have been reported, relapse after discontinuation of drug administration is extremely frequent and lifelong suppressive therapy is indicated. Intrathecal amphotericin B administration should be considered in patients who fail azole therapy – systemic azole administration is generally continued when this course is taken. Corticosteroid administration may be considered in patients whose meningitis is complicated by the development of cerebral vasculitis, although unequivocal evidence of benefit is lacking.

Patients undergoing treatment for meningitis require close observation. Evaluations should include a review of systems, physical examination, lumbar puncture to follow the opening pressure, cell count, protein, glucose, and CFA titer, and, potentially, radiographic imaging. Evidence of disease progression necessitates immediate intensification of therapy (minimally a trial of an increased dose of the current therapy or conversion to an entirely different antifungal and, in some cases, consideration of intrathecal administration of amphotericin). The occurrence of complications may require urgent intervention. One frequently encountered example is the development of hydrocephalus. The treatment of coccidioidal meningitis is often complex and should probably be attempted only by, or in close collaboration with, clinicians experienced in its management.

The role of direct injection of amphotericin B into the CSF space remains poorly defined. When used, injection is accomplished via the lumbar, lateral cervical, or cisternal route by direct puncture or through the use of implanted devices such as an Ommaya reservoir. The latter may be implanted for injection into either a lateral cerebral ventricle or the lumbar space. CSF flow patterns should be defined by radionuclide or dye studies when determining the optimal route for the delivery of amphotericin to the sites of central nervous system infection because CSF flow may be disrupted by blockages or loculations.

When administering intrathecal amphotericin by the lumbar route, some clinicians prefer using the "hyperbaric" technique, which allows delivery of the drug in high concentration to the basilar meninges, where the major burden of infection is ordinarily found. In addition, the rapid removal of drug from the lumbar area theoretically decreases the likelihood of some of the possible local complications induced by amphotericin, such as radiculitis, myelitis, arachnoiditis, and spinal artery thrombosis. Concomitant azole therapy is usually maintained in patients receiving intrathecal amphotericin.

The development of hydrocephalus, either communicating or noncommunicating, occurs frequently and should be suspected when the patient's neurologic status deteriorates; nausea, vomiting, ataxia, or weakness develops; or if the CSF protein concentration increases to high levels. Hydrocephalus should be managed by the placement of a CSF shunting device, but a change in antifungal therapy may not be warranted. Central nervous system vasculitis may complicate coccidioidal meningitis. Although no comparative data exist, some clinicians suggest administration of corticosteroids along with maximal antifungal therapy in patients with this complication.

Other infections

In the absence of immunosuppressive disease or therapy, antifungal treatment is not required in the case of a stable, solitary pulmonary nodule. Coccidioidomycosis of the airways may be effectively treated with an azole.

Chronic pulmonary cavities respond poorly to antifungal therapy and, if asymptomatic, may best be left untreated. Complications include bacterial superinfections and hemoptysis. On occasion, hemoptysis may be the result of the development of a mycetoma. Cavitation may progress even in the face of chemotherapy. These complications are potential indications for surgical intervention. Rarely, a coccidioidal cavity may rupture into the pleural space, resulting in pyopneumothorax. This complication should be managed surgically with concomitant administration of an antifungal agent.

Chronic progressive fibrocavitary pulmonary infection requires prolonged antifungal therapy; surgical resection of the affected tissues may be of value in some cases in which the disease is sufficiently localized.

The musculoskeletal system is a common site of involvement in cases of disseminated infection. In addition to antifungal chemotherapy, surgical debridement may be warranted in some cases of osteomyelitis. Synovectomy may be beneficial in the management of chronic coccidioidal arthritis.

BIOLOGIC RESPONSE MODIFIERS AND DISEASE-MODIFYING AGENTS IN PATIENTS WITH RHEUMATOLOGIC DISEASE

In the patient with rheumatic disease receiving biologic response modifiers (BRMs) and/or classical disease-modifying agents (DMAs) who develop coccidioidomycosis, recent recommendations suggest that, along with initiation of antifungal therapy, these may be continued, with careful repeated evaluation. In patients who develop pulmonary infection, BRMs and DMAs should be at least temporarily discontinued but may be resumed after resolution of the infection. BTMs and DMAs should be discontinued in patients with disseminated infection. It may be reasonable to extend this approach to patients whose infection antedates the need for BRMs and/or DMAs. Whether to administer prophylactic antifungals in the patient with past, but now inactive coccidioidomycosis is uncertain but may be considered.

PROPHYLAXIS

It has been recommended that individuals inadvertently exposed to potential aerosols of *Coccidioides* spp. in the laboratory receive fluconazole or itraconazole for 6 weeks as prophylaxis. Prophylaxis, although not invariably successful, can also be considered for transplant recipients without active infection but with detectable serum antibody to coccidioidal antigen or with a past history of coccidioidomycosis.

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180. *Pneumocystis jirovecii* (*carinii*)

Shelley A. Gilroy and Nicholas J. Bennett

BACKGROUND

Pneumocystis jirovecii (pronounced "yee-row-vet-zee"), formerly known as *Pneumocystis carinii*, is an opportunistic pathogen that causes pneumonia in the immunocompromised individual. The initials "PCP" stood for *Pneumocystis carinii* pneumonia but were kept for ease of use after the organism was renamed. Disease occurs when both cellular and humoral immunity are impaired. Serologic studies have shown that *Pneumocystis* has a worldwide distribution but the prevalence of antibodies to specific antigens varies among different geographic regions. PCP first came to attention when it caused interstitial pneumonia in severely malnourished and premature infants in Central and Eastern Europe during World War II. Prior to the acquired immunodeficiency syndrome (AIDS) epidemic in the 1980s, fewer than 100 cases were reported annually in the United States. PCP is one of several life-threatening opportunistic infections in patients with human immunodeficiency virus (HIV) infection worldwide and is still the most common AIDS-defining illness in patients with advanced HIV infection. The decline in the number of PCP cases in the United States occurred after the introduction of anti-pneumocystis prophylaxis in 1989 and highly active antiretroviral therapy (HAART) in 1992. In patients without HIV infection, the incidence of PCP has increased in those being treated with immunosuppressive and chemotherapeutic agents and in hematopoietic stem cell (HSCT) and solid organ transplant recipients.

The taxonomic classification of the *Pneumocystis* genus and the organism's name has changed throughout the years. In the 1980s, biochemical analysis identified the organism as a unicellular fungus. *Pneumocystis jirovecii* is found in three distinct morphologic stages: the trophozoite, in which it often exists in clusters, the sporozoite (precystic form), and the cyst, which contains several intracystic bodies (spores). The cyst is the diagnostic form of *P. jirovecii* and stains with Giemsa, Papanicolau, and Grocott methenamine silver nitrate (GMS) and immunocytochemical techniques using monoclonal antibodies. Giemsa- and Papanicolau-stained smears show indirect evidence of *P. jirovecii* infection by the demonstration of foamy exudates in the form of alveolar casts.

The environmental source for *Pneumocystis* is unknown. Studies in animals and humans suggest that it is transmitted by the airborne route. The organism can be found in the respiratory tract of hospitalized patients with viral or bacterial infections and healthy individuals without pneumonia. These individuals may serve as a reservoir for infection to susceptible hospitalized patients. The time necessary from colonization to infection is unknown. Once *Pneumocystis* enters the lungs it attaches to the alveoli. Alveolar macrophages are the first line of defense and are responsible for clearing the organism from the lung. This function is impaired in patients with HIV or cancer and in transplant recipients receiving immunosuppressive therapy. Tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1), proinflammatory cytokines, have been shown to be important in host defenses against the organism in the early stages of infection. As the host defenses become compromised, *Pneumocystis* organisms proliferate and fill alveolar lumens, subsequently leading to interstitial plasma pneumonia.

Extrapulmonary *Pneumocystis* infection is rare. Dissemination may occur via direct spread, hematogenous spread, or via lymphatic vessels in the absence of pneumonia. It can occur in HIV-infected patients receiving aerosolized pentamidine for prophylaxis. The most common organs or tissues infected are the lymph nodes, spleen, liver, bone marrow, and the small intestine.

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CLINICAL MANIFESTATIONS

PCP is an AIDS-defining illness, typically occurring in HIV-infected patients not taking HAART, with a T-helper cell count (CD4) less than 200 cells/mm^3. Symptoms include insidious onset of dyspnea with a dry cough, fever, diarrhea, and weight loss. Acute dyspnea with chest pain may indicate a pneumothorax. Physical examination typically reveals tachypnea, tachycardia, and fever with normal findings or mild crackles or rhonchi on lung auscultation. Oral thrush or oral hairy leukoplakia may also be present. A resting PaO_2 of less than 80 mm Hg occurs in 80% of cases. Desaturation with exercise is a highly sensitive marker of PCP, even if the PaO_2 is normal. A clinical picture of PCP in HIV-infected patients with a high CD4 count should prompt consideration of immune reconstitution inflammatory syndrome (IRIS), defined as a clinical deterioration caused by restoration of a patient's capacity to mount an inflammatory immune response against infectious and noninfectious agents once HAART has begun.

In children early signs are poor feeding, diarrhea, and coryza. Physical findings include nasal flaring, intercostal retraction, and cyanosis.

Immunocompromised patients without AIDS typically present with acute respiratory insufficiency or shorter duration of illness and fewer days of dyspnea and fever. PCP can occur with or without lymphopenia or low CD4 counts.

The most significant risk factors for PCP are defects in cell-mediated immunity, prolonged glucocorticoid use, cancer (particularly hematologic malignancies), HSCT, rheumatologic diseases, severe combined immunodeficiency, and severe malnutrition. The most common chemotherapeutic drugs associated with increased risk of PCP are fludarabine, vincristine, and cyclophosphamide. Patients receiving biologic agents, particularly alemtuzumab and the TNF inhibitor infliximab, are also at risk for infection.

In early mild disease the chest radiograph will be normal. High-resolution computed tomographic scanning (HRCT) is more useful.Typical findings are diffuse micronodules, patchy ground-glass, symmetric or asymmetric opacities, reticulation, septal thickening, and/or airspace consolidation (Figure 180.1). Apical interstitial infiltrates and pneumothorax occur more often in patients receiving prophylactic treatment with aerosolized pentamidine. Solitary or multiple nodules, which may cavitate, and pneumatoceles are less common. Pleural effusions and intrathoracic adenopathy are rare.

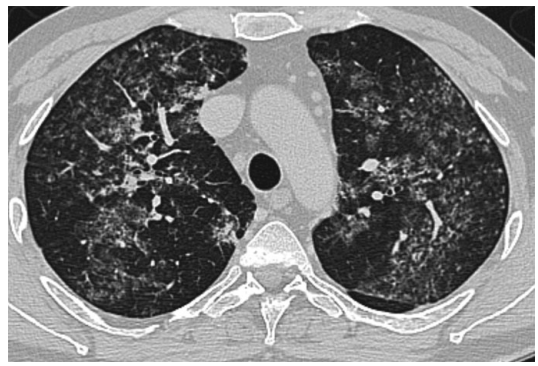

Figure 180.1 High-resolution computed tomographic image of the upper lung zones demonstrates diffuse micronodules, patchy ground-glass opacities, as well as some fine reticulation, all suggestive of an interstitial process consistent with P*neumocystis* pneumonia. (Courtesy of Frederic Hellwitz, MD, Department of Radiology, Albany Medical College, Albany, NY). Reprinted with permission from Thieme Publishers.

DIAGNOSIS

Pneumocystis has no effective culture-based test and the diagnosis, if suspected on clinical grounds, usually relies on obtaining invasive respiratory specimens. Tests on routine sputum specimens are insensitive and should not be performed, although induced sputum (performed with a respiratory therapist after inhalation of nebulized hypertonic saline) is about 50% sensitive. The sensitivity varies but approaches 90% in some institutions depending on technique proficiency and the experience of the laboratory. A negative result would not rule out PCP. Optimal testing requires bronchoscopy and bronchiolar lavage. Lung biopsy is diagnostic.

The classic histology findings are "foamy alveolar casts," in which there is proteinaceous fluid within the alveoli (Figure 180.2). With a silver stain such as GMS, pneumocystis can be visualized as teacup-shaped organisms (Figure 180.3). Immunofluorescence techniques such as direct fluorescent antigen (DFA) can also be employed and are sensitive and specific. PCR testing is not readily available and is more difficult to interpret (carriage versus infection) due to its increased sensitivity.

In certain clinical settings, it may not be practical or safe to obtain invasive specimens, and noninvasive specimens are preferred. Serologic testing specific to PCP is available, but cannot reliably distinguish between past and present infection. The majority of people will, at some

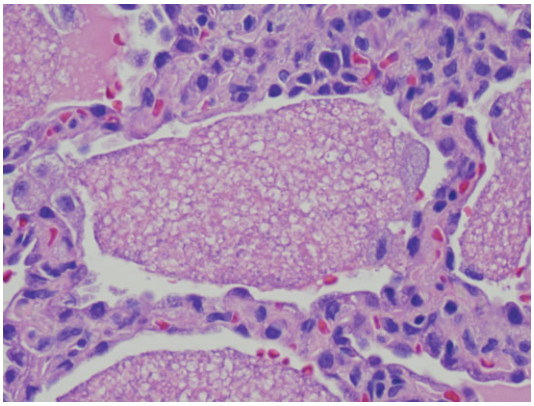

Figure 180.2 Hematoxylin and eosin stain of lung alveolae, showing foamy infiltrates (foamy alveolar casts). (Courtesy of Anna-Luise Katzenstein, MD, Department of Anatomic Pathology, State University of New York Upstate Medical University, Syracuse, NY.) Reprinted with permission from Thieme Publishers.

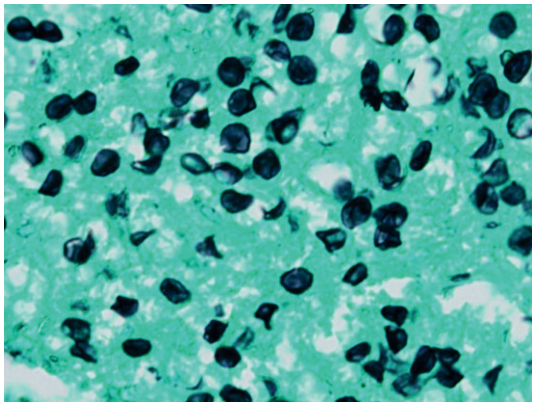

Figure 180.3 Grocott's methenamine silver stain of lung alveolae, highlighting the *Pneumocystis* organisms in black. (Courtesy of Anna-Luise Katzenstein, MD, Department of Anatomic Pathology, State University of New York Upstate Medical University, Syracuse, NY.) Reprinted with permission from Thieme publishers.

point, become colonized with *Pneumocystis* and seroconvert, although some efforts have been made towards using the specific antibody titers or responses to specific proteins as being more indicative of active infection.

The *Pneumocystis* cell wall contains the same 1–3 β-D-glucan (BDG) as candida and aspergillus, and an assay for serum levels of BDG (known as Fungitell commercially) has proven to be sensitive and specific for PCP, when appropriate cutoff levels are used. Because of the cross-reactivity of the assay to multiple fungi, interpretation of assay results should be done in the clinical context of the patient. PCP may be associated with somewhat higher levels of BDG than are seen in invasive candidiasis or aspergillosis. In patients with non-HIV PCP, and in children with PCP, levels tend to be higher than in HIV-associated PCP but there are no levels at which PCP can be reliably ruled in or out. In all cases, serum levels can be used to track response to treatment.

TREATMENT AND PROPHYLAXIS

Recommended antimicrobial regimens are detailed in Table 180.1. The mainstay treatment of PCP is trimethoprim–sulfamethoxazole. The dosing is usually 15–to 20 mg/kg/day in three divided doses for 14 to 21 days, orally or intravenously depending on severity of illness. Adjunct corticosteroids have been shown to have benefit in HIV-associated PCP with significant hypoxemia (an alveolar–arterial oxygen gradient of greater than 35 mm Hg, or an arterial oxygen partial pressure of 70 mm Hg on room air). The role of steroids is in blunting the immune reaction to microorganism degradation which can result in an acute respiratory distress syndrome-like process. Guideline dosing for methylprednisolone is 40 mg twice daily on days 1–5, 40 mg once a day on days 6–10, 20 mg once a day on days 11–21.

Alternative medications, for instance in the case of allergy to sulfa-based antibiotics, include atovaquone, pentamidine, and dapsone, of which the latter is usually given in combination with trimethoprim or pyrimethamine and leucovorin.

Trimethoprim–sulfamethoxazole, pentamidine, or dapsone can all be used for prevention of PCP (Table 180.2). Prophylaxis is recommended for high-risk individuals, particularly those with HIV infection and CD4+ T-cell counts less than 200 (or a history or previous PCP regardless of CD4 count). Other causes of immune suppression or deficiency also increase the risk of *Pneumocystis*, to varying degrees. Neonates with severe combined immune deficiencies (SCID) and recipients of bone marrow transplants are at particularly high risk. Individuals with CD40 ligand deficiency are associated with an increased risk of PCP and should be placed on prophylaxis. Interestingly, although the 22q11 deletion syndrome (also known as DiGeorge or velocardiofacial syndrome) is primarily a T-cell deficiency,

Table 180.1 Treatment

Drug	Adult dose	Pediatric dose	Notes
Trimethoprim–sulfamethoxazole	15–20 mg/kg/d trimethoprim IV or PO in 4 divided doses for 21 d	As adult dose. Off-label use below 2 mo of age	Drug of choice. Risk of anemia, kernicterus in neonates under 28 d old
Pentamidine	4 mg/kg/day IV for 21 d	4 mo of age and older, as adult dose	
Dapsone	100 mg PO once daily, in combination with trimethoprim 15 mg/kg/d PO in 3 divided doses for 21 d	No pediatric data for treatment	
Atovaquone	1500 mg PO daily (or divided twice daily) for 21 d	Age >13 dose as adult Age 3–24 mo 45 mg/kg/d (max 1500 mg/d) in 2 divided doses PO for 21 days Other ages 30–40 mg/kg/d (max 1500 mg/d) in 2 divided doses	Take with food
Methylprednisolone	40 mg twice daily on days 1–5, 40 mg once a day on days 6–10, 20 mg once a day on days 11–21; begin as early as possible and within 72 h of PCP therapy	<12 yr 1 mg/kg every 6 h on days 1–7, 1 mg/kg twice daily on days 8–9, 0.5 mg/kg twice daily on days 10–11, 1 mg/kg once a day on days 12–16; begin as early as possible and within 72 h of PCP therapy	Best evidence in patients with moderate to severe HIV-related PCP

Table 180.2 Prophylaxis

Drug	Adult	Pediatric	Notes
Trimethoprim–sulfamethoxazole	One DS tab (160 mg trimethoprim) PO daily or 3 days a week (may be consecutively or every other day)	(2 months of age and older) 150 mg/m^2/d trimethoprim (max 320 mg/d) in 2 divided doses PO 3 times a week	Drug of choice
Pentamidine	300 mg by inhalation, monthly	5 yo and older, same as adult	May require specialized equipment and respiratory therapists to administer
Dapsone	100 mg PO daily or 200 mg PO weekly	(1 month of age and older) primary and secondary prophylaxis, 2 mg/kg PO once a day (max 100 mg/d); or 4 mg/kg PO once weekly (max 200 mg/dose)	
Pyrimethamine	50 mg PO once weekly PLUS leucovorin 25 mg PO once weekly PLUS dapsone 50 mg PO once daily OR 75 mg PO once weekly PLUS leucovorin 25 mg PO once weekly PLUS dapsone 200 mg PO once weekly		
Atovaquone	1500 mg PO daily	Age >13 dose as adult Age 3–24 mo 45 mg/kg PO daily (max 1500 mg/d) Other ages 30 mg/kg PO daily (max 1500 mg/d)	Take with food

and may result in CD4 counts similar to those seen in end-stage HIV infection, PCP has not been convincingly reported in patients with 22q11del. In these patients T-cell function is often intact and the CD4/CD8 ratio is preserved, whereas in HIV infection T-cell responses are blunted and the CD4/CD8 ratio is inverted. Nevertheless, some experts recommend PCP prophylaxis in individuals with 22q11del and very low CD4+ T-cell counts (under 500), especially if T-cell function has not yet been assessed or if any form of immune modulation or suppression is also present.

The use of steroids and other immunosuppressive agents is associated with varying levels of risk for PCP, and the indications for prophylaxis

are often dictated by the specific combination and duration of therapy, rather than the use of any one particular drug.

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181. Miscellaneous fungi and algae

Cheryll N. Cash and George A. Pankey

Many nonendemic fungi and algae cause disease among the increasing populations of individuals at risk. These microorganisms, known as opportunistic agents, can cause disease if two major criteria are met: (1) the patient suffers from some predisposing factor that has mechanically or immunologically decreased the capacity to resist infection, and (2) the infecting agent can survive and multiply at body temperature. At present, more than 200 of these opportunists have been reported to cause infection.

Some opportunistic fungal infections are associated with predisposing factors such as ketoacidosis, neutropenia, or a defect in cell-mediated immunity. However, any trauma, disease state, or pharmacologic insult to the host's defenses increases the chance of fungal invasion, even from a patient's own resident flora.

The microorganisms considered here are ubiquitous but uncommon causes of disease in humans. Therefore, the diagnosis is usually made when a patient with an infectious disease does not respond to antibacterial therapy; when the microbiology laboratory isolates one of these agents; or when the pathologist identifies a fungus or algae in tissue, bronchoalveolar lavage, cerebrospinal fluid, etc. When a physician suspects a fungal pathogen, the laboratory should be informed and special requests made, for example, lysis centrifugation to maximize the yield from blood cultures or a specific fungal media to be inoculated.

Table 181.1 Opportunistic fungi and algae

Hyalohyphomycoses
Long septate hyphae in tissue
Fusarium
Penicillium marneffei
Scedosporium
Phaeohyphomycoses (Dematiaceae)
Short septate hyphae, pseudohyphae, and/or yeast with melanin in cell walls
Alternaria
Bipolaris
Cladosporium (cladophialophora)
Curvularia
Dactylaria
Exophiala
Exserohilum
Fonsecaea
Phialophora
Rhinocladiella
Wangiella
Yeast or yeast-like fungi
Pichia (Hansenula)
Malassezia (Pityrosporum) furfur: Yeast only in deep tissue; "spaghetti and meatball" in stratum corneum (tinea versicolor)
Rhodotorula: "red yeast"
Saccharomyces cerevisiae
Trichosporon beigelii
Protothecosis
Achlorophyllic unicellular algae produce spherical cells that multiply by cytoplasmic cleavage, forming a morula in tissue
Prototheca wickerhamii
Prototheca zopfii

DIAGNOSIS

Many of the pathogens considered require special media or conditions for culture. A culture is imperative for specific identification. The challenge is not isolating the agent once it is suspected, but rather determining the relevance of the isolate to the clinical picture. Mere isolation of an agent does not confirm pathogenesis. To prove causation, the culture must be associated with tissue invasion, as seen on biopsy or by repeated positive cultures of specific fungi from a usually sterile body fluid. The appearance of these agents in tissue is extremely variable and is typically broken down into hyalohyphomycoses, phaeohyphomycoses, opportunistic yeast, yeast-like fungi, and protothecosis (Table 181.1).

Virtually all of these species grow readily at 25°C to 30°C (77°F to 86°F). Most of these opportunistic fungi can be identified to genus in a clinical microbiology laboratory. However, a

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Table 181.2 Therapy for infections by opportunistic fungi and algae

Pathogen	Characteristics	Diagnosis	Therapy
Hyalophyphomycoses – long septate hyphae in tissue			
***Fusarium* species**	Purpuric skin lesions with central necrosis, keratitis, pulmonary disease	Blood cultures: (50% positive) Histopathology: similar to *Aspergillus*	Reversal of neutropenia (G-CSF, GM-CSF) [a]LAmB + [b]Voriconazole (can switch to 200 mg q12h when stable)
Penicillium marneffei	Endemic in Southeast Asia, southern China, Taiwan, and Hong Kong Pulmonary disease, osteomyelitis, adenitis, skin lesions AIDS defining	Histopathology: from BAL Culture: easily from biopsy	[a]LAmB for 2 wk, followed by itraconazole (cs) 200 mg q12h for 12 wk Fluconazole not effective
Scedosporium prolificans ***S. apiospermum*** (***Pseudallescheria boydii***)	Normal host by traumatic implantation Mycetoma, meningitis, osteomyelitis, pneumonia (near drowning), sinusitis, endocarditis, spondylodiskitis, and keratitis	Histopathology: similar to *Aspergillus* and *Fusarium* Culture: from biopsy (correlate clinically) Molecular: cross-react with *Aspergillus* galactomannan	Surgical resection No optimal antifungal agent [b]Voriconazole (can switch to 200 mg q12h when stable) LAmB not effective
Phaeohyphomycoses (Dematiaceae) – pigmented environmental molds, irregular septated hyphae			
Exserohilum rostratum	Skin and subcutaneous tissue; sinusitis; occasional dissemination Local infection from skin and eye trauma in immunocompetent host Responsible for multistate meningitis and parameningeal outbreak from contaminated steroid injections	Molecular: fungal DNA by PCR (CDC) fungal culture (negative result does not rule out infection)	[a]LAmB for 6 wk, then oral voriconazole 200 mg q12h for 4 mo Dose modified to achieve serum trough levels of 2 to 5 μg/mL If CNS disease, use only voriconazole
Exophiala	Inhalation or traumatic implantation Subcutaneous nodules, keratitis, and/or skin abscess	Melanin in dematiaceous fungi with Fontana-Masson staining	Surgical excision Complete 12 wk of therapy with voriconazole 4 mg/kg IV or oral 200 mg (both every 12 h) or Posaconazole 200 mg orally every 6 h or Itraconazole (cs) 200 mg q12h ±LAmB for first 2 wk
Cladosporium	Distributed in air or as rotten organic material and contaminant on foods Causes keratitis, onychomycosis, and skin abscess Chromoblastomycosis	Cross-react with *Aspergillus* galactomannan	Surgical excision Complete 6 mo therapy with itraconazole (cs) 200 mg q12h or [b]Voriconazole (can switch to 200 mg orally every 12 h when stable)
Yeast or yeast-like fungi			
Pichia (***Hansenula***) ***P. anomala***	Catheter-related fungemia, prosthetic valve endocarditis NICU outbreaks		Remove intravascular catheter [a]LAmB if unresponsive: [b]Voriconazole or Itraconazole (cs) 200 mg twice daily + flucytosine 50–150 mg/kg/d divided into 4 doses
Rhodotorula "**red yeast**"	Contaminant of air, soil, lakes, and dairy products; colonizes plants and humans Fungemia, meningitis, peritonitis	Cross-react with *Aspergillus* latex agglutination test	Remove intravascular catheter [a]LAmB or Posaconazole 200 mg orally every 6 h

Table 181.2 *(continued)*

Pathogen	Characteristics	Diagnosis	Therapy
Saccharomyces cerevisiae	Colonizer of mucosal surfaces Pathogen in immune-compromised host Fungemia, prosthetic valve endocarditis, liver abscess, oral leukoplakia Associated with probiotic use		Removal of intravascular catheter [a]LAmB ± flucytosine 50–150 mg/kg/d divided into 4 doses Fluconazole and itraconazole resistant
Malassezia furfur	Fungemia associated with lipid infusion, folliculitis in AIDS, tinea versicolor Lipophilic fungus	KOH	Remove intravascular catheter; stop lipid IVs [b]Voriconazole for persistent fungemia Tinea versicolor: itraconazole (cs) 200 mg orally q12h, or topical selenium sulfide
Trichosporon beigelii	Fungemia, prosthetic valve endocarditis, chronic meningitis, peritonitis	Cross-reacts with cryptococcal latex agglutination	Correct neutropenia [a]LAmB [b]Voriconazole for LAmB-resistant strains
Protothecosis – Achlorophyllic algae, pervasive in nature, looks like a fungus microscopically. Only 2 species are known human pathogens in both immunocompetent and immunocompromised patients.			
Prototheca	Systemic infection, algaemia, peritonitis	Culture VITEK® 2	Remove intravascular catheter Excise isolated lesion [a]LAmB and/or [b]Voriconazole

Abbreviations: AIDS = acquired immunodeficiency syndrome; BAL = bronchial alveolar lavage; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte macrophage colony-stimulating factor; itraconazole (cs) = itraconazole cyclodextrin suspension (for better absorption); IV = intravenous; KOH = potassium hydroxide; PCR = polymerase chain reaction.

[a] LAmB = liposomal amphotericin B (5–10 mg/kg/d IV).

[b] Voriconazole (load 6 mg/kg IV every 12 hrs × 2 doses; maintenance 4 mg/kg IV every 12 hrs (maintain trough levels 2–5 μg/mL).

mycology expert is usually needed to identify the species. Fortunately, treatment of all species within a genus is frequently the same. Reliable intradermal or serologic tests are not available and direct microscopy using Gram stain, potassium hydroxide, India ink, and Papanicolaou preparations of lesion scrapings and sputum are often not helpful.

Species-specific PCR is presently available for pathogens such as *Aspergillus*. A lack of standardization has limited its acceptance as a diagnostic tool. PCR offers the possibility for broad-range identification while maintaining sensitivity. However, PCR does not establish pathogenicity of the identified organism.

THERAPY

Treatment of these infections can be challenging. Total excision, whenever feasible, should accompany any treatment regimen. There are no solid data on optimal drug therapy for many fungal infections because of the lack of controlled randomized trials. It is unlikely that anyone could ever collect enough cases to conduct double-blind therapeutic trials. At present, susceptibility testing can be performed for *Aspergillus, Candida*, and *Cryptococcus neoformans*, which most commonly produce disease in immunocompromised patients. Antifungal susceptibility testing is still in its infancy and variations in susceptibility occur with these organisms just as they do with bacteria. There are few data about in vitro correlation to in vivo results. When these fungi are isolated, they should be sent to a reference laboratory for susceptibility testing, including synergy studies.

Responses to antifungal drugs fail for multiple reasons: (1) the drug has no in vitro activity; (2) neutropenia was not reversed; (3) oral itraconazole or posaconazole was given while fasting or with antacids; (4) adequate blood levels were not obtained; (5) the dosage was too low or combination therapy was not used; (6) the drug is fungistatic rather than fungicidal; and (7) the drug is unable to concentrate in the area of concern, such as the brain. Voriconazole, itraconazole, and posaconazole trough levels must be monitored to ensure that therapeutic blood levels are achieved. Liposomal formulations of amphotericin B allow much higher dosages without increasing toxicity (Table 181.2). The echinocandins are

rarely active in vitro against these miscellaneous fungi and algae.

An infectious disease consultation should be obtained for all patients. Optimal therapies (Table 181.2) remain controversial at best. Surgical excision of localized skin and subcutaneous lesions is critical.

Major therapeutic approaches to treating fungal infections include correction of the neutropenia with colony-stimulating factors and decreased doses of immunosuppressant drugs. When immunosuppression cannot be corrected, prolonged antifungal therapy will be necessary, although morbidity and mortality will remain high.

PREVENTION

Immunocompromised patients should be educated on preventive measures regarding the risk of fungal infection from the environment. Prompt recognition of these pathogens in infected skin lesions after trauma is necessary for early therapy. Proper intravascular catheter care and neutropenia precautions and prevention are critical for hospitalized patients.

SUGGESTED READING

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PART XXIII

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182. Cytomegalovirus

Rima I. El-Herte and Jeffery L. Meier

Cytomegalovirus (CMV) permanently resides in its human-restricted host by toggling between productive and latent states of infection. CMV infection is serologically marked by immunoglobulin (Ig) G antibody against CMV. CMV seroprevalence varies widely by geographic region, ranging from 45% to 100% for women of reproductive age. In the US population, CMV seroprevalence is 50% overall and varies by age, socioeconomic status, sexual activity/practice, and race/ethnicity. Over 90% of all persons are CMV seropositive by age 80, 55% of women are seropositive by age 30, and the annual CMV seroconversion (primary infection) rate is ~2% for women of reproductive age. Congenital CMV infection afflicts ~1% of all babies born in the United States, is the leading infectious cause of birth defects, and the most common non-genetic cause of sensorineural hearing loss.

CMV is transmitted through close mucosal contact with body fluids bearing infectious CMV particles, i.e., saliva, urine, breast milk, semen, and cervical secretions. Infants and young children experiencing a primary (acute) CMV infection often continue to shed CMV in urine and, sometimes, saliva for several weeks to months. Immunosuppression or underlying illness may bring about viral shedding in body fluids at any stage of the infection. CMV persists in virtually all tissues and resides latently in monocytes, dendritic cells, and myeloid precursors. Viable tissue or leukocytes of CMV-seropositive donors are a source of CMV infection in seronegative persons. Risk for intrauterine CMV transmission is greatest for maternal primary CMV infection and less for reinfection with another CMV strain or CMV reactivation.

In immune-competent persons, the primary CMV infection is typically unapparent clinically. Occasionally, it causes self-limiting illness presenting as a heterophile-negative mononucleosis, nonspecific viral syndrome, or febrile hepatitis. Protracted illness or tissue-invasive disease rarely ensues. A primary infection occurring in the first trimester of pregnancy carries the greatest risk for severe CMV disease in the fetus. Maternal infection in the third trimester of pregnancy carries greatest risk for intrauterine infection but lower risk of neonatal disease.

Acquired immunodeficiency syndrome (AIDS), hematopoietic stem cell transplantation (HSCT), solid organ transplantation (SOT), and potent immunosuppressive therapies are conditions that profoundly impair cellular immunity and, thereby, predispose to life-threatening or debilitating CMV disease resulting from primary, reactivation, or recurrent CMV infection. CMV produces a wide spectrum of disease that can involve any organ. Leading clinical manifestations of CMV-related disease vary among the different types of immunocompromised patient populations. Tissue-invasive CMV disease commonly presents as retinitis, gastrointestinal disease, hepatitis, pneumonitis, and encephalitis. CMV is indirectly linked to allograft dysfunction, superinfection, post-transplant lymphoproliferative disorder, and reduced survival of human immunodeficiency virus (HIV)-positive persons.

DIAGNOSIS

In the immunocompromised person, CMV serology is unreliable in diagnosing active CMV infection. Determination of CMV IgG status of the pretransplant donor and recipient informs post-transplant CMV infection risk and management. A primary CMV infection in an acutely ill but otherwise healthy person is suggested by serologic evidence of IgM antibody to CMV antigen. Unfortunately, CMV IgM finding is often falsely positive and does not discriminate between CMV IgM produced following primary infection, reactivation, or reinfection. A highly elevated CMV IgM level increases the probability that primary CMV infection is the cause of the acute illness. Presence of low-avidity CMV IgG index

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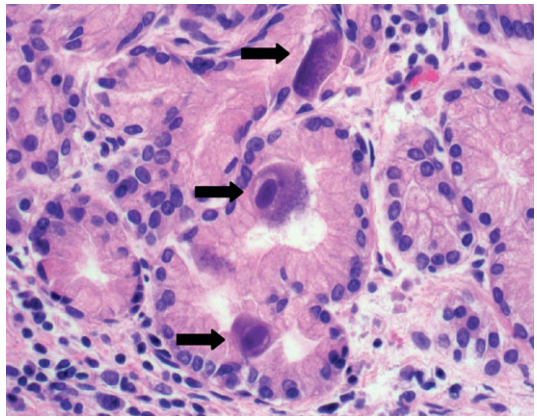

Figure 182.1 Cytomegalic inclusion disease. Arrows point to characteristic CMV-infected cells, which are large and contain intranuclear and ground-glass cytoplasmic inclusions. H&E staining.

confirms the diagnosis of primary CMV infection (avidity measures maturity of IgG, so that low avidity suggests recent infection). CMV IgG seroconversion between acute and convalescence periods of primary infection is uncommon, because CMV IgG is produced in substantial amounts during acute illness. A confirmed primary CMV infection during pregnancy (CMV IgM positivity and low-avidity IgG index) warrants expert consultation to evaluate possible congenital infection. This typically entails fetal ultrasound and consideration of amniocentesis for detection of CMV DNA by polymerase chain reaction (PCR).

Tissue-invasive CMV disease is defined by presence of active CMV infection in the tissue of patients with clinical findings attributed to the infection. Not all patients with active CMV infection have clinically significant disease. Cytomegalic cells with distinctive intranuclear and intracytoplasmic inclusions (Figure 182.1) are hallmarks of active CMV infection. Detection of CMV in tissue by culture, immunohistochemical analysis (CMV antigen), or *in situ* hybridization (CMV nucleic acid) also indicates active CMV infection, but requires clinical and histopathologic correlations to make the CMV disease diagnosis. Ophthalmologists typically diagnose CMV retinitis based on fundoscopic findings of distinctive retinal changes with perivascular infiltrate, atrophy, and hemorrhage. In transplant recipients, the CMV syndrome is characterized by a constellation of clinical (fever or malaise) and laboratory (leukopenia and thrombocytopenia) abnormalities plus evidence of CMV in blood, as detected by culture, antigen test, or nucleic acid assay. Probable CMV disease in transplant recipients is defined as clinical illness and organ dysfunction likely attributed to CMV in blood, bronchoalveolar lavage fluid (BALF), or cerebrospinal fluid (CSF). In AIDS, the diagnoses of CMV encephalitis, polyradiculopathy, and myelitis are supported by detection of CMV DNA in CSF.

Quantification of CMV DNA by PCR predicts or assesses CMV disease and prognosis. Having a measurable amount of CMV DNA in blood, CSF, BALF, vitreous fluid, or amniotic fluid is evidence of CMV replication. Latent CMV DNA levels in these fluids are below the lower limit of detection reported in clinical assays. In HSCT and SOT recipients, the level of CMV DNA in blood (DNAemia) guides use of anti-CMV therapy for pre-empting or treating CMV disease. While this test is useful in assessing response to anti-CMV therapy in transplant patients, the monitoring of CMV DNAemia has poor positive predictive value for progression or relapse of AIDS-associated retinitis. The COBAS AmpliPrep/COBAS TaqMan CMV test (Roche Molecular Diagnostics) is the first US Food and Drug Administration (FDA)-approved assay that uses the World Health Organization (WHO) International Standard to quantify CMV DNA load in plasma. Importantly, CMV DNAemia might also be absent during tissue-invasive CMV disease. In AIDS-associated CMV retinitis, for example, CMV DNAemia is often absent. Risk of sequelae in congenitally infected newborns correlates with level of CMV DNAemia in the neonates. Detection of CMV DNA in amniotic fluid indicates congenital CMV infection.

Measurement of CMV pp65 antigen in blood leukocytes is an alternative approach for detecting and semi-quantifying level of active CMV infection, though it is less sensitive than nucleic acid amplification and is reduced by neutropenia. Assessment of CMV-specific T-cell response (i.e., interferon-γ [IFN-γ] release in response to CMV antigen) for predicting CMV reactivation and disease may have clinical utility in the transplant population.

THERAPY

The FDA approved use of ganciclovir, valganciclovir, cidofovir, and foscarnet for specific CMV treatment indications. Table 182.1 summarizes the recommended dosing schedules for these agents and of their use in clinical practice.

Table 182.1 Preventive and treatment regimens for CMV

Agent	Indications	Dosing regimen	Toxicities	Monitoring	Comments
Intravenous					
Ganciclovir	Treatment of visceral or disseminated disease Prophylaxis or pre-emptive therapy in transplant recipients	Induction: 5 mg/kg q12h × 14–21 d Maintenance: 5 mg/kg qd (modify dose in renal failure) 5 mg/kg qd or BID (modify dose in renal failure)	Catheter-related complications, neutropenia, thrombocytopenia, renal failure	Induction: CBC 2×/wk, Cr weekly Maintenance: CBC qwk, Cr q1–3wk	If ANC 500–750, consider SQ G-CSF If ANC ≤500 or platelets ≤25 K, hold ganciclovir Increased toxicity of zidovudine or imipenem; increased level of didanosine Causes infertility, teratogenicity, and embryotoxicity in animals
Foscarnet	Treatment of visceral or disseminated disease	Induction: 90 mg/kg q12h (or 60 mg/kg q8h) × 14–21 d Maintenance: 90–120 mg/kg qd (modify dose in renal failure) Maximum dose is 120 mg/kg qd	Catheter-related complications, nephrotoxicity, paresthesias, cation chelation, genital ulcerations, nausea, marrow suppression	Induction: CBC, Cr, cations (K^+, Mg^{2+}, Ca^{2+}), and phosphate 2–3× qwk Maintenance: Cr, cations, and phosphate qwk, CBC q2wk	If Cr >2.8, hold foscarnet until Cr ≤2.1 mg/dL Adjust dosage for reduced renal function Hydration reduces renal toxicity Caution if seizures
Cidofovir	Treatment of retinitis (limited experience with use for salvage therapy for CMV disease in other viscera)	Induction: 5 mg/kg/wk × 2; infuse over 1 h Maintenance: 5 mg/kg q2wk; infuse over 1 h (reduce dose to 3 mg/kg if Cr increase 0.3 mg/dL)	Nephrotoxicity with Fanconi syndrome, neutropenia, uveitis, ocular hypotony, probenecid rash Probenecid contraindicated in persons with severe sulfa allergy	Induction: Cr and UA every dose Maintenance: Same plus intraocular pressure qmo	1–2 L saline hydration, with 1 L given before cidofovir infusion; probenecid, given 3 h before (2 g), at 3 h (1 g) and 8 h (1 g) after cidofovir infusion Caution if diabetes mellitus Do not use if Cr >1.5 mg/dL CrCl ≤55 mL/min, ≥100 mg/dL proteinuria, or receiving other nephrotoxic agents
Intraocular					
Ganciclovir implant	Treatment of retinitis	Surgical: Intraocular implantation via pars plana of (4.5 mg) implant; replacement q6–8mo Concomitant systemic therapy: see oral valganciclovir maintenance	Transient blurred vision, retinal detachment, hemorrhage, infection	Ophthalmologic follow-up	Requires addition of systemic therapy to reduce CMV disease risk in contralateral eye and other organs Implant releases 1 μg/h of ganciclovir Contraindicated if there is external eye infection and thrombocytopenia
Ganciclovir intravitreal injection	Treatment of retinitis	Induction: 200 μg to 2 mg in 0.1 mL twice per week for 2–3 wk Maintenance: once weekly	Less systemic side effects; procedural-related complications such as retinal detachment, vitreous hemorrhage, endophthalmitis, and cataract	Ophthalmologic follow-up	Requires addition of systemic therapy to reduce CMV disease risk in contralateral eye and other organs Contraindicated in external eye infection and thrombocytopenia
Foscarnet intravitreal injection	Treatment of retinitis	2.4 mg in 0.1 mL twice per week for 2–3 wk	Less systemic side effects; procedural-related complications such as retinal detachment, vitreous	Ophthalmologic follow-up	Requires addition of systemic therapy to reduce CMV disease risk in contralateral eye and other organs

Table 182.1 *(continued)*

Agent	Indications	Dosing regimen	Toxicities	Monitoring	Comments
			hemorrhage, endophthalmitis, and cataract		Contraindicated in external eye infection and thrombocytopenia
Oral					
Valganciclovir	Treatment of visceral or disseminated disease Prophylaxis or pre-emptive therapy in transplant	Induction: 900 mg BID × 14–21 d Maintenance: 900 mg qd (modify dose in renal failure 900 mg qd or BID, with food (modify dose in renal failure)	Neutropenia, thrombocytopenia	Induction: CBC 2×/wk, Cr weekly Maintenance: CBC qwk, Cr q1–3wk	If ANC 500–750, consider SQ G-CSF If ANC ≤500 or platelets ≤25 K, if Hg <8 mg/dL consider holding dose Increased toxicity of zidovudine or imipenem; increased level of didanosine Causes infertility, teratogenicity, and embryotoxicity in animals
Valacyclovir	Prophylaxis in solid organ transplant recipients	2 g QID (modify dose in renal failure)	Hallucinations, confusion, Marrow toxicity	CBC and Cr q2wk	Less effective than ganciclovir; therefore, use limited to low-risk patients
CMV hyperimmunoglobulin					
CMV immunoglobulin intravenous (CytoGam) (*Cytotect Biotest, Megalotect in Europe)	Treatment of CMV pneumonitis in bone marrow transplant recipient Prophylaxis in solid organ transplant recipients *Prevention of congenital CMV infection *Treatment of congenital CMV infection	400 mg/kg days 1, 2, and 7 200 mg/kg day 14 plus IV ganciclovir (see IV ganciclovir) 50–150 mg/kg q2–4wk (various dosing regimens have been used) *100 mg/kg (100 U/kg) q 4 weeks until delivery *200 mg/kg (200 U/kg) q4wk until delivery	Fever, myalgia, arthralgia, nausea, wheezing, hypotension, aseptic meningitis	Vital signs before, during, and after infusion	Derived from pooled adult human plasma Increase infusion rate as tolerated, 15–60 mg/kg/h Caution if IgA deficiency *Used in Europe in pregnancy In USA, off-label use of CMV immune globulin in pregnancy is controversial

Abbreviations: SQ = subcutaneous injection; CBC = complete blood count; Cr = serum creatinine; ANC = absolute neutrophil count; CMV = cytomegalovirus; UA = urine analysis; G-CSF = granulocyte colony-stimulating factor

Fomivirsen, a therapeutic agent administered by intraocular injection, is an FDA-approved agent that is no longer manufactured, and oral ganciclovir is not available in the United States. Investigational anti-CMV drugs (e.g., cyclopropavir, brincidofovir, and letermovir) are in clinical development.

AIDS

CMV end-organ disease in AIDS mostly involves persons with CD4+ T-lymphocyte counts ≤50 cells/mm^3. CMV retinitis accounts for 85% of all AIDS-associated CMV disease. Treatment of CMV retinitis is selected from options of oral valganciclovir alone or with intravitreal injection of foscarnet or ganciclovir, or intravenous (IV) ganciclovir, foscarnet, or cidofovir. The treatment approach is selected based on individual patient characteristics (ability to absorb oral medication, adhere to treatment, achieve immune recovery, etc.) and extent/location of the retinal lesion. Systemic anti-CMV therapy is needed to prevent CMV disease from developing in the contralateral eye and other organs. The ganciclovir intraocular implant is no longer manufactured. Intravitreal foscarnet or ganciclovir may be used in this situation. Concomitant antiretroviral therapy (ART) is key for recovering immune control of CMV. CMV retinitis is treated for 14 to 21 days at induction

therapy dosing. Maintenance therapy (secondary prophylaxis) is continued for at least 3 to 6 months after CD4+ T-lymphocyte count >100 cells/mm^3 and CMV retinitis is quiescent. Secondary prophylaxis is resumed when the CD4+ T-lymphocyte count falls below 100 cells/mm^3. Immune restoration uveitis may develop as an ART-induced inflammatory response to CMV that is managed with periocular or oral corticosteroids. An early first relapse (≤3 months) of CMV retinitis will often respond to reinstituting the same initial treatment regimen. Prolonged use of ganciclovir or valganciclovir is associated with the emergence of ganciclovir-resistant CMV. Subsequent therapy is guided by DNA sequencing-based determination of antiviral resistance mutations in the CMV phosphotransferase (UL97) and polymerase (UL54) genes produced from PCR-amplified specimens produced. Low-level ganciclovir-resistant CMV resulting from viral phosphotransferase mutations may still respond to intravitreal injection of ganciclovir or the ganciclovir intraocular implant. A CMV with high-level ganciclovir resistance resulting from mutations in both viral phosphotransferase and polymerase requires treatment with a different class of anti-CMV drug. The polymerase mutations often confer cross-resistance to cidofovir and, less frequently, confer cross-resistance to foscarnet.

AIDS-associated CMV esophagitis and colitis are treated initially with IV ganciclovir (or IV foscarnet). Oral valganciclovir is an option if absorption is not a concern. Treatment duration is 21 to 28 days or until the disease resolves. Secondary prophylaxis is not always needed. CMV pneumonitis is treated with IV ganciclovir, oral valganciclovir, or IV foscarnet. CMV neurologic disease may initially require double therapy with IV ganciclovir and IV foscarnet; both agents fall short in achieving target drug levels in CSF. Cidofovir is less effective than ganciclovir or foscarnet in reducing AIDS-related CMV DNAemia.

Transplantation

Use of either antiviral prophylaxis (chemoprophylaxis) or pre-emptive therapy in the first 3 to 6 months after transplant is an effective strategy for preventing CMV disease in HSCT and SOT recipients. In chemoprophylaxis, an anti-CMV drug is given to all patients in a specific population to suppress CMV replication. Pre-emptive therapy limits anti-CMV drug use to patients who develop asymptomatic CMV replication that is discovered through successive testing to exceed a threshold level of CMV DNAemia or antigenemia. The viral load threshold used for initiating pre-emptive therapy varies by the assay used, transplant type, degree of immunosuppression, and other factors that influence risk of CMV disease. In the highest-risk patients, chemoprophylaxis may have advantages over pre-emptive therapy. SOT patients at highest risk for CMV disease are CMV-negative recipients of CMV-positive organs (D+/R−) and recipients of donor lung, heart, or intestine.

Oral valganciclovir or IV ganciclovir is used for chemoprophylaxis. Pre-emptive therapy is initiated with full-treatment doses of oral valganciclovir or IV ganciclovir for at least 2 weeks (induction phase), followed by suppressive therapy (maintenance phase). Foscarnet is reserved for patients who are intolerant to or failing ganciclovir or valganciclovir. High-dose acyclovir or valacyclovir is less effective than ganciclovir for chemoprophylaxis, but is sometimes used in low-risk renal transplant recipients. Late-onset CMV disease in HSCT and SOT recipients is more likely to occur in patients having graft-versus-host disease or received chemoprophylaxis. CMV replication during or after lengthy exposure to ganciclovir or valganciclovir increases probability of CMV having developed resistance to ganciclovir. Insufficient dosing of valganciclovir or IV ganciclovir favors development of ganciclovir-resistant CMV.

CMV disease in HSCT and SOT recipients is treated with IV ganciclovir or oral valganciclovir. Ganciclovir IV is preferred in children, in patients having life-threatening CMV disease, and when absorption of valganciclovir may be suboptimal. A commonly used schedule for induction therapy is 14 to 28 days, often followed by maintenance (secondary prophylaxis) therapy. Immune suppression should be decreased if possible. Genotypic antiviral resistance testing should be performed if drug resistance is suspected. A CMV with minor mutations in the phosphotransferase gene (UL97) may respond to treatment with higher doses of IV ganciclovir. A CMV with major mutations in this gene should be treated with IV foscarnet. Viral polymerase gene (UL54) mutations conferring resistance to ganciclovir are likely to confer cross-resistance to cidofovir. Most ganciclovir-resistant CMV strains are susceptible to foscarnet. Cidofovir IV is considered a therapy of last resort because efficacy data in SOT are lacking, results in HSCT are mixed, and risk of nephrotoxicity is high. The combination of IV ganciclovir and CMV hyperimmune globulin is

used for CMV pneumonia in HSCT recipients. Monitoring of CMV DNAemia or pp65 antigenemia levels gauges treatment response and informs decision on treatment duration.

Congenital infection

Screening of pregnant women for CMV is not standard of care in the United States, because there is no proven therapy for congenital CMV infection in utero. A nonrandomized study of CMV IV hyperimmune globulin given during pregnancy for acute fetal CMV infection suggests efficacy, but a small randomized trial did not demonstrate protection. Ganciclovir is classified as pregnancy category C and is teratogenic in small animals. Six weeks of IV ganciclovir therapy started in neonates with symptomatic congenital CMV infection appears to decrease risk for hearing impairment, but dose-limiting bone marrow toxicity is common.

The otherwise normal host

Symptomatic CMV illness in otherwise healthy persons (e.g., heterophile-negative mononucleosis, viral syndrome, or hepatitis) is usually self-limiting. Use of oral valganciclovir or IV ganciclovir is reserved for debilitating protracted illness or tissue-invasive disease.

ANTIVIRAL AGENTS

Ganciclovir and valganciclovir

Ganciclovir is a guanosine analog. The intracellular half-life of the active metabolite is 16.5 hours. Ganciclovir concentration in vitreous fluid and CSF is somewhat lower and more variable than in serum. Orally administered valganciclovir, a prodrug of ganciclovir, attains levels similar to that of IV ganciclovir at standard treatment dose. Ganciclovir also has activity against herpes simplex virus 1 (HSV-1), HSV-2, varicella-zoster virus (VZV), Epstein–Barr virus (EBV), human herpesvirus 6 (HHV-6), HHV-7, and herpes B virus.

The kidneys eliminate ganciclovir metabolites, requiring adjustment of ganciclovir dose according to creatinine clearance. Granulocytopenia is a common adverse effect that can be managed with colony-stimulating factor and avoidance of other marrow-suppressive agents. Thrombocytopenia, anemia, central nervous system toxicity (e.g., headache, seizures, and confusion), and renal failure may also be observed. Ganciclovir caused infertility, teratogenicity, and embryotoxicity in animal studies. The IV route of administration risks catheter-related infection, whereas the intraocular implant risks endophthalmitis, hemorrhage, and other retinal-vitreous problems.

Foscarnet

Foscarnet (phosphonoformic acid) directly inhibits viral DNA polymerase activity. It is cleared by the kidneys, so dosage adjustment according to creatinine clearance is required. The major toxicity is renal impairment, which may be reduced by hydration. Mineral and electrolyte abnormalities, such as hypocalcemia, hyperphosphatemia, hypophosphatemia, hypokalemia, and hypomagnesemia, are common. Although manageable, these abnormalities can precipitate seizures. Chelation of ionized calcium by foscarnet may result in numbness, tingling, and paresthesias, and can be prevented by slowing the infusion rate. Other notable adverse events include anemia, granulocytopenia, genital ulcers, and catheter-related sepsis. Foscarnet should not be used in persons receiving amphotericin B, aminoglycosides, or other nephrotoxic agents.

Cidofovir

This active metabolite inhibits the viral DNA polymerase, terminates viral DNA chain elongation, and has an intracellular half-life of 17 to 65 hours. Cidofovir is nephrotoxic and contraindicated in persons with renal insufficiency (Cr >1.5 mg/dL, CrCl ≤ 55 mL/min, or $\geq 2+$ proteinuria) or receiving other nephrotoxic agents. Nephrotoxicity is minimized by IV prehydration and administration of probenecid. Probenecid is contraindicated in persons with history of a severe sulfa allergy. Neutropenia, ocular hypotony, and metabolic acidosis (Fanconi syndrome) are other potential toxicities of the drug. Cidofovir is gonadotoxic, embryotoxic, and carcinogenic in animals.

Cytomegalovirus hyperimmune globulin

CMV hyperimmune globulin IV (CMVIG) is pooled human IgG enriched 4- to 8-fold in anti-CMV antibody titer compared with standard preparations of IV immunoglobulin. CMVIG is used at some centers for passive immunoprophylaxis to prevent or attenuate CMV disease in

high-risk (D+/R−) lung, heart, and intestine transplant populations. CMVIG is combined with IV ganciclovir for treatment of CMV pneumonitis in HSCT recipients. The use of CMVIG to prevent and treat congenital CMV infection is the subject of ongoing investigations.

PRIMARY PREVENTION

Primary prevention strategies target CMV-seronegative persons at risk of serious CMV disease. Vaccines are under development. Transmission of CMV by transfusion is prevented by administration of CMV-seronegative or leukocyte-depleted blood products. Use of condoms is thought to prevent sexual transmission of the virus. Attention to hand hygiene is advised to prevent CMV transmission from changing diapers and wiping oral secretions of toddlers who may be shedding the virus. Avoidance of contact with saliva when kissing a child may also reduce transmission risk.

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183. Dengue

Nguyen Thanh Hung

Dengue is caused by any of four closely related viruses, or serotypes (dengue 1–4). Dengue viruses are small single-stranded RNA viruses, and belong to the genus *Flavivirus*, family Flaviviridae. Dengue is transmitted between people by the mosquitoes *Aedes aegypti* and *Aedes albopictus*, which are found throughout the world. In the last 50 years, there has been a dramatic increase in the global incidence of dengue virus infections with an estimated 50 million infections occurring annually in at least 100 countries in Asia, the Pacific, the Americas, Africa, and the Caribbean. Dengue virus infections may cause symptomatic infections or asymptomatic seroconversion. Symptomatic dengue infection has a wide range of clinical presentations which includes severe and nonsevere manifestations. While most patients recover following a self-limiting nonsevere clinical course, a small proportion progress to severe disease, mostly characterized by plasma leakage with or without hemorrhage.

CLINICAL MANIFESTATIONS

After an incubation period of 3 to 7 days, the illness begins abruptly and is followed by three phases – a febrile phase, a critical phase, and a recovery phase.

Febrile phase

The febrile phase is characterized by high temperature (≥38.5°C) accompanied by headache, vomiting, myalgia, joint pain, and a transient macular rash. High fever may cause neurologic disturbances and febrile seizures in young children. Hemorrhagic manifestations include a positive tourniquet test, easy bruising and bleeding at venipuncture sites, fine petechiae, epistaxis, gingival bleeding, and mild gastrointestinal bleeding (Figure 183.1, Panel A, B, and C). A palpable liver may be noted, especially in young infants and children. The full blood count examination reveals leukopenia, mild-to-moderate thrombocytopenia, and normal hematocrit value. This acute febrile phase usually lasts 2 to 7 days, and most patients recover spontaneously after this phase.

Critical phase

During the transition from the febrile to afebrile phase, patients without an increase in capillary permeability will improve uneventfully. In a small proportion of patients, systemic vascular leak syndrome becomes apparent, evidenced by increasing hemoconcentration, pleural effusions, and ascites (Figure 183.2). The degree of increase above the baseline haematocrit often reflects the severity of plasma leakage. In less severe cases, these changes are minimal and transient, reflecting a mild degree of plasma leakage, and patients will recover spontaneously. In more severe cases, when plasma loss is critical, shock ensues. Shock (dengue shock syndrome) is often preceded by warning signs. The warning signs of impending deterioration include abdominal pain or tenderness; persistent vomiting; mucosal bleeding; lethargy, restlessness; tender hepatomegaly; and an increase in hematocrit concurrent with a rapid decrease in platelet count. The patient in shock may die within 12 to 24 hours if appropriate treatment is not promptly administered, or recover rapidly following proper intravenous fluid therapy. Uncorrected shock can lead to severe complications with development of multiple organ dysfunctions, respiratory failure, metabolic acidosis, severe gastrointestinal bleeding, and a poor prognosis.

Hemorrhagic manifestations are most common during this critical period. In children, significant bleeding is usually associated with profound and prolonged shock. However, major skin bleeding and/or mucosal bleeding may occur in adults with only minor plasma leakage (Figure 183.1, Panel C). Moderate-to-severe thrombocytopenia, transient increase in the

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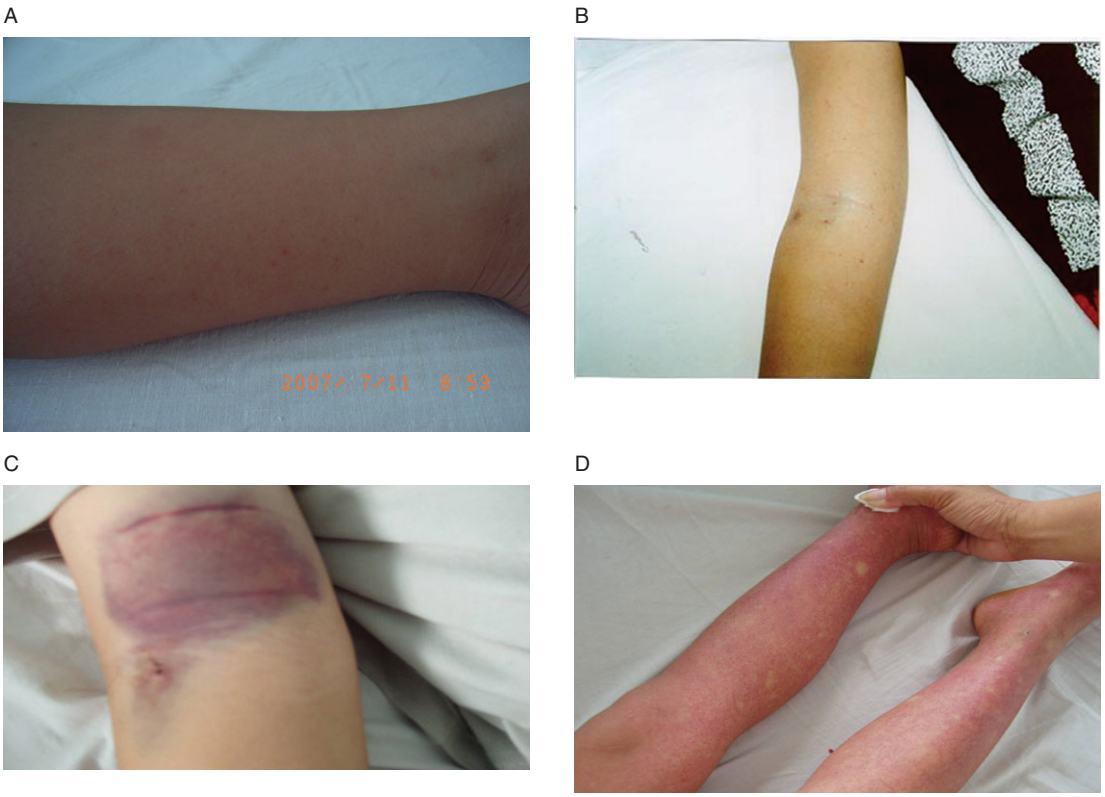

Figure 183.1. Hemorrhagic manifestations in dengue patients.
Panel A illustrates a petechial rash in a child with dengue. Panel B illustrates minor bleeding around injection sites. Panel C illustrates a hematoma in a patient with severe dengue. Panel D illustrates a characteristic confluent petechial rash in the recovery phase.

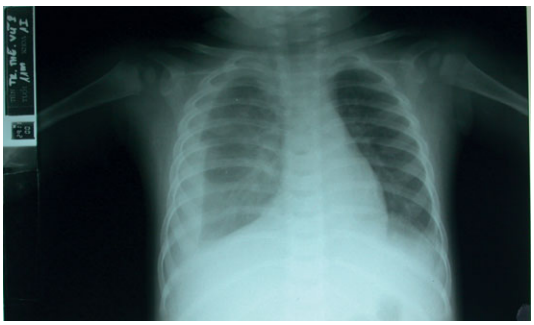

Figure 183.2. Systemic vascular leak syndrome evidenced by pleural effusion in an infant dengue patient.

activated partial-thromboplastin time, and a decrease in fibrinogen levels are frequently noted. Severe organ impairment such as severe hepatitis, encephalitis, or myocarditis and/or severe bleeding may infrequently occur without obvious plasma leakage or shock.

Convalescent phase

Most dengue patients will recover rapidly and uneventfully within 24-48 hours after shock has been reversed. Indicators of recovery include improved general condition, stable vital signs, and the return of appetite, diuresis and sinus bradycardia. Some patients develop a characteristic confluent petechial rash with small round areas of normal skin on their lower extremities (Figure 183.1, Panel D). Some patients have signs of fluid overload (respiratory distress, pulmonary edema, or heart failure associated with gross peripheral edema, large pleural effusions, and ascites) due to excessive intravenous therapy and reabsorption of extravasated plasma from the interstitial compartment.

DIAGNOSIS

Clinicians should suspect dengue in persons who live in or travel to a dengue-endemic area (South-East Asia, the Americas, the Western Pacific, and

the Eastern Mediterranean) with acute febrile syndromes associated with two of these signs/symptoms: nausea, vomiting; rash; aches and pains; tourniquet test positive; leukopenia; and any warning sign as mentioned above. Laboratory diagnosis of dengue is made by detecting the virus and/or any of its components such as virus genome and dengue antigen or by investigating the serologic responses present after infection. Clinicians should keep in mind that laboratory diagnosis is usually not necessary for clinical management except in atypical cases or when constructing a differential diagnosis. A diagnosis of dengue infection is confirmed by the detection of the virus, the viral genome, or nonstructural protein 1 (NS1) antigen in the acute sera which are collected during the febrile phase, or seroconversion of IgM/IgG from negative to positive or a 4-fold increase in antibody titer in paired sera. A positive IgM serology or a hemagglutinin inhibition test (HIA) antibody titer of 1280 or higher are considered a probable dengue infection. Both probable and confirmed dengue cases should be notified to health authorities.

DENGUE CASE CLASSIFICATION

Patients were previously classified as having either dengue fever or dengue hemorrhagic fever. Dengue hemorrhagic fever was further classified into four severity grades, with grades III and IV being defined as dengue shock syndrome. There have been many reports of difficulties in the use of this classification. With the recent revision of the World Health Organization dengue classification scheme, patients are now classified as having either dengue or severe dengue. Patients who recover without major complications are classified as having dengue, whereas those who have any of the following conditions are classified as having severe dengue: severe plasma leakage leading to shock (dengue shock syndrome), accumulation of serosal fluid sufficient to cause respiratory distress; severe bleeding; and severe organ impairment.

DIFFERENTIAL DIAGNOSIS OF DENGUE

Early in the febrile phase, the differential diagnosis of dengue includes other arboviral infections, measles, rubella, enterovirus infections, adenovirus infections, and influenza. Depending on local frequency and epidemiologic characteristics of febrile diseases, other diseases such as typhoid, malaria, leptospirosis, viral hepatitis, rickettsial diseases, bacterial sepsis, and meningococcal disease should be considered as part of the differential diagnosis. Clinicians should also remember that some dengue patients with liver enlargement and severe abdominal pain may mimic surgical conditions such as acute appendicitis and hepatic abscess. Misdiagnosing and performing unnecessary surgery will pose these dengue patients at risk of severe hemorrhage.

MANAGEMENT

Treatment is supportive with special emphasis on careful fluid management. Patients without complications can be managed as outpatients and followed closely every day from day 3 of their illness, until they have been afebrile for more than 48 hours without the use of antipyretics. Practically the hematocrit and platelet count should be determined at the first visit, and then checked once to twice daily. Oral rehydration should be encouraged with oral rehydration solution (ORS), fruit juice, and other fluids containing electrolytes and sugar. Give acetaminophen/paracetamol for high fever if the patient is uncomfortable. Do not give acetylsalicylic acid (aspirin), ibuprofen, or other nonsteroidal anti-inflammatory agents (NSAIDs) because of the risks of gastritis or bleeding. Instruct the patients or caregivers to return to the nearest hospital immediately if the patients have any of the warning signs.

For the patients with warning signs, judicious volume replacement of lost plasma by intravenous fluid therapy with isotonic crystalloid solutions from this early stage may modify the course and the severity of disease. Parenteral fluid therapy is only required for 24 to 48 hours in most patients since the capillary leak resolves spontaneously after this time.

Patients with dengue shock syndrome need emergency treatment with fluid resuscitation. The recommended regimen for the treatment of dengue shock patients is as follows: immediate and rapid replacement of the plasma loss with isotonic crystalloid solutions or, in the case of profound shock, colloid solutions; continued replacement of further plasma losses to maintain effective circulation for 24 to 48 hours; correction of metabolic and electrolyte disturbances; and blood transfusion – in patients with severe bleeding. Platelet concentrates, fresh frozen plasma, and cryoprecipitate may also be used in cases of severe bleeding. Dengue shock patients should be under close observation around the clock, until it is certain that danger has passed. Generally, the duration of intravenous therapy should not

exceed 24 to 48 hours after the patient is out of shock. Electrolyte levels and blood gases should be determined periodically in severe cases. In patients with severe and complicated dengue, mechanical ventilation, vasopressor and inotropic therapies, renal-replacement therapy, and other treatment of organ impairment may be required.

PREVENTION

Effective vaccines against dengue and specific medications to treat a dengue infection are not yet available. Dengue is transmitted between people by the mosquitoes *A. aegypti* and *A. albopictus*, so the best measure to prevent dengue is to reduce mosquitoes and avoid mosquito bites. Eliminating the places where the mosquito lays her eggs, such as artificial containers that hold water in and around the home, and cleansing water containers, help reduce mosquitoes. The adult mosquitoes like to bite indoors during the day and at night when the lights are on. Travelers in dengue-endemic areas should avoid mosquitoes during the day by using insect repellents and sleeping under a mosquito bed net or using air-conditioning. Current research is exploring new antiviral or other therapeutic drugs as well as innovative approaches to preventing transmission.

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184. Enteroviruses

Michael N. Oxman

Enteroviruses (EVs), so named because most members infect the alimentary tract and are shed in the feces, cause a variety of diseases in humans and lower animals. They constitute one of the six major subgroups, or genera, of the family Picornaviridae [*pico*, "small"; *rna*, "ribonucleic acid"]. The other genera of Picornaviridae are the *Rhinovirus*, *Cardiovirus*, *Aphthovirus*, and two newly designated genera, *Hepatovirus*, the prototypic member of which is human hepatitis A virus; and *Parechovirus*, which contains two serotypes that were previously classified as echoviruses types 22 and 23, and at least 14 additional serotypes.

PHYSICAL AND BIOCHEMICAL PROPERTIES

EVs, like all members of the picornavirus family, are small, nonenveloped, spherical (icosahedral) viruses approximately 30 nm in diameter. Their capsids consist of 60 structural subunits, each composed of 4 unique polypeptides: VP1, VP2, VP3, and VP4. Their genome consists of a linear, single-stranded, unsegmented molecule of RNA (of approximately 7500 nucleotides) that has the same polarity as messenger RNA.

EVs are stable over a wide range of pH (pH 3 to 10), permitting them to retain infectivity during passage through the gastrointestinal tract. They are not inactivated by ether, alcohol, or other lipid solvents, but are readily inactivated by formaldehyde or phenol. EVs retain infectivity for days at room temperature, weeks at refrigerator temperature, and indefinitely when frozen at −20°C or lower. Molar $MgCl_2$ further increases their thermostability, facilitating the use of oral polio vaccines in tropical areas where availability of refrigeration is limited.

CLASSIFICATION OF ENTEROVIRUSES

Historically, human EVs have been sub-classified into polioviruses, group A and group B Coxsackieviruses, and echoviruses on the basis of antigenic relationships, differences in host range, and types of disease produced (Table 184.1). By 1969, 67 species (serotypes) of human EV had been identified and classified according to these criteria, although reclassification and redundancy have reduced this number from 67 to 61. New EVs discovered since 1970 have been assigned to the EV species and numbered sequentially, beginning with 68.

PATHOGENESIS OF ENTEROVIRUS INFECTIONS

After ingestion of fecally contaminated material, virus implants in susceptible tissues of the pharynx and distal small intestine. Whereas some replication occurs in the pharynx, the primary site of infection is the distal small intestine; virus traverses the intestinal lining cells without causing detectable cytopathology and reaches Peyer's patches in the lamina propria, where significant replication occurs. Within 1 or 2 days, virus spreads to regional lymph nodes and, on about the third day, small quantities escape into the bloodstream (the "minor viremia") and are disseminated throughout the reticuloendothelial system and to other receptor-bearing target tissues. In most cases, infection is contained at this stage by host defense mechanisms with no further progression, resulting in asymptomatic infection. In a minority of infected persons, replication continues in reticuloendothelial tissues producing, by about the fifth day, heavy sustained viremia (the "major viremia") that coincides with the "minor illness" of poliovirus infection and with the "nonspecific febrile illness" caused by other human EVs.

The major viremia disseminates large amounts of virus to target organs, such as the spinal cord, brain, meninges, heart, skeletal muscles, and skin, where further virus replication results in inflammatory lesions and cell necrosis. In most such patients, host defense mechanisms quickly terminate the major viremia and halt virus

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Table 184.1 Classification of human enteroviruses (EV)[a]

Enterovirus group	Number of serotypes	Numerical designation	Growth in primate cell culture	Pathogenicity for suckling mice	Pathogenicity for monkeys
Poliovirus	3	1–3	+	–	+
Coxsackievirus, group A	23	A1–A22, A24[b]	+/–[c]	+	–[d]
Coxsackievirus, group B	6	B1–B6	+	+	–
Echovirus	29	1–9, 11–21, 24–27, 29–34[e]	+	–	–
Enterovirus	4	68–71[f] +	Variable	Variable[f]	Variable[g]

[a] Many EV strains have been isolated that do not conform to these criteria.

[b] Coxsackievirus A23 has been reclassified as echovirus 9, leaving 23 Coxsackievirus group A serotypes.

[c] Except for a few serotypes (e.g., A7, A9, A16), primary isolates of group A Coxsackieviruses grow poorly or not at all in cell culture; virus isolation requires inoculation of suckling mice.

[d] Coxsackievirus A7 is neurovirulent in monkeys.

[e] Echovirus 10 has been reclassified as reovirus type 1; echovirus 28 has been reclassified as rhinovirus 1A; echovirus 22 and echovirus 23 have been reclassified as parechovirus 1 and parechovirus 2, respectively, members of a new *Parechovirus* genus that now includes at least 16 serotypes that infect, primarily, male infants less than 1 year of age and cause a wide variety of illnesses. Echovirus 34 is a variant of Coxsackievirus A24.

[f] EV-70 and EV-71 are pathogenic for suckling mice.

[g] EV-70 and EV-71 are neurovirulent in monkeys.

replication in target organs; only rarely is virus replication in target organs extensive enough to be clinically manifest. Serotype-specific neutralizing antibodies may be detected in the serum within 4 or 5 days of infection, and they generally persist for life. Evidence for the critical role of antibodies in terminating infection is provided by the occurrence of chronic persistent EV infections in agammaglobulinemic children. Host defenses do not, however, terminate virus replication in the intestine, and fecal shedding continues for weeks after both symptomatic and asymptomatic EV infections. Immunity to EV is serotype specific; neutralizing antibodies in the blood prevent EV dissemination and disease. Reinfection is relatively uncommon and is confined to the alimentary tract; it is asymptomatic, and the duration of virus shedding is markedly reduced.

EPIDEMIOLOGY

Human EVs are worldwide in distribution, and humans are their only known reservoir. The prevalence of EV infection varies markedly with season and climate, and with the age and socioeconomic status of the population. In tropical and semitropical regions, EV infections are frequent throughout the year. In temperate climates, the incidence of infection is markedly increased in the summer and early fall; within the United States, climatic and socioeconomic factors affect the prevalence of EV infections. EV isolation rates from young children are 2- to 3-fold higher in southern than in northern cities and 3- to 6-fold higher in lower than in middle and upper socioeconomic districts. In the United States, one to three EV serotypes usually predominate in a given location each year. Some serotypes are present each year, whereas others disappear and may re-emerge after years of inactivity.

Transmission of human EV is chiefly by the fecal–oral route directly from person to person or through fomites; spread by respiratory secretions plays a lesser role. After infection by most serotypes, virus can be recovered from the oropharynx and intestine of both symptomatic and asymptomatic individuals, but virus is shed in greater amounts and for a longer period (a month or more) in the feces.

Infants and young children have the highest rates of EV infection and illness, and EVs are most efficiently disseminated by infected children younger than 2 years of age. Spread is facilitated by crowding and poor hygiene. Secondary attack rates in families are 90% for polioviruses, 75% for Coxsackieviruses, and 50% to 70% for echoviruses. Maternal antibodies passively acquired transplacentally or in breast milk prevent or modify EV infections in early infancy,

and may interfere with oral polio vaccine in breastfed infants.

Although the epidemiology of most EVs is similar, patterns of infection with some serotypes are distinctive. EV-70 and Coxsackievirus A24, etiologic agents of acute hemorrhagic conjunctivitis, are transmitted by direct inoculation of the conjunctivae by fingers, fomites, and ophthalmologic instruments contaminated with infected tears. Replication of these viruses in the alimentary tract, if it occurs at all, is limited. Coxsackievirus A21 is shed primarily from the upper respiratory tract, where it produces a rhinovirus-like illness. It is transmitted by respiratory secretions.

The incubation period for EVs varies from less than 1 day to more than 3 weeks, but it is generally 2 to 7 days. It is shortest when symptoms are the result of virus replication at the portal of entry and longest when they reflect tissue injury following viremia (e.g., Coxsackievirus myocarditis).

CLINICAL MANIFESTATIONS OF ENTEROVIRUS INFECTIONS

The majority of nonpolio EV infections (50% to 80%) are asymptomatic. Most symptomatic infections consist of *undifferentiated febrile illnesses* ("summer grippe"), often accompanied by upper respiratory symptoms. These are generally mild and last only a few days. This syndrome is totally nonspecific; it can be caused by any EV serotype. The characteristic EV syndromes, such as aseptic meningitis, hand-foot-and-mouth disease (HFMD), and pleurodynia, are, in fact, unusual manifestations of EV infection.

Some syndromes are associated with certain EV serotypes or subgroups (Table 184.2), but even these associations are not specific. The same syndrome may also be caused by a number of other EV serotypes. Conversely, a single EV serotype may cause several different syndromes, even within the same outbreak.

CENTRAL NERVOUS SYSTEM SYNDROMES

Aseptic meningitis

EVs are responsible for more than 80% of cases of aseptic meningitis in developed countries. Almost every serotype has been implicated. Although attack rates are generally highest in children, cases also occur in adults, especially during larger outbreaks. Initial symptoms, which are typical of the *undifferentiated febrile illness* (e.g., fever, headache, malaise, myalgia, and sore throat), are followed, usually within a day, by signs and symptoms of meningitis, including a more severe headache that is often retrobulbar, photophobia, meningismus, stiffness of the neck and back, and nausea and vomiting, especially in children. The illness is sometimes biphasic like poliomyelitis. The cerebrospinal fluid (CSF) is clear and under slightly increased pressure. The total cell count, which can vary from less than $10/mm^3$ to more than $3000/mm^3$, averages 50 to $500/mm^3$. Initially, neutrophils may predominate (although they rarely exceed 90%), but they are quickly replaced by mononuclear cells. Pleocytosis may be absent in up to 30% of infants and children with EV meningitis diagnosed by CSF PCR assay. The glucose concentration is usually normal, although levels less than 40 mg/dL are occasionally observed. The protein concentration is normal or slightly elevated but rarely exceeds 100 mg/dL. Fever and signs of meningeal inflammation subside in 3 to 7 days, although pleocytosis may persist for an additional week or more. The great majority of children and adults recover fully without sequelae. However, enteroviral meningitis during the first year of life may result in permanent neurologic damage in up to 10% of affected infants, manifested by paresis, reduced head circumference, spasticity, and impaired intellect.

Some cases may be accompanied by a rash, which, if petechial, may raise the specter of meningococcemia.

Paralytic disease

Acute flaccid paralysis (AFP) may occur in the course of many nonpolio EV infections. It is similar but less severe than that caused by polioviruses. Muscle weakness is more common than frank paralysis, and recovery is usually complete, although occasional patients suffer cranial nerve palsies or severe, sometimes fatal, bulbar involvement. In contrast to paralytic poliomyelitis, which in the pre-vaccine era occurred in epidemics, cases of paralysis associated with nonpolio EV are generally sporadic. However, several nonpolio EVs produce AFP with sufficient frequency to cause local outbreaks and epidemics. A variant of Coxsackievirus A7, once thought to be a fourth serotype of poliovirus, has caused outbreaks, as well as numerous sporadic cases of AFP. Paralytic disease resembling poliomyelitis, with a significant incidence of residual paralysis and muscle atrophy, has been observed in patients with acute

Table 184.2 Clinical manifestations of nonpolio enterovirus (EV) infections[a]

Clinical syndrome	Group A Coxsackieviruses[b]	Group B Coxsackieviruses	Echoviruses[c]	Enteroviruses
Asymptomatic infection	All serotypes	All serotypes	All serotypes	All serotypes
Undifferentiated febrile illness ("summer grippe") with or without respiratory symptoms	All serotypes	All serotypes	All serotypes	68, 70, 71
Aseptic meningitis (often associated with an exanthem)	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 14, 16, 17, 18, 22, 24	1, 2, 3, 4, 5, 6	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 18, 19, 20, 21, [22], [23], 25, 30, 31, 33	70, 71
Encephalitis	2, 4, 5, 6, 7, 9, 10, 16	1, 2, 3, 4, 5	2, 3, 4, 6, 7, 9, 11, 14, 17, 18, 19, [22], 25, 30, 33	70, 71
Paralytic disease (poliomyelitis-like)	4, 5, 6, 7, 9, 10, 11, 14, 16, 21, 24	1, 2, 3, 4, 5, 6	1, 2, 4, 6, 7, 9, 11, 14, 16, 17, 18, 19, 30	70, 71
Myopericarditis	1, 2, 4, 5, 7, 8, 9, 14, 16	1, 2, 3, 4, 5, 6	1, 2, 3, 4, 6, 7, 8, 9, 11, 13, 14, 16, 17, 19, [22], 25, 30	
Pleurodynia	1, 2, 4, 6, 9, 10, 16	1, 2, 3, 4, 5, 6	1, 2, 3, 6, 7, 8, 9, 11, 12, 14, 16, 19, [23], 25, 30	
Herpangina	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 16, 22	1, 2, 3, 4, 5, 6	6, 9, 11, 16, 17, [22], 25	71
Hand-foot-and-mouth disease	4, 5, 6[d], 7, 9, 10, 16, 24	2, 5	4, 7, 11, 19	71
Exanthems	2, 4, 5, 6, 7, 9, 10, 16	1, 2, 3, 4, 5, 6	2, 4, 5, 6, 9, 11, 16, 18, 25	71
Common cold	2, 10, 21, 24	1, 2, 3, 4, 5	2, 4, 8, 9, 11, 20, 25	
Lower respiratory tract infections (bronchiolitis, pneumonia)	7, 9, 16	1, 2, 3, 4, 5	4, 8, 9, 11, 12, 14, 19, 20, 21, 25, 30	68[e], 71
Acute hemorrhagic conjunctivitis[f]	24			70
Generalized disease of the newborn	3, 9, 16	1, 2, 3, 4, 5	3, 4, 6, 7, 9, 11, 12, 14, 17, 18, 19, 20, 21, [22], 30	

[a] A great many EV serotypes have been implicated in most of these syndromes, at least in sporadic cases. The serotypes listed are those that have been clearly and/or frequently implicated. Serotypes with the strongest association are underlined.

[b] Because isolation of many of the group A Coxsackieviruses requires suckling mouse inoculation, they are likely to be underreported.

[c] Echovirus types [22] and [23] have been reclassified as parechoviruses 1 and 2, the first members of a new picornavirus genus, *Parechovirus*.

[d] A variant of Coxsackievirus A6 has been associated with mucocutaneous bullous reactions resembling Stevens–Johnson syndrome.

[e] EV-68 (EV-D68) causes severe lower respiratory tract infection in children, most of whom have a history of asthma.

[f] Conjunctivitis without hemorrhage is frequently seen in association with other manifestations in patients infected with many group A and group B Coxsackieviruses and echoviruses, especially Coxsackieviruses A9, A16, and B1–B5, and echoviruses 2, 7, 9, 11, 16, and 30.

hemorrhagic conjunctivitis caused by EV-70. EV-71 is a highly neurotropic virus associated with a variety of central nervous system (CNS) syndromes, including aseptic meningitis, encephalitis, acute cerebellar ataxia, Bell's palsy, AFP, and bulbar poliomyelitis. It has been responsible for large outbreaks of AFP in Eastern Europe, Russia, and Asia.

Encephalitis

Encephalitis is a well-recognized but uncommon manifestation of EV infection. EVs account for only 10% to 20% of the cases of encephalitis of proven etiology in the United States. In most cases, encephalitis complicates the course of aseptic meningitis; parenchymal involvement is indicated by the onset of confusion, coma, abnormalities of motor function, hemiparesis, vasomotor instability, cranial nerve palsies, cerebellar ataxia, and focal or generalized seizures, singly or in various combinations. Cerebral involvement is usually generalized, but focal encephalitis does occur and may be clinically indistinguishable from herpes simplex encephalitis. Recovery from enteroviral encephalitis is usually complete, although neurologic sequelae and deaths do occur, especially in young infants and during EV-71 epidemics. CNS disease is usually preceded by HFMD or herpangina.

OTHER REPORTED NEUROLOGIC COMPLICATIONS

EVs, particularly Coxsackie A viruses, appear to be an important cause of febrile seizures in children during EV season. Other neurologic syndromes, including Guillain–Barré syndrome, transverse myelitis, and Reye's syndrome, have been reported in patients with a number of different EV infections.

EPIDEMIC PLEURODYNIA (BORNHOLM DISEASE)

Epidemic pleurodynia is an acute febrile viral illness characterized by the sudden onset of intense paroxysmal lower thoracic or abdominal pain. Synonyms include Bornholm disease, devil's grip, epidemic myalgia, epidemic benign dry pleurisy, and Sylvest disease. The name *pleurodynia* (*pleura*, "side"; *odyne*, "*pain*") reflects the characteristic intercostal location of the pain and does not connote disease of the pleura. Pleurodynia is usually an epidemic disease, but sporadic cases do occur.

Pleurodynia is characterized by the abrupt onset of fever and sharp, paroxysmal pain over the lower ribs or upper abdomen. In about 25% of patients, this is preceded by a 1- or 2-day prodrome of headache, malaise, anorexia, sore throat, and diffuse myalgia. The pain varies in intensity, but is often severe. It is accentuated, sometimes elicited, by deep breathing, coughing, and movement, and can usually be elicited by pressure on the affected muscles. In adults, the pain is primarily in muscles of the thorax, especially the intercostals. A pleural friction rub is occasionally present. In children, abdominal muscles are more often involved. Occasionally it may involve muscles in the neck or limbs. Palpable, often visible, muscle swelling may be observed.

Multiple paroxysms of pain occur, each lasting from a few minutes to several hours. The initial paroxysm is usually the most severe, and patients frequently appear relatively well between paroxysms. The acute illness generally lasts for 2 to 6 days, with a range of 12 hours to 3 weeks. The disease is often biphasic; the initial pain and fever resolve and the patient is asymptomatic for a day or more, and then the pain and fever recur, frequently at the same site. Rarely, patients will have several recurrences over a period of several weeks or will have a late recurrence after being symptom free for a month or more. Group B Coxsackieviruses, especially B3 and B5, are the principal cause. Transmission is primarily from person to person, and multiple family members may be attacked almost simultaneously or in rapid succession at intervals of 2 to 5 days.

Pleurodynia results from EV infection of skeletal muscle, not of the pleura or peritoneum. As in most enteroviral diseases, infection is initiated in the alimentary tract, with infection of skeletal muscle resulting from viremia. Pleurodynia may be confused with any of a number of more serious diseases. When the pain is thoracic, these include pneumonia, pulmonary infarction, rib fracture, costochondritis, and myocardial infarction. When the pain is abdominal, it can be difficult to differentiate pleurodynia from serious causes of acute abdominal pain, such as peritonitis, cholecystitis, appendicitis, perforated peptic ulcer, and acute intestinal obstruction. Pleurodynia may also be confused with the pain of pre-eruptive herpes zoster, herniated intervertebral disk, and renal colic. Generalized polymyositis and focal myositis often localized to the thighs has also been caused by infections with Coxsackieviruses A9, B2, and B6, and echoviruses 9 and 11. Myoglobinemia and elevated levels of creatine phosphokinase are often present.

Treatment of pleurodynia is symptomatic. Analgesics, as well as heat applied to affected muscles may be useful. Despite the tendency of the disease to relapse, patients with epidemic pleurodynia eventually recover completely.

MYOCARDITIS AND PERICARDITIS CAUSED BY ENTEROVIRUSES

EVs are the major infectious cause of myocarditis and pericarditis in North America and western Europe. Neonatal infections frequently result in severe myocarditis, widespread involvement of other organs, and high mortality, whereas in older children and adults, pericarditis often predominates and the disease is generally benign and self-limited. In fact, cardiac involvement during EV infections is often unrecognized. However, idiopathic dilated cardiomyopathy may be a late sequela of both recognized and unrecognized EV myocarditis.

Endomyocardial biopsy, with *in situ* hybridization and reverse transcription–polymerase chain reaction (RT–PCR), has improved our ability to establish the etiology of myocarditis and pericarditis. The group B Coxsackieviruses are the most common etiologic agents of myocarditis

and pericarditis. They account for 50% of sporadic cases of acute myocarditis and for all cases in epidemics. Human adenoviruses, dengue, and parvovirus B19 are other important causes of myocarditis. Group B Coxsackieviruses account for 30% or more of sporadic cases of acute nonbacterial pericarditis.

Most cases occur in males, but in females the risk of cardiac involvement is increased during pregnancy and immediately postpartum.

Idiopathic dilated cardiomyopathy may represent the end stage of EV myocarditis. This notion is supported by the development of chronic cardiomyopathy in approximately 10% of patients observed long term after group B Coxsackievirus myocarditis and by the demonstration of progressive fibrosis in such patients by serial endomyocardial biopsies.

Treatment of EV myopericarditis is supportive. It includes control of pain, and monitoring for arrhythmias, heart failure, and hemodynamic compromise. Bed rest is an important component of therapy because of evidence in mice with Coxsackievirus B3 myocarditis that exercise increases myocardial necrosis and mortality during the acute disease. Cardiac assist devices may be lifesaving. Corticosteroids should not be administered; their use during the acute phase of viral myocarditis has been associated with rapid clinical deterioration.

The majority of children and adults with enteroviral myopericarditis recover without sequelae. Acute mortality is low (0% to 5%), and deaths result from arrhythmias or congestive heart failure in patients with myocarditis; cardiac tamponade is extremely rare in enteroviral pericarditis.

Approximately 20% of patients experience one or more episodes of recurrent myopericarditis within 1 year of their initial illness, and persistent electrocardiographic (ECG) abnormalities are observed in 10% to 20% of patients. Cardiomegaly persists in 5% to 10% of patients, and long-term follow-up suggests that 10% or more may develop chronic cardiomyopathy. Constrictive pericarditis rarely occurs following enteroviral pericarditis.

INSULIN-DEPENDENT DIABETES MELLITUS

Epidemiologic evidence suggests a role for EV, especially group B Coxsackieviruses, in the etiology of insulin-dependent diabetes mellitus (IDDM). A number of serologic studies have found evidence of a higher frequency of Coxsackievirus B infection in children with new-onset IDDM than in matched controls, and maternal EV infections during pregnancy have been associated with the subsequent development of IDDM in offspring during early childhood. Moreover, enteroviral RNA has been identified by RT–PCR in children with new-onset IDDM at a higher frequency than in matched controls, and Coxsackieviruses B4 and B5 have been identified in pancreatic tissue of children dying of ketoacidosis at the onset of IDDM.

MUCOCUTANEOUS SYNDROMES CAUSED BY ENTEROVIRUSES

EVs are the leading cause of exanthematous disease in the United States and other developed countries. Almost all EVs can cause maculopapular eruptions, and most serotypes may cause petechial or papulovesicular exanthems and enanthems. Moreover, a given EV may cause more than one pattern of mucocutaneous disease, even within a single infected household. Consequently, except for HFMD, which is usually caused by Coxsackievirus A16 or EV-71, there are no clinical or epidemiologic characteristics of any given EV rash that point to a specific EV as its cause.

The epidemiology of EV exanthems and enanthems is the epidemiology of EV infections in general. The vast majority occur during the summer and early fall. The incidence of enanthems and exanthems in infected persons varies among different EVs and even among different strains of the same EV. For example, enanthems and exanthems are often seen in >50% of infected children during outbreaks of infection caused by echovirus 9 or Coxsackievirus A16 but are rare during outbreaks caused by echovirus 6 or Coxsackievirus A7. Host factors, especially age, are also important; infants and young children are more likely to develop mucocutaneous lesions, whereas other manifestations of EV infection, such as aseptic meningitis, are more likely to develop in older children and adults. Thus, during outbreaks of echovirus 9 infection, rash is often seen in the majority of infected children younger than 5 years of age, but in less than 5% of infected adults, and it is not uncommon when evaluating an adult with aseptic meningitis and no rash to find that a child in the same household is convalescing from an illness characterized by a maculopapular rash. Enteroviral lesions in the oropharyngeal mucosa

and skin are manifestations of a systemic virus infection, in contrast to the pathogenesis of the lesions of acute herpetic gingivostomatitis, human papillomavirus infections (warts), and acute hemorrhagic conjunctivitis, which are the direct result of exogenous virus infection and replication in epithelial cells at the portal of entry.

The obligatory alimentary tract replication and viremia before mucocutaneous lesions develop explains the 3- to 10-day incubation period and the frequent occurrence of prodromal signs and symptoms. Moreover, the simultaneous dissemination of virus to a number of target organs explains the concurrent appearance of other manifestations of EV infection, such as aseptic meningitis and myopericarditis.

Enanthems

The oropharyngeal mucosa is involved to some degree during most symptomatic enteroviral infections. This is usually manifest by mild pharyngitis and mucosal erythema, but it may also result in a variety of enanthems. These may consist of macules, papules, vesicles, petechiae, or ulcers, and they may occur alone or in association with exanthems and other manifestations of systemic enteroviral infection. They are often transient and frequently unrecognized, but they occasionally lead to diagnostic confusion, for example, when they resemble Koplik spots and accompany a morbilliform exanthem in a child infected by echovirus 9. Two enanthems are sufficiently unique to warrant separate description.

HERPANGINA

Herpangina is a syndrome characterized by sudden onset of fever, sore throat, pain on swallowing, and a vesicular enanthem of the posterior pharynx. It is seen primarily in children between ages 3 and 10. The disease begins abruptly, after a 3- to 10-day incubation period, with fever, sore throat, and pain on swallowing. There may also be anorexia, vomiting, and abdominal pain. Fever tends to be greater in younger children, who may suffer febrile convulsions; older children and adults frequently complain of headache and myalgia. On examination there is pharyngeal erythema but little or no tonsillar exudate. The characteristic lesions are discrete 1- to 2-mm vesicles and ulcers surrounded by 1- to 5-mm zones of erythema. Lesions are few, averaging 4 to 5 per patient, with a range of 1 or 2 to 20. They occur on the anterior tonsillar pillars, the posterior edge of the soft palate, and the uvula, and less frequently on the tonsils, the posterior pharyngeal wall, and the posterior buccal mucosa. They begin as small papules, progress to vesicles, and ulcerate within 24 hours. The shallow ulcers, which are moderately painful, may enlarge over the next 1 or 2 days to a diameter of 3 to 4 mm. Symptoms generally disappear in 3 or 4 days, but the ulcers may persist for up to a week. Most cases are mild and resolve without complications, but herpangina is occasionally associated with exanthems, aseptic meningitis, or other serious manifestations of systemic EV infection.

Outbreaks of herpangina are common during the summer, and sporadic cases are also observed. Group A Coxsackieviruses account for the majority of outbreaks.

ACUTE LYMPHONODULAR PHARYNGITIS

Acute lymphonodular pharyngitis is a variant of herpangina that has been described in children infected with Coxsackievirus A10. The lesions have the same distribution as typical cases of herpangina, but instead of evolving into vesicles and ulcers, they remain papular and are infiltrated with lymphocytes to form 2- to 3-mm gray-white nodules surrounded by narrow zones of erythema. The disease is otherwise indistinguishable from herpangina.

HAND-FOOT-AND-MOUTH DISEASE

HFMD (vesicular stomatitis with exanthem) is a mild enteroviral disease characterized by a vesicular eruption in the mouth and over the extremities. It occurs most frequently in children younger than 5 years of age. After an incubation period of 3 to 6 days, the disease begins with mild fever ranging from 38°C to 39°C, anorexia, malaise, and, often, a sore mouth. Within 1 or 2 days vesicular lesions appear in the oral cavity, most frequently on the anterior buccal mucosa and the tongue, but also on the labial mucosa, gingivae, and hard palate. In the majority of preschool children, but in only about 10% of infected adults, the oral lesions are accompanied by vesicular skin lesions, most often on the dorsal or lateral surfaces of the hands and feet and on the fingers and toes but not infrequently on the palms and soles. Less often, lesions occur on the buttocks or more proximally on the extremities and, rarely, on the genitalia. They are generally 3 to 7 mm in diameter and surrounded by a narrow zone of erythema. They range from 2 or 3 to 30 or more. HFMD is caused most frequently by Coxsackievirus A16; less frequently by EV-71 and Coxsackieviruses A5, A9, and A10; and occasionally by Coxsackieviruses A4, A7, B2, and

B5. Outbreaks and sporadic cases occur primarily in the summer and early fall. HFMD may be accompanied by more serious manifestations, especially when caused by EV-71. A variant of Coxsackievirus A6 has been associated with widespread mucocutaneous bullous lesions resembling Stevens–Johnson syndrome.

Exanthems

EV exanthems themselves are benign, but they are clinically important for at least three reasons: (1) They constitute direct evidence of EV dissemination and thus provide a clue to the presence and the etiology of coexistent disease referable to other infected target organs, such as the heart and the CNS; (2) they represent the "tip of the iceberg" of EV infection in the community; and (3) they are often confused with other infectious exanthems, some of which have more serious consequences, require specific control measures, or are amenable to specific anti-infective therapy. Misdiagnosis of EV rashes assumes added significance as we consider the threat of bioterrorism involving the use of smallpox.

The most common cutaneous manifestation of EV infection is an erythematous maculopapular rash that appears together with fever and other manifestations of systemic infection. This is also a common manifestation of infection by a variety of other organisms, but it is more often caused by EV. Only certain EVs (e.g., echovirus 9) cause this syndrome with high frequency, but almost all can produce it at least occasionally. The rash begins on the face and quickly spreads to the neck, trunk, and extremities. It consists of 1- to 3-mm erythematous macules and papules that may be discrete (*rubelliform*, resembling rubella) or confluent (*morbilliform*, resembling measles). It usually lasts for 2 to 5 days and does not itch or desquamate. Enteroviral exanthems are generally not accompanied by significant lymphadenopathy. Enteroviral rashes are sometimes petechial and occasionally purpuric, most frequently in echovirus 9 and Coxsackievirus A9 infections.

Vesicular exanthems are most often seen as a component of HFMD (see earlier), but several EVs, including echovirus 11, Coxsackievirus A9, and EV-71, may cause vesicular exanthems without an associated enanthem. The lesions resemble those caused by varicella-zoster and herpes simplex viruses. In contrast to varicella, however, vesicular rashes caused by EV are usually peripheral in distribution and consist of relatively few lesions that heal without crusting. When they are not associated with HFMD, vesicular lesions caused by EV are often confused with insect bites or poison ivy. Echovirus 11 and several Coxsackievirus serotypes have been associated with skin lesions resembling papular urticaria, lesions that usually result from insect bites.

Enteroviral rashes are generally accompanied by fever; they develop at or within 1 or 2 days of its onset. In some cases, however, the rash does not develop until the fever subsides, a pattern resembling that of *roseola infantum* (exanthem subitum), caused by human herpesvirus 6.

Herpangina is most often confused with bacterial pharyngitis, tonsillitis, or pharyngitis caused by other viruses. Other considerations include HFMD, primary herpes simplex virus infections, particularly acute herpetic pharyngotonsillitis, and herpes zoster involving the palate.

The vesicular lesions of HFMD resemble those caused by herpes simplex and varicella-zoster viruses. Patients with primary herpetic gingivostomatitis usually have more toxicity, cervical lymphadenopathy, and more prominent gingivitis. Their cutaneous lesions are usually perioral but may occasionally involve a finger that has been in the mouth. Recurrent herpes simplex (herpes labialis) usually involves the vermillion border of the lip or the adjacent skin, is rarely accompanied by lesions on the hands or feet, often has a neuralgic prodrome, and frequently has a history of recurrent episodes. The cutaneous lesions of varicella are generally more extensive and are centrally distributed, sparing the palms and soles. Oral lesions are far less prominent in varicella, and its prevalence in winter and spring further distinguish it from HFMD. Like vesicular lesions caused by herpes simplex and varicella-zoster virus, EV vesicles are generally more superficial and evolve more rapidly than those caused by variola and vaccinia viruses.

Aphthous stomatitis is distinguished from HFMD by the absence of fever and other signs of systemic illness, the absence of cutaneous lesions, and often by a history of recurrence. Maculopapular exanthems caused by EV are distinguished from measles and rubella by their summertime occurrence; the usual absence of posterior cervical, suboccipital, and postauricular lymphadenopathy; and their relatively short incubation period. The absence of significant coryza and conjunctivitis further distinguishes the typical enteroviral exanthems from measles. In addition, the probability of measles and rubella

is markedly reduced in persons with a well-documented history of adequate immunization.

When enteroviral rashes are maculopapular they may be confused with drug reactions; when they are petechial they may be confused with bacterial or rickettsial rashes. When enteroviral rashes are petechial or purpuric it is impossible to rule out meningococcemia on clinical grounds alone, and when the rash is associated with aseptic meningitis (as is often the case in echovirus 9 and Coxsackievirus A9 infections), it is clinically indistinguishable from meningococcal meningitis. Enteroviral enanthems and exanthems are generally benign self-limited illnesses that require only symptomatic therapy for headache and sore throat. When illness mimics meningococcemia or meningococcal meningitis, antimicrobial chemotherapy should be initiated until bacterial infection is ruled out.

RESPIRATORY TRACT DISEASE CAUSED BY ENTEROVIRUSES

A number of EVs have been associated with mild upper respiratory tract illness in children and adults, especially Coxsackieviruses A21, A24, and B1 through B5 and echoviruses 9 and 11. Many produce illnesses that resemble the common cold. In contrast to most other EVs, Coxsackievirus A21 is shed primarily from the upper respiratory tract rather than in feces. EVs have also been associated with childhood tracheitis, bronchitis, croup, bronchiolitis, and pneumonia. Surveillance data indicate that EVs account for 2% to 10% of viral respiratory disease and that 10% to 15% of symptomatic EV infections are associated with respiratory symptoms. The respiratory illnesses caused by EVs are clinically indistinguishable from similar illnesses caused by viruses more commonly considered to be respiratory tract pathogens, such as rhinoviruses, influenza viruses, parainfluenza viruses, respiratory syncytial virus, and adenoviruses. However, infections with these viruses occur most frequently during the winter, whereas EV infections occur primarily in the summer and early fall. EV-68 (EV-D68) infections were uncommon until very recently. In 2014, EV-68 has caused a national epidemic of severe, sometimes fatal, lower respiratory tract infection in children. Symptoms resemble asthma, with respiratory distress and hypoxia, often requiring ICU admission. Most of the cases have a history of asthma and are afebrile.

ACUTE HEMORRHAGIC CONJUNCTIVITIS

Acute hemorrhagic conjunctivitis (AHC) is an acute, highly contagious, self-limited disease of the eye characterized by sudden onset of pain, photophobia, conjunctivitis, swelling of the eyelids, and prominent subconjunctival hemorrhages. AHC has occurred in explosive epidemics throughout the world.

AHC is highly contagious. In contrast to most enteroviral infections, it is transmitted by direct inoculation of the conjunctivae with virus-contaminated fingers or fomites or ophthalmologic instruments. EV-70 and the Coxsackievirus A24 variant are temperature-sensitive viruses that replicate optimally at 33°C to 35°C, the temperature of the conjunctivae. During epidemics, all age groups are affected.

AHC begins with the sudden onset of eye pain and foreign-body sensation, lacrimation, photophobia, blurred vision, and bulbar conjunctivitis. Signs and symptoms rapidly increase in severity with the development of palpebral conjunctivitis, conjunctival edema, swelling of the eyelids, subconjunctival hemorrhages in the bulbar conjunctivae, and a serous or seromucoid ocular discharge containing large numbers of polymorphonuclear leukocytes. Subconjunctival hemorrhages are the hallmark of the disease. AHC often begins unilaterally, but it rapidly spreads to the other eye. Signs and symptoms peak within 24 to 36 hours of onset, by which time most patients have also developed hypertrophy of palpebral follicles and papillae, preauricular lymphadenopathy, and punctate epithelial keratitis with tiny corneal erosions.

Poliomyelitis-like motor paralysis occurs as a rare complication of AHC caused by EV-70, but not in AHC caused by Coxsackievirus A24. It occurs predominantly in adult males. The neurologic disease generally does not begin until 2 to 5 weeks after AHC (range of 5 to 60 days or more), thus its relationship to the conjunctivitis is often overlooked.

Treatment is symptomatic. Topical antihistamine/decongestant eyedrops and cold compresses may reduce discomfort. Corticosteroids are contraindicated. Transmission of AHC can be prevented by careful handwashing, avoidance of contaminated washcloths and towels, and sterilization of all ophthalmologic instruments.

DIAGNOSIS

The enteroviral etiology of a disease may be suspected on clinical and epidemiologic grounds, but the multiplicity of agents capable of causing most clinical syndromes associated with EV infections makes it impossible to establish a specific etiologic diagnosis on the basis of such information alone. Virus isolation from the site of pathology (e.g., CSF in aseptic meningitis, brain biopsy in encephalitis, myocardial tissue and pericardial fluid in myopericarditis) has been the "gold standard" of enteroviral diagnosis. Isolation of an EV from the nasopharynx or feces is less definitive, because isolation of an EV from these sites may be due to an intercurrent asymptomatic EV infection or prolonged virus shedding from an earlier EV infection and be etiologically unrelated to the observed illness.

The recent availability of methods for the detection and identification of EV RNA via RT–PCR makes it possible to provide an accurate diagnosis of EV infection within a few hours, with a sensitivity greater than virus isolation and a specificity of 100%. Amplification permits identification of most EVs, whereas sequencing a portion of the gene encoding VP1 can yield a serotype-specific diagnosis. Serologic testing has a very limited role because of the diversity of serotypes and the lack of a common antigen.

TREATMENT AND PREVENTION

Specific antiviral chemotherapeutic and chemoprophylactic agents are not yet available for EV infections. Thus treatment is symptomatic. Corticosteroids should not be administered during acute EV infections. Strenuous exercise and intramuscular injections, both of which may precipitate paralysis of the involved muscles during EV viremia, should also be avoided during the acute, presumably viremic, phase of symptomatic EV infections. Intravenous immunoglobulin (IVIG), which contains high titers of neutralizing antibodies to many EVs, appears to have been useful in some agammaglobulinemic patients with chronic enteroviral meningoencephalitis. IVIG may also have a role in the treatment of enteroviral infections in patients with compromised B-lymphocyte function. Infants with generalized neonatal EV infections are unlikely to have received transplacental antibodies to the causative virus from their mothers. Consequently it seems reasonable to administer IVIG to such infants in an attempt to terminate their viremia and limit virus replication in infected tissues. Prophylactic IVIG should also be considered for patients with compromised B-lymphocyte function, including bone marrow transplant recipients. Several promising inhibitors of EV replication belong to a class of anti-EV drugs known as capsid-binding inhibitors or (WIN) compounds that bind within a hydrophobic pocket under the floor of the receptor-binding canyon in the EV capsid. One of these compounds, pleconaril, has broad and potent anti-EV activity, excellent bioavailability, and a very favorable safety profile. Clinical trials have demonstrated benefit in children and adults with EV meningitis and in adults with respiratory infections caused by EV and rhinoviruses. However, the drug is not currently available. Live attenuated and inactivated poliovirus vaccines have been remarkably successful in preventing paralytic poliomyelitis. An inactivated EV-71 vaccine has recently demonstrated efficacy in a large phase III clinical trial.

Pre-exposure administration of immune serum globulin reduces the risk of paralytic poliomyelitis. Because immune serum globulin also contains neutralizing antibodies to many nonpolio EVs, it would probably prevent many nonpolio EV diseases as well. This approach probably reduces the frequency of severe enteroviral infections in agammaglobulinemic patients receiving replacement therapy. However, the benign nature of most EV infections, the fact that exposures are rarely recognized (most result from contact with an asymptomatically infected person), and the relatively short half-life of exogenous immune serum globulin make this approach to prevention impractical in most situations. Nursery outbreaks of severe enteroviral disease provide an exception. The administration of IVIG to all infants in the nursery offers protection to those infants without transplacentally acquired neutralizing antibody who have not yet been infected.

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185. Epstein–Barr virus and other causes of the mononucleosis syndrome

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Epstein–Barr virus (EBV) will infect nearly everyone at some point during his or her lifetime. In the United States, EBV is acquired by ~85% of non-Hispanic black and Mexican-American children by age 14, ~52% of non-Hispanic white children by age 14, and ~95% of all persons by the end of their third decade of life. Lower socioeconomic status increases likelihood of acquiring EBV in childhood.

Oropharyngeal epithelial cells (e.g., in tonsillar crypts) are the source of infectious EBV in saliva. Close oral contact with infectious saliva, i.e., via kissing, is the primary mode of EBV transmission. Sexual intimacy increases EBV transmission risk during adolescence and early adulthood. Casual contact does not transmit the infection. EBV-seropositive donor blood products and tissues may transmit infection, when EBV reactivates from latently infected B lymphocytes.

Table 185.1 EBV-related illness

Acute
Infectious mononucleosis (IM)
Atypical IM presentations or complications
Chronic
Chronic active infection (rare)
Oral hairy leukoplakia
Lymphoproliferative disorders
From congenital or acquired immunosuppression
X-linked (Duncan disease)
Other disorders
African Burkitt's lymphoma
Nonkeratinizing nasopharyngeal carcinoma
Primary central nervous system lymphoma in AIDS
Rare types of smooth muscle cell tumors and thymomas
Hodgkin's disease (EBV DNA in 40%–65% of tumors)

Abbreviations: EBV = Epstein–Barr virus; AIDS = acquired immunodeficiency syndrome.

INFECTIOUS MONONUCLEOSIS

Presentation

Most EBV infections go unnoticed. EBV-related illness, should it develop, varies in spectrum of presentation (Table 185.1). Infectious mononucleosis (IM) is the paradigmatic EBV illness. This is an acute or subacute illness that occurs 5 to 7 weeks after EBV is acquired and corresponds to an overly exuberant immunologic reaction. Rates of this illness are highest for adolescents and young adults ages 15 to 25, and approximately 50% to 80% of college students experience an IM-like illness after a primary EBV infection. Infants and young children seldom exhibit an IM-like illness after a primary EBV infection. Older adults retain the ability to develop the illness but most persons in this age group have already been EBV infected.

Finding a distinctive set of clinical and non-specialized laboratory abnormalities is usually sufficient to make the EBV IM diagnosis (Table 185.2). The EBV IM diagnosis is highly likely in persons presenting with the clinical triad of fever, pharyngitis, and cervical lymphadenopathy; absolute peripheral lymphocytosis; atypical lymphocytosis that is >10% of the differential; and heterophile antibodies. As these criteria are relaxed, the probability of EBV causing the mononucleosis (mono)-like syndrome decreases accordingly. Conversely, failure to fulfill these criteria does not rule out EBV. Heterophile antibody is not detected in approximately 5% to 20% of EBV IM cases and might not become detectable until later in the illness. Atypical lymphocytosis may not peak until later in the illness. Unusual clinical presentations are more likely to occur in infants, young children, older adults, and immunosuppressed persons.

Malaise and fatigue are often prominent IM symptoms, may take more time to resolve than other symptoms, and tend to linger for longer periods in patients having higher severity of acute illness. Convalescence for fatigue and impaired functional status occasionally drags

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Table 185.2 Clinical and laboratory findings in uncomplicated infectious mononucleosis

Percentage of patients	>50%	10%–50%	≤10%
Symptoms	Sore throat, malaise, fatigue, headache, sweats	Anorexia, myalgia, chills, nausea	Cough, arthralgias, abdominal discomfort
Signs	Lymphadenopathy, fever, pharyngitis	Splenomegaly, hepatomegaly, palatal petechiae, periorbital edema	Rash, jaundice Oral or genital ulcers
Labs	>50% mononuclear cells >10% atypical lymphocytes Heterophile antibodies Mild LFT increase Mild thrombocytopenia Cold agglutinins	Mild neutropenia Antinuclear antibodies Rheumatoid factor Cardiolipin antibodies	Bilirubinemia >3 mg/100 mL Hematuria Pyuria Proteinuria

Abbreviation: LFT = liver function test.

out to 6 months after the acute illness, but this is neither the result of EBV activity nor marked by abnormal physical examination, serological, or laboratory findings. In a recent study, sore throat was the most common IM symptom in young adults. Mild retro-orbital headache is common and short-lived. Upper respiratory tract symptoms may also be present.

Fever in the range of 38°C to 39.5°C (+/− sweats and chills) is common, subsides in 1 to 2 weeks, and rarely persists for up to 4 weeks. Fever above 40°C should prompt a search for superimposed bacterial infection (i.e., bacterial pharyngitis or peritonsillar abscess). Exudative tonsillopharyngitis is a common finding in EBV IM and usually resolves in the first 2 weeks of illness. Petechiae may appear on the uvula and at the junction of soft and hard palates. Symmetric posterior cervical lymphadenopathy elevates IM in the differential diagnosis, whereas anterior cervical lymphadenopathy has many potential etiologies. EBV IM-related lymphadenopathy may take several weeks to resolve. Splenomegaly is common. Mild abdominal discomfort may be present. Severe abdominal pain or left upper quadrant abdominal pain radiating to the left shoulder raises concern of splenic rupture or infarction. Biochemical findings of mild-to-moderate hepatitis are common, though transaminase levels >500 IU/L and jaundice are possible. Rash is infrequent in adolescents and adults; it typically appears as a faint morbilliform eruption. Peripheral blood lymphocytosis often peaks during the second or third week of illness. Mild neutropenia and thrombocytopenia are common.

In elderly persons, the illness of primary EBV infection is less likely to include pharyngitis, lymphadenopathy, splenomegaly, and atypical lymphocytosis, and is more likely to have unusual features, i.e., jaundice or prolonged febrile course. Infants and young children are more likely to have a heterophile-negative illness with coryza, exudative pharyngitis, rash, and hepatosplenomegaly.

Table 185.3 Complications of infectious mononucleosis

Neurologic Encephalitis, meningitis, cerebellitis, Guillain–Barré syndrome, Bell's palsy, optic neuritis, psychosis, polyradiculitis, transverse myelitis, Reye's syndrome
Splenic Rupture of enlarged spleen (traumatic or spontaneous), splenic infarction
Respiratory Upper airway obstruction from hypertrophy of lymphoid tissue, interstitial pneumonitis
Hematologic Autoimmune hemolytic anemia, severe thrombocytopenia, agranulocytosis, aplastic anemia, hemophagocytic syndrome
Hepatic Fulminant hepatitis, hepatic necrosis
Cardiac Myocarditis, pericarditis
Immunologic Anergy, lymphoproliferative syndromes, hypogammaglobulinemia
Dermatologic Cold-mediated urticaria, leukocytoclastic vasculitis, ampicillin-associated rash, erythema multiforme, erythema nodosum

Complications

Approximately 1% of persons with EBV IM experience a complication. Various types of complications are possible (Table 185.3). In some cases, the complication overshadows the other

IM features or is not accompanied by typical IM symptoms or signs. Most complications resolve without sequelae. Rare fatalities have resulted from encephalitis, splenic rupture, hepatic failure, myocarditis, or neutropenia-associated sepsis. Impending airway obstruction results from tonsillar lymphoid hyperplasia and edema. Enlarged spleens are susceptible to traumatic rupture; spontaneous rupture or infarction is rare. Hemolytic anemia, thrombocytopenia, or neutropenia may develop in relation to autoantibody production. Cytopenia is usually self-limiting. Aplastic anemia and hemophagocytic syndrome are rare life-threatening complications. Neurologic complications take on forms of encephalitis, cerebellitis, meningitis, optic neuritis, peripheral neuritis, facial nerve palsy, and Guillain–Barré syndrome.

EBV IM may evolve into a life-threatening lymphoproliferative disorder in persons with profound acquired or congenital cellular immunodeficiency. In a rare inherited disease, the X-linked lymphoproliferative syndrome, young males develop fulminant EBV IM. Many die of hemorrhage and infection; survivors have aplastic anemia, dysgammaglobulinemia, and lymphoma. EBV very rarely causes chronic active infection that results in interstitial pneumonitis, massive lymphadenopathy, hepatosplenomegaly, bone marrow failure, dysgammaglobulinemia, Guillain–Barré syndrome, and uveitis. These patients have high EBV burden in blood or tissues, as well as very high titers of EBV-specific antibodies. Chronic fatigue syndrome is not driven by EBV, but does rarely follow an acute EBV IM episode.

Laboratory testing

Serum heterophile IgM antibodies of the Paul–Bunnell–Davidsohn type are a reliable proxy indicator of EBV IM. These antibodies are distinguished from Forssman and serum sickness heterophile antibodies (that also bind to animal red blood cell components), may not be detected until the second or third week of illness, and fade away in 3 to 6 months. Their levels do not correlate with severity of illness. Contemporary methods of standard, automated, and point-of-care heterophile antibody testing rarely find presence of these antibodies in sera of patients with other clinical conditions, i.e., viral hepatitis, primary human immunodeficiency virus (HIV) infection, malaria, babesiosis, and lymphoma.

EBV-specific antibody testing is performed when key features of IM are lacking or atypical. Measurement of antibodies against viral capsid antigen (anti-VCA) and EBV nuclear antigens (anti-EBNA) in immunocompetent persons is usually sufficient to provide the results needed to confirm or reject the diagnosis of primary EBV infection. Detection of anti-VCA IgM, which is present in 85% to 95% of IM cases, substantiates the diagnosis. Anti-VCA IgM fades away in weeks to months after the acute illness. Anti-VCA IgG seroconversion from negative to positive detection in acute illness and convalescence, respectively, is confirmation of the diagnosis. However, anti-VCA IgG seroconversion is an infrequent finding, because anti-VCA IgG is often near peak level during the acute illness. Anti-VCA IgG persists for life. Undetectable levels of anti-EBNA antibodies in conjunction with presence of anti-VCA IgM or IgG also marks a primary EBV infection. Anti-EBNA antibodies usually become detectable in convalescence and persist for life.

Interpret EBV-specific antibody levels cautiously, as these values may differ by place and method or be confounded by some types of preexisting or coincident conditions. EBV-specific antibody tests are not validated for use in immunosuppressed patient populations and can produce misleading or ambiguous results in this population. Primary cytomegalovirus (CMV) infection in an otherwise normal host may result in detection in EBV VCA IgM as a consequence of either EBV immune-reactivation (the VCA IgM binds to EBV antigen and anti-EBNA antibodies are present) or nonspecific IgM reactivity.

PCR-based measurement of EBV DNA load in serum or plasma may have an auxiliary role as a diagnostic supplement in serologically indeterminate EBV infections. IM in otherwise healthy persons results in release of fragmented EBV DNA in serum or plasma that does not continue for long. The magnitude of EBV DNA load correlates with severity of the acute illness. Although an international World Health Organization (WHO) standard reference for EBV DNA quantification helps standardize PCR test results, major questions remain about the positive and negative predictive values of the various types of PCR assays for the diagnosis of EBV IM.

OTHER CAUSES OF MONO SYNDROME

A mononucleosis-like (mono) syndrome may result from other etiologies. CMV, toxoplasma, HIV, rubella, hepatitis viruses, and other causes of acute pharyngitis are often considered in the list of etiologic possibilities. Clinical and non-

Table 185.4 Differential diagnosis of mononucleosis-like syndrome

Variables	EBV	CMV	Toxoplasma	HIV	Bacterial[a] and respiratory virus[b] pharyngitis	Rubella	HAV, HBV, HCV
Fever	++	++	+	++	++	+	++
Sore throat	++	+	+	++	++ abrupt	+/− coryza	−
Exudative pharyngitis	+	+/−	−	+/− aphthous ulcers	+	−	−
Anterior cervical LN	++	+	++	++	++	+	+/−
Posterior cervical LN	++	+	++	++	+/− mild	++	+/−
Rash	+/− but common with ampicillin	+	+/−	++	+/− scarlatiniform	++	+/−
Hepatitis	++	++	+	+	−	+/−	++
Jaundice	+/−	+/−	−	−	−	−	++
Splenomegaly	++	+	+/−	+/−	−	+/−	+
Atypical lymphs	++	++	+ ≤10% of cells	+/− ≤10% of cells	−[a] +/− ≤10% of cells[b] (adenovirus, B19)	+/− ≤10% of cells	+ ≤10% of cells
Heterophile antibodies	++ absent in ≥10%	−	−	−	−	−	−

Key: ++ = present in >50% of cases; + = present in 10% to 50% of cases; +/− = present in 10% of cases; − = absent or rare.
Abbreviations: EBV = Epstein–Barr virus; CMV = cytomegalovirus (glandular fever); HIV = human immunodeficiency virus (acute retroviral syndrome); HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; LN = lymphadenopathy; lymphs = peripheral lymphocytes.
[a] Primarily β-hemolytic streptococci (group A, C, and G); consider diphtheria, *Arcanobacterium haemolyticum*, *Neisseria gonorrhoeae*, mycoplasma, fusobacterium, and Vincent's angina.
[b] Influenza, adenovirus, parainfluenza, rhinovirus, and coronavirus.

specialized laboratory findings may help distinguish these other etiologies from EBV (Table 185.4). However, the definitive diagnosis usually rests on the results of pathogen-specific laboratory tests (Table 185.5). EBV should be included in the differential diagnosis of heterophile-negative mono syndrome.

Primary CMV infection accounts for the majority of heterophile-negative mono episodes (see Chapter 182, Cytomegalovirus). CMV mono may closely resemble EBV IM. Both CMV and EBV characteristically produce fever, hepatitis, and atypical lymphocytosis. Cervical lymphadenopathy and pharyngitis tend to be milder in CMV mono. Primary CMV infection in the immunocompetent patient is confirmed by serologic evidence of a positive anti-CMV IgM plus low-avidity anti-CMV IgG index or CMV IgG seroconversion. Detection of CMV antigen or DNA in peripheral blood also supports the diagnosis.

Acute retroviral syndrome (ARS) caused by primary HIV infection may manifest as a mono syndrome. In ARS, rash is anticipated, exudative pharyngitis is infrequent, tonsillar hypertrophy is minimal, and oral or genital ulcers are sometimes observed. A transient peripheral lymphopenia may be followed 2 to 3 weeks later by lymphocytosis, in which a small proportion of cells may be reactive. Detection in blood of HIV RNA or p24 antigen but not HIV antibody (or an indeterminate confirmatory result for HIV antibody) is indicative of a primary HIV infection.

Streptococcal pharyngitis is more frequently abrupt in onset than is EBV pharyngitis. Viruses – such as respiratory viruses and some nonpolio enteroviruses – are the most common cause of acute pharyngitis. These viral and bacterial causes of acute pharyngitis do not typically produce hepatosplenomegaly, atypical lymphocytosis, or prominent posterior cervical lymphadenopathy. Adenovirus is exceptional in that it is a common cause of mono-like symptoms in young children and can occasionally produce atypical lymphocytosis. Toxoplasma-induced mono syndrome is uncommonly encountered in the United States and does not produce exudative pharyngitis or peripheral atypical lymphocytosis exceeding 10% of the differential. Rubella also

Table 185.5 Diagnostic studies in mononucleosis-like syndrome

Variables	EBV	CMV	Toxoplasma	HIV	Bacterial[a] and respiratory virus[b] pharyngitis	Rubella	HAV, HBV, HCV
Antibody response: acute[c]	+ Heterophile + IgM VCA +/− anti-EA − anti-EBNA	+ IgM CMV, low-avidity CMV IgG	+ IgM Toxo, low-avidity Toxo IgG	− HIV Ab	None	+ IgM rubella	+ IgM HAV, + IgM HBc, − HCV Ab
Antibody response: convalescent	+/− 4-fold increase IgG VCA +/− anti-EA (EIA) + anti-EBNA (EIA)	+ 4-fold increase IgG CMV	+ IgG Toxo seroconversion (several test-types available)	+ HIV Ab +Confirmatory immunoblot or multispot	+ Elevated or rising ASO or anti-DNase B[a] + 4-fold increase IgG influenza[b]	+ 4-fold increase IgG rubella	+ IgG HAV, + or − anti-HBs + IgG HBc, + HCV Ab
Nucleic acid or antigen detection	None	+/− CMV antigen or DNA in blood WBC or DNA in plasma	None	+ plasma HIV RNA PCR +/− p24 Ag	+ Rapid Strept test[a] Respiratory virus panel PCR[b] Influenza antigen[b]	None	+ HBs Ag + plasma HCV RNA PCR
Culture	Impractical	+ Urine, saliva	Impractical	Impractical	+ Throat swab, blood agar[a] Nasopharyngeal wash for respiratory viral culture[b]	Impractical	None

Key: + = typically present; +/− = sometimes present; − = usually absent.

Abbreviations: EBV = Epstein–Barr virus; CMV = cytomegalovirus; Toxo = toxoplasma; HIV = human immunodeficiency virus; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; VCA = EBV viral capsid antigens; EA = EBV early antigens; EBNA = EBV nuclear antigens; EIA = enzyme-linked immunoassay; HBc = HBV capsid antigens; HBs = HBV surface antigen; p24 = HIV core protein; PCR = polymerase chain reaction.

[a] Applies primarily to group A streptococcus; special media required to culture *Corynebacterium diphtheriae*, *Neisseria gonorrhoeae*, and *Arcanobacterium haemolyticum*.

[b] Applies primarily to influenza virus, adenovirus, and parainfluenza viruses.

[c] IgM and heterophile status determined with acute serum. Paired acute and convalescent sera are best analyzed simultaneously to accurately determine change in antibody titer.

causes fever and lymphadenopathy, but the additional features of rash, coryza, arthralgias, and minimal atypical lymphocytosis helps distinguish the German measles from EBV IM. Viral hepatitides A to E are usually not accompanied by a troubling level of pharyngitis or marked lymphadenopathy. Acute mono-like illness has also been described for human herpesvirus 6 (HHV-6), herpes simplex, parvovirus B19, nonpolio enteroviruses, lymphohematologic disorders, and systemic drug reactions (e.g., phenytoin, carbamazapine, minocycline, and sulfa drugs).

MANAGEMENT

Epstein–Barr virus

The management of EBV IM rarely demands more than general supportive care, which includes adequate rest, hydration, antipyretics, and analgesics. Acetaminophen is commonly used. Aspirin should be avoided because of the potential risk of bleeding or thrombocytopenia. Complications of IM may require additional supportive measures – e.g., maintenance of airway during obstructive tonsillar enlargement or encephalitis, transfusions for severe hemolytic anemia or thrombocytopenia, splenectomy for splenic rupture. Activity should be restricted in proportion to the degree of symptoms and any splenomegaly. Most students can return to school in less than 2 to 3 weeks.

Enlarged spleens are structurally weakened by mononucleosis and at risk of rupture by trauma. Reported cases of splenic rupture have almost always occurred within the first month after illness onset, though splenic rupture at 7 weeks has been reported. Ultrasonography detects splenomegaly that is not appreciated on physical examination, and non-palpable splenomegaly usually

resolves in 4 to 6 weeks. This supports expert opinion that contact sports should be avoided for 4 to 6 weeks after symptom onset or until absence of splenomegaly is verified. A 2008 consensus statement in sports medicine warns against using one-time ultrasonography imaging for determining presence of splenomegaly and risk of rupture. Normal spleen size is significantly larger for tall athletes, and spleen size in IM-associated splenomegaly may not exceed the normal range. In a prospective study, serial use of ultrasonography in 17 college-aged athletes with EBV IM revealed splenic enlargement in all subjects that peaked within 23 days from time of symptom onset (mean 12.3 days; SD 5.3 days), and subsequently decreased in size ~1% per day on average. While serial use of ultrasonography may increase accuracy in determining the timeframe for resolution of splenomegaly, the cost-effectiveness and reliability of this strategy have been questioned. The athlete (or legally authorized representative) should be informed about issues pertaining to risk of splenic rupture when deciding together whether the athlete can return to contact sports.

EBV IM-associated exudative tonsillopharyngitis commonly leads to a search for β-hemolytic streptococci. Anywhere from 3% to 30% of surveillance throat cultures obtained during IM grow group A streptococci, reflecting the range in prevalence of community streptococcal carriage. Up to 30% of individuals harboring this bacterium eventually show serologic evidence of streptococcal infection. Treatment is with penicillin (500 mg twice daily) for 10 days or an alternative antibiotic selected according to recommendations issued in the Infectious Disease Society of America (IDSA) Practice Guidelines, which are publically accessible. This treatment also prevents poststreptococcal sequelae. One retrospective study concludes that risk of rash from oral amoxicillin is not increased in EBV IM, unlike early reports for ampicillin.

Acyclovir, ganciclovir, and foscarnet inhibit EBV replication during lytic infection but do not inhibit amplification of latent EBV genomes in proliferating B cells. Oropharyngeal shedding of EBV in persons with IM is greatly inhibited by valacyclovir, an orally administered prodrug of acyclovir, and acyclovir given in intravenous or high-dose oral formulations. Suppression of EBV shedding by the antiviral drug is not undermined by concomitant corticosteroid therapy, and the shedding returns after discontinuation of the antiviral agent. However, the collective evidence from several controlled trials indicates that acyclovir is not clinically beneficial in acute EBV IM, and the proportion of circulating B cells containing EBV is not consistently reduced. Clinicians may consider using antiviral therapy as an adjunct to corticosteroid therapy for serious complications of EBV IM.

Use of a corticosteroid for treatment of uncomplicated IM is not recommended. Several small controlled trials of varying design have not consistently found corticosteroid to be clinically beneficial and have not fully addressed the potential adverse effects. Studies showing benefit reveal modest reduction in duration of fever and tonsillopharyngeal symptoms. In a double-blinded, placebo-controlled study, the combination of prednisolone and acyclovir did not significantly decrease duration of IM symptoms. Corticosteroids have not been shown to decrease lymphadenopathy or hepatosplenic disease. Rare anecdotal reports have associated corticosteroid use with encephalitis, myocarditis, and peritonsillar abscess. The possibility of corticosteroid adversely affecting long-term immunity or number of latently infected cells with malignancy potential is a theoretical concern that has not been adequately addressed.

Corticosteroids appear to be useful in the management of certain IM complications. Corticosteroids may quickly ameliorate impending airway obstruction from tonsillar enlargement. A short course of a corticosteroid may also be considered in exceptional situations of severe protracted IM (i.e., fever, prostration, weight loss). Corticosteroids may reduce the severity of autoimmune thrombocytopenia and hemolytic anemia, and their use can be considered for intractable cases of encephalitis, myocarditis, and pericarditis. When required, corticosteroid therapy is initiated with 60 mg of prednisone equivalent per day given orally or intravenously for 2 to 3 days, and then tapered over a period of 1 to 2 weeks.

Therapy of other causes of mono syndrome

The mono-like symptoms of acute infections with CMV, toxoplasma, HIV, rubella, and the hepatitis viruses are usually self-limiting. Additional details about the individual case are sought to determine whether interventions, other than supportive care, should be applied. Pregnancy and cellular immunodeficiency are important factors to consider in the decision. Profound cellular

immune deficiency usually requires use of antimicrobial treatment for acute CMV (see Chapter 182, Cytomegalovirus) and toxoplasma (see Chapter 199, *Toxoplasma*) infections. Primary CMV, toxoplasma, and rubella infections in pregnancy pose a risk to the baby (TORCH syndrome), warranting a consultation with an obstetrician with expertise in this area. Primary toxoplasmosis of pregnancy necessitates antimicrobial therapy (see Chapter 199, *Toxoplasma*). Antiretroviral therapy given during pregnancy can substantially reduce perinatal HIV transmission, but its use requires knowledge of the attendant toxicities and risks (see Chapter 95, Pregnancy and the puerperium: infectious risks). Immediate antiretroviral therapy should be considered in persons with acute HIV infection (see Chapter 99, HIV-1 infection: antiretroviral therapy).

PREVENTION

There is not a vaccine for prevention of EBV infection or disease. Hospitalized patients with IM need not be isolated. Asymptomatic viral shedding long after the acute illness remains a potential risk for EBV transmission. Restricting intimate contact can decrease EBV transmission but is not practical unless the EBV infection would be intolerable.

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186. Hantavirus cardiopulmonary syndrome in the Americas

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INTRODUCTION

Hantavirus cardiopulmonary syndrome (HCPS) is a viral zoonosis that may result in cardiogenic shock and respiratory failure with significant associated mortality. Hantavirus infection has been identified throughout much of North, Central, and South America. In the United States 586 cases of HCPS have been reported through December 2012 with a case-fatality rate of 35%. Half of these cases have been in the Four Corners area in the southwest. The incidence is even greater in South America, particularly in Argentina, Brazil, Chile, and Paraguay. In Chile alone, 795 cases have been reported through December 2012, with a case-fatality rate of 35%.

VIROLOGY

HCPS is caused by an infection with a hantavirus. There have been over 20 New World hantaviruses identified since their discovery in 1993. The New World hantaviruses differ from the Old World hantaviruses that cause hemorrhagic fever with renal syndrome (HFRS) and are found primarily in Asia and Europe. The most common hantavirus causing HCPS in Canada and the United States is Sin Nombre virus (SNV). Other hantaviruses that cause significant disease in Central and South America include Andes virus (ANDV) in Chile and Argentina, Choclo virus in Panama, and Laguna Negra virus in Paraguay. The hantaviruses are small single-stranded negative-sense RNA viruses that belong to the family Bunyaviridae, a family known to include other viruses that cause significant zoonotic illnesses.

EPIDEMIOLOGY

Hantavirus infection is spread to humans by a rodent reservoir. The primary rodent responsible for human transmission in North America is the deer mouse, *Peromyscus maniculatus*. These asymptomatic rodent hosts shed the virus in urine, feces, and saliva. Humans are thought to be infected when the aerosolized excreta are inhaled. People are exposed most often when they are cleaning enclosed areas where dried excreta are disturbed. Exposure through rodent bite has also been identified. Human-to-human transmission has only been documented with ANDV infections in Chile and Argentina. In Chile, approximately one-third of cases occur in household clusters, and most secondary cases in these clusters result from person-to-person transmission. In a recent prospective study of household contacts of patients with HCPS in Chile, Ferrés *et al*. reported a significantly higher risk of the development of HCPS in sex partners and other close household contacts as compared to members of the household who slept in different rooms and denied sexual contact.

CLINICAL SYNDROME

Most cases involve an individual with a prolonged exposure history, so it is often difficult to determine the exact incubation period. In a small series from Chile where individuals had brief periods of exposure to high-risk areas, the median incubation period between exposure and onset of clinical disease was 18 days, with a range of 11 to 32 days. Clinical disease begins with a febrile prodrome consisting of 2 days to a week of fevers and myalgias, often with associated headache, backache, abdominal pain, nausea, and diarrhea. After several days with nonspecific prodromal symptoms, the cardiopulmonary phase starts abruptly with cough and dyspnea. This stage of disease may be mild, requiring only supplemental oxygen, or severe, causing rapid pulmonary edema and respiratory failure requiring mechanical ventilation. Severe disease is also characterized by cardiogenic shock, hemoconcentration, and lactic acidosis that may result in profound shock, cardiac arrhythmias, and death. The cardiopulmonary phase

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usually lasts 2 to 4 days. If the patient survives the cardiopulmonary phase, the patient will proceed into the diuretic phase with subsequent resolution of the pulmonary edema. Convalescence is prolonged and may include weakness, fatigue, and impaired exercise tolerance with abnormal diffusion capacity.

DIAGNOSIS

Early presumptive diagnosis is critical because patients often progress to shock and death before definitive diagnosis can be made. The appropriate exposure history is helpful but not always present. Clinical diagnosis during the prodrome is difficult as there may be no cough, a normal chest radiograph, and no lab abnormalities except for thrombocytopenia.

A definitive diagnosis of HCPS is based on serologic testing for hantavirus-specific immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies. These antibodies become positive during the febrile prodrome, but the clinician must have a high degree of suspicion to order the tests. In addition, the serologic test results are usually not available for at least 8 to 24 hours.

The serologic tests available in the United States include the enzyme-linked immunosorbent assay (ELISA), which is available at many state health departments via the Centers for Disease Control and Prevention (CDC), and a strip immunoblot assay (SIA). An acute infection is characterized by a positive IgM and negative IgG or a 4-fold rise in IgG titers. Nested reverse transcription–polymerase chain reaction (RT–PCR) can detect hantavirus RNA in peripheral mononuclear cells and in serum but is limited to research laboratories. Hantavirus RNA has been detected in peripheral blood cells up to 2 weeks before the onset of symptoms or detection of antihantavirus antibodies and for up to 13 weeks after onset of illness. Postmortem diagnosis may also be established by detection of hantavirus antigens in tissue by immunohistochemistry.

A presumptive diagnosis can generally be made at the onset of the cardiopulmonary phase on the basis of the clinical presentation, radiologic findings, and a review of the peripheral blood smear. Characteristic hemodynamic findings may also be helpful in establishing a diagnosis. The chest radiograph will show findings consistent with pulmonary edema, including bilateral pulmonary infiltrates, Kerley B lines, indistinct hilar borders, and peribronchial cuffing, which progress rapidly over the next 12 hours. A peripheral blood smear should be evaluated by an experienced pathologist. Clues to the diagnosis include the following: thrombocytopenia (platelet count $\leq 150 \times 10^3$ mm^3), left-shift (presence of myeloblasts), a lack of toxic granulation in neutrophils, hemoconcentration (hematocrit >50 in men and >48 in women), and >10% immunoblasts among lymphocytes. When evaluating a patient in whom there is a high clinical suspicion of HCPS, presence of four of five of these peripheral blood criteria has a sensitivity of 96% and a specificity of 99%. Unfortunately, these criteria apply only once the patient is already in the cardiopulmonary phase and therefore cannot be used for diagnosis in the prodromal stage. Other clinical findings in the cardiopulmonary phase include a low cardiac index associated with a high systemic vascular resistance, in contrast to parameters found in septic shock. Alanine aminotransferase and aspartate aminotransferase levels, while normal during the prodrome, are generally abnormal at the onset of the cardiopulmonary phase and often peak during the diuretic phase as the patient is improving.

TREATMENT

When there is clinical suspicion of HCPS, the patient should be transported to a facility in which cardiovascular and ventilatory support is available. Volume resuscitation should be avoided, as this can exacerbate the pulmonary edema. Supplemental oxygen should be provided, including ventilatory support if necessary. A pulmonary artery catheter should be placed for the monitoring of cardiac index and systemic vascular resistance. Early use of pressors should be utilized when appropriate. Norepinephrine is preferred as the initial agent in patients with hypotension, whereas dobutamine is preferred when there is a decrease in cardiac output but blood pressure is maintained. High-dose norepinephrine can be used in addition to dobutamine, if necessary.

If extracorporeal membrane oxygenation (ECMO) is available, the patient should be evaluated by the critical care and ECMO team, including cardiothoracic or vascular surgery, as soon as a presumptive diagnosis is made. In patients who are continuing to deteriorate despite full ventilatory and pressor support, ECMO should be considered. The University of New Mexico Hospital (UNMH) in Albuquerque, New Mexico, has the most experience with the use of ECMO for this condition. The criteria for the use of ECMO at this institution include a cardiac index less than

2.3 L/min/m^2, PaO_2/FiO_2 of less than 50, and a lack of response to conventional support. Exclusion criteria include age over 70 years, severe pre-existing comorbid disease, and neurologic impairment. Of the 51 patients treated with ECMO at UNMH between 1994 and 2010, 34 (67%) survived to discharge. Furthermore, survival was 80% among the 25 patients treated between 2003 and 2010 who underwent elective insertion of arterial and venous vascular sheaths once a presumptive or definitive diagnosis of HCPS was established, were intubated nearly concurrently with vascular sheath placement, and then placed on ECMO if decompensation occurred.

There is no approved therapy for the treatment of HCPS. Intravenous ribavirin did not lead to any survival benefit in a placebo-controlled trial in North America, and treatment with high-dose methylprednisolone was ineffective in a randomized, placebo-controlled trial in patients with HCPS in Chile. Promising preliminary data have been reported from an open, phase I trial of treatment with fresh frozen plasma containing anti-ANDV neutralizing antibodies recently conducted in Chile. While promising, these data remain unpublished, and there are no neutralizing antibody products available at this time for evaluation in further clinical trials or clinical use for any of the major pathogenic hantaviruses in North or South America.

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187. Herpes simplex viruses 1 and 2

Richard J. Whitley

THE VIRUS

Herpesviruses are generally defined as large enveloped virions with an icosapentahedral nucleocapsid consisting of 162 capsomeres arranged around a double-stranded DNA core. The two antigenically distinct types of herpes simplex virus (HSV) are HSV-1 and HSV-2. Considerable homology exists between the HSV-1 and HSV-2 genomes, with most of the polypeptides specified by one viral type being antigenically related to polypeptides of the other viral type. Although this results in considerable cross-reactivity between the HSV-1 and HSV-2, glycoproteins G (gG) are unique antigenic determinants that allow for differentiation between these two viruses (e.g., gG-1 and gG-2). Surrounding the viral genome and nucleocapsid is a tightly adherent membrane known as the *tegument*. A lipid envelope containing the viral glycoproteins loosely surrounds the tegument.

PATHOLOGY AND PATHOGENESIS

Cutaneous HSV infection causes ballooning of infected epithelial cells, with nuclear degeneration, loss of intact cellular membranes, and the formation of multinucleated giant cells. Ultimately, cells lyse and release clear fluid containing large quantities of virus, with subsequent accumulation of cellular debris and inflammatory cells between the epidermal and dermal layers. Multinucleated giant cells are usually present at the base of the vesicle. An intense inflammatory response extends from the base of the vesicle into the dermis, producing the erythema that classically surrounds a cluster of HSV vesicles. As the lesions heal, vesicular fluid becomes purulent as more inflammatory cells are recruited to the site of infection. Scab formation then follows. Scarring is uncommon.

When infection involves mucous membranes, shallow ulcers are more common than vesicles because of rapid rupture of the very thin cornified epithelium present at mucosal sites. Nevertheless, the histopathologic findings of mucosal lesions are similar to those of skin lesions.

EPIDEMIOLOGY

Although HSV-1 is found most commonly in the oropharynx, it is an increasingly common cause of first episode genital herpes, accounting for at least half of all new infections, and can infect any organ system. Factors that influence the frequency of primary HSV-1 infection include geographic location, socioeconomic status, and age. Throughout childhood and adolescence, African Americans maintain approximately twice the prevalence of HSV-1 antibodies as white children, with 40% of African American children being seropositive for HSV-1 by 5 years of age. By the age of 60 years, however, both African Americans and whites have a similarly high prevalence of HSV-1 antibody (up to 90%).

Recurrences of herpes labialis have been associated with physical or emotional stress, fever, exposure to ultraviolet light, tissue damage, and immune suppression. As with primary infections, recurrent disease may occur in the absence of clinical symptoms. At any given time, 1% of healthy children and 1% to 5% of normal adults asymptomatically excrete HSV-1, as demonstrated by viral culture. Recent studies employing polymerase chain reaction (PCR) suggest that these numbers may be at least 3-fold higher.

HSV-2 causes 75% to 80% of the cases of recurrent genital HSV infections in the United States. As would be expected, antibodies to this virus are rarely found before the onset of sexual activity. Among adolescents and adults, factors that correlate with seroprevalence for HSV-2 include sex (higher for women than for men), race (higher for African Americans than for whites), marital status (higher for persons previously married than for single or married persons), number of sexual partners (increasing likelihood with

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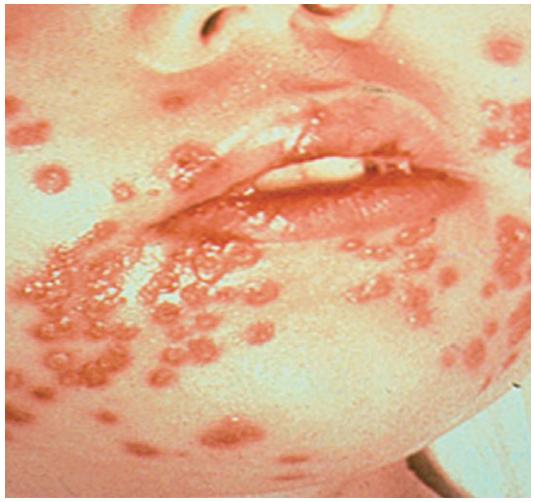

Figure 187.1 Herpes simplex gingivostomatitis.

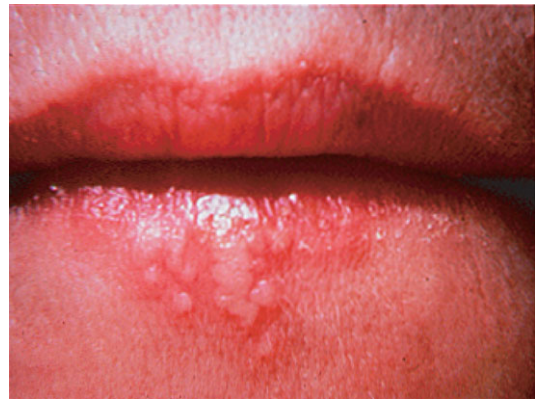

Figure 187.2 Recurrent herpes simplex labialis.

increasing number of partners), and income level (higher probability for those persons earning lesser amounts of money).

The propensity for recurrence of genital HSV infection depends on a variety of factors, including sex (more common in men), viral type (more common with HSV-2), and the presence and titer of neutralizing antibodies (more common in the presence of high neutralizing antibody titers). Overall, 60% to 90% of patients with primary genital HSV-2 infection will experience clinically apparent recurrence of infection.

CLINICAL MANIFESTATIONS

Oropharyngeal HSV infection

Primary oropharyngeal infection with HSV-1 occurs most commonly in young children between 1 and 3 years of age. It is usually asymptomatic. The incubation period ranges from 2 to 12 days, with an average of 4 days. Symptomatic disease is characterized by fever to 104°F, oral lesions, sore throat, fetor oris, anorexia, cervical adenopathy, and mucosal edema. Oral lesions initially are vesicular but rapidly rupture, leaving 1- to 3-mm shallow gray-white ulcers on erythematous bases. These lesions are distributed on the hard palate, the anterior portion of the tongue, along the gingiva, and around the lips (Figure 187.1). In addition, the lesions may extend down the chin and neck due to drooling. Total duration of illness is 10 to 21 days.

Primary infection in young adults has been associated with pharyngitis and often a mononucleosis-like syndrome. In such patients, ulcerative lesions on erythematous bases frequently are apparent on the tonsils.

Primary gingivostomatitis results in viral shedding in oral secretions for an average of 7 to 10 days. Virus is also shed in the stool.

Recurrent orolabial HSV lesions are often preceded by a prodrome of pain, burning, tingling, or itching. These symptoms generally last for less than 6 hours, followed within 24 to 48 hours by the appearance of painful vesicles, typically at the vermillion border of the lip (Figure 187.2). Lesions usually crust within 3 to 4 days, and healing is complete within 8 to 10 days. Recurrences occur only rarely in the mouth or on facial skin of immunocompetent patients.

Genital HSV infection

Genital HSV disease (Figure 187.3) is usually acquired by sexual contact with an infected partner. Historically, virtually all cases of genital herpes were caused by HSV-2 but, with changing sexual behavior, at least 50% of cases today are the consequence of HSV-1. The incubation period of primary disease ranges from 2 to 12 days. Lesions persist for an average of 21 days. In 70% of patients, primary infections are associated with fever, malaise, myalgias, inguinal adenopathy, and other signs and symptoms of systemic illness. Complications include extragenital lesions, aseptic meningitis, and sacral autonomic nervous system dysfunction with associated urinary retention. Women tend to experience more severe primary infections and are more likely to develop complications.

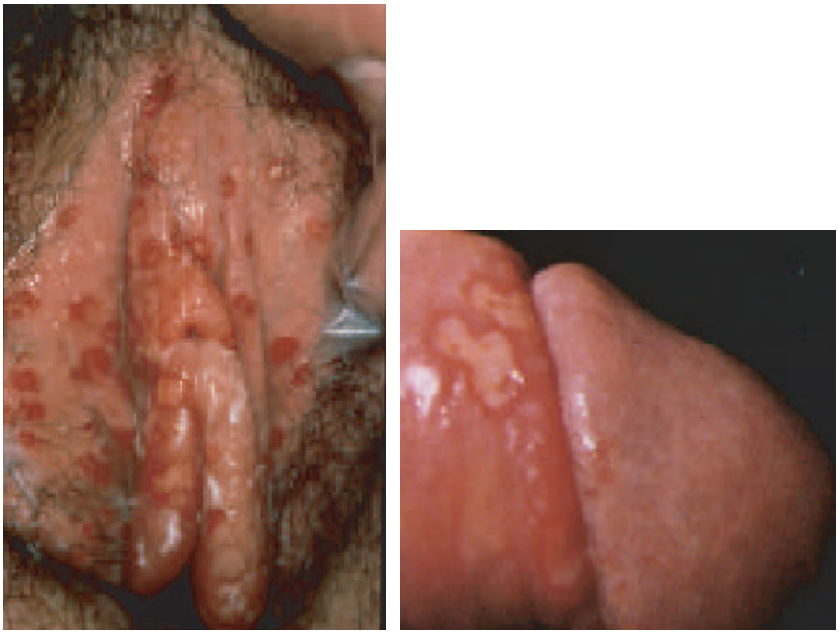

Figure 187.3 Genital HSV infection in woman (primary infection) and man (recurrence).

In males, primary genital HSV infection usually manifests as a cluster of vesicular lesions on erythematous bases on the glans or shaft of the penis. In females, primary genital HSV lesions usually involve the vulva bilaterally. Concomitant HSV cervicitis occurs in 90% of women with primary HSV-2 infection of the external genitalia. In women, the lesions rapidly ulcerate and become covered with a gray-white exudate. Lesions may be exquisitely painful. Recurrent genital HSV-2 infection can be either symptomatic or asymptomatic. A prodrome of itching, burning, tingling, or tenderness may be noted several hours before a recurrence. The duration of disease is shorter during recurrent infection (7 to 10 days), and fewer lesions are present. In men, lesions usually appear on the glans, or shaft, of the penis. In women, lesions occur most commonly on the labia minora, labia majora, and perineum. Cervical excretion of HSV occurs in 10% of women with recurrent genital lesions. Systemic symptoms are uncommon in recurrent genital HSV disease. Genital HSV-1 infections are much less likely to recur.

Transmission usually occurs in the absence of clinical symptoms, and occurs more often from men to women. Importantly, HSV-2 seropositive but asymptomatic individuals are just as likely to transmit infection as those who are symptomatic.

Other primary HSV skin infections

Alteration in the barrier properties of skin, as occurs in atopic dermatitis, can result in localized HSV skin infection (eczema herpeticum). Most cases resolve over a 7- to 9-day period without specific therapy. Localized cutaneous HSV infection after trauma is known as herpes gladitorium (wrestler's herpes or traumatic herpes).

HSV infection of the digits results in herpetic whitlow. Such lesions may be the result of autoinoculation, as in the case of infants, or exogenous exposure, as occurs among medical and dental personnel who fail to wear gloves.

Ocular HSV infection

Herpetic infection of the eye usually presents as either a blepharitis or a follicular conjunctivitis. As disease progresses, branching dendritic lesions develop. Symptoms include severe photophobia, tearing, chemosis, blurred vision, and preauricular lymphadenopathy. An ophthalmologist should always be involved in the care of such patients.

Central nervous system HSV infection

Central nervous system (CNS) signs and symptoms of HSV disease can begin suddenly or can follow a 1- to 7-day period of nonspecific

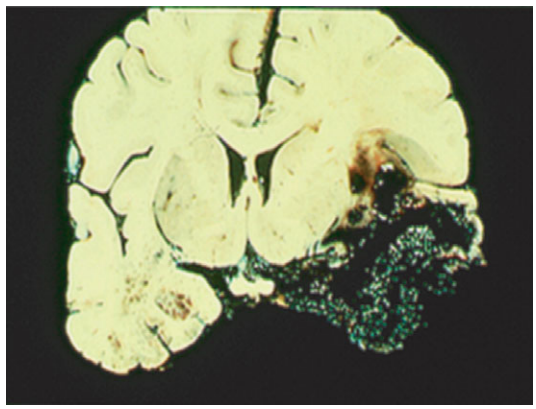

Figure 187.4 Brain with temporal lobe necrosis.

influenza-like symptoms. Prominent CNS features include headache, fever, altered consciousness, and focal neurologic findings such as focal seizures. Clinical signs and symptoms may reflect the characteristic frontal and temporal lobe localization, such as memory loss, anosmia, olfactory hallucinations, speech disorders, and behavioral disturbances, often accompanied pathologically by focal necrosis (Figure 187.4).

Neonatal HSV infections

Neonatal HSV infection can be classified as (1) disease localized to the skin, eye, and/or mouth (SEM) (45% of cases); (2) encephalitis, with or without SEM involvement (30% of cases); and (3) disseminated infection that involves multiple organs, including the CNS, lung, gastrointestinal tract, liver, adrenals, skin, eye, and/or mouth (25% of cases). Infants with disseminated and SEM disease usually present for medical attention within the first 2 weeks of life, whereas infants with disease localized to the CNS usually present between the second and third weeks of life. Presenting signs and symptoms can include any combination of irritability, seizures (both focal and generalized), lethargy, tremors, poor feeding, temperature instability, bulging fontanelle, respiratory distress, jaundice, disseminated intravascular coagulopathy, shock, and cutaneous vesicles. It is important to note that >40% of infants with disseminated disease and >30% of infants with encephalitis will never have skin vesicles during the course of illness. Even in cases of SEM disease, almost 20% of neonates do not have skin lesions.

HSV in the immunocompromised host

Patients compromised by immunosuppressive therapy, underlying disease, or malnutrition are at increased risk for severe HSV infection. Disseminated disease may occur with widespread dermal, mucosal, and visceral involvement. Alternatively, disease may remain localized but persist for much longer periods of time than would be seen in immunocompetent hosts.

DIAGNOSIS

Type-specific serologic tests allow the distinction between HSV-1 and HSV-2. These tests can be utilized to determine those people at risk for infection or those previously infected but who remain unaware of their status. The diagnosis of HSV is best achieved by either the isolation of HSV by culture or the detection of viral DNA by PCR. If skin lesions are present, a scraping of the vesicles should be transferred in appropriate viral transport medium on ice to a diagnostic virology laboratory. Other sites from which virus may be isolated include the cerebrospinal fluid (CSF) but rarely, urine, throat, nasopharynx, conjunctivae, and duodenum. The presence of intranuclear inclusions and multinucleated giant cells on a Tzanck prep are indicative of, but not diagnostic for, HSV infection. The application of PCR to lesion scrapings is becoming increasingly valuable for proof of HSV, especially late in the course of vesicular evolution.

In HSV encephalitis, CSF findings are variable but often include a moderate pleocytosis with a predominance of mononuclear cells, elevated protein level, and normal or slightly decreased glucose. The electroencephalogram (EEG) generally localizes spike and slow wave activity to the temporal lobe, even when obtained very early in the disease course. Computed tomography (CT) of the brain may initially be normal or reveal only edema, but as the disease progresses can demonstrate temporal lobe involvement as well. Detection of HSV DNA in the CSF by PCR has become the diagnostic method of choice; however, it must be performed only by a reliable laboratory.

TREATMENT

Herpes labialis

The treatments of choice for herpes labialis are acyclovir, valacyclovir, or famciclovir. Orally administered acyclovir at a dosage of 400 mg five

Table 187.1 Antiviral therapy in herpes simplex virus (HSV) infections

Type of infection	Drug	Route and dosage[a]	Comments
Genital HSV	Acyclovir	200 mg PO 5×/d ×10 d	Preferred route in normal host
Initial episode		5 mg/kg IV q8h ×5 d	Reserved for severe cases
Recurrent episode	Valacyclovir	1 g PO BID ×10 d	
Suppression	Famciclovir	250 mg PO TID ×10 d	
	Acyclovir	200 mg PO 5×/d ×5 d	
	Valacyclovir	500 mg PO BID × 3 d	
	Famciclovir	1 g PO BID × 1 d	
	Acyclovir	400 mg PO BID	
	Valacyclovir	500 mg or 1 g PO qd	
	Famciclovir	250 mg PO BID	
Herpes labialis	Acyclovir	400 mg PO 5×/d × 5 d	
	Valacyclovir	2 g PO BID for 1 d, taken about 12 h apart	
	Famciclovir	1500 mg administered once	
Mucocutaneous HSV in immunocompromised patient	Acyclovir	200–400 mg PO 5×/d ×10 d	
		5–10 mg/kg IV q8h ×7–10 d	
	Valacyclovir	500 mg BID PO	
	Famciclovir	500 mg TID PO	
HSV encephalitis	Acyclovir	10–15 mg/kg IV q8h ×14–21 d	
Neonatal HSV	Acyclovir	20 mg/kg IV q8h ×14–21 d	
Suppression		250 mg/m^2 q8h × 6 mo	
Herpetic conjunctivitis	Trifluridine	1 drop q2h while awake × 7–14 d	Alternative: vidarabine ointment

[a] The dosages are for adults with normal renal function unless otherwise noted.

Adapted from Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep.* 2010;59(RR-12):1–110.

times daily for 5 days reduces the duration of pain and time to the loss of crusts by about one-third, but only if treatment is started during the prodromal or erythematous stage of recurrent infection. Similar benefit is achieved with valacyclovir (2 g twice daily for 1 day, taken about 12 hours apart). Clinical benefit is achieved only if therapy is initiated very early after recurrence. Recently, 1-day therapy with famciclovir was approved by the US Food and Drug Administration. When administered during prodrome, 1500 mg administered once accelerates healing.

Topical therapies provide little benefit in the management of herpes labialis. Although these therapies are licensed, this author does not recommend their use. Similarly, data do not support the use of long-term suppressive treatment with acyclovir for the prevention of herpes labialis.

Genital herpes

The treatments of choice include acyclovir (oral or intravenous), valacyclovir (oral), or famciclovir (oral). Although topical acyclovir is approved for treatment of genital herpes, it is not recommended. Treatment of primary genital herpes in the normal host decreases the duration of symptoms, viral shedding, and time to healing of lesions (Table 187.1). However, neither systemic nor topical treatment of primary HSV lesions reduces the frequency or severity of recurrences. Episodic administration of oral or topical acyclovir for the treatment of recurrent genital HSV lesions provides only a modest benefit, with duration of lesions being shortened at most by 1 to 2 days. However, daily administration of oral acyclovir, valacyclovir, or famciclovir can effectively suppress recurrences of genital herpes in 60% to 90% of patients. Importantly, suppressive therapy does not totally prevent reactivation; thus, transmission can occur, albeit less frequently. Treatment should be interrupted approximately yearly to reassess the need for continued suppression.

Both valacyclovir and famciclovir are now licensed for the treatment and suppression of genital HSV. There is a pharmacokinetic advantage with these medications. For recurrent infection, valacyclovir is usually administered at 500 mg twice daily for 3 days, and famciclovir is administered at 1 g twice daily for 1 day.

The transmission of genital HSV infection can be decreased by administration of valacyclovir (500 mg once daily) to the infected partner.

Mucocutaneous HSV infections in immunocompromised patients

In immunocompromised patients, the three aforementioned antiviral drugs all diminish the duration of viral shedding, as well as substantially accelerate the time to cessation of pain and to total healing of HSV lesions. In addition, prophylactic administration of these drugs to such patients significantly reduces the incidence of symptomatic HSV infection (see Table 187.1).

Herpes simplex keratoconjunctivitis

Idoxuridine (Stoxil), trifluridine (Viroptic), and vidarabine ophthalmic drops all are effective and licensed for treatment of HSV keratitis. Trifluridine is the most efficacious and the easiest to administer, and as such is the drug of choice for HSV ocular disease (see Table 187.1).

Herpes simplex encephalitis

In patients with HSV encephalitis, acyclovir administration greatly reduces mortality and has a modest impact on morbidity. Dosage and length of therapy are shown in Table 187.1. Outcome is more favorable when therapy is instituted early in the disease course.

Neonatal HSV infections

Intravenous acyclovir is the drug of choice in the treatment of neonatal HSV infection (see Table 187.1). Therapy is most efficacious if instituted early in the course of illness. Because of the exceptional safety profile of acyclovir, an intravenous dosage of 60 mg/kg/day divided every 8 hours should be given. Duration of therapy is 14 to 21 days. Suppressive therapy with acyclovir is indicated after completion of intravenous therapy. The dosage is 250 mg/m^2 every 8 hours for 6 months.

Infants with ocular involvement caused by HSV should receive topical antiviral medication in addition to parenteral therapy. Trifluridine is the treatment of choice for ocular HSV infection in the neonate (see Table 187.1).

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188. Human herpesviruses 6, 7, 8

Ruth M. Greenblatt

Human herpesviruses (HHV) 6, 7, and 8 are capsid-enclosed DNA viruses that produce lytic and latent infection of lymphocytes and other cell types. Reactivation of latent infection occurs intermittently, with replication of virus in tissues and shedding in various secretions. HHV-6, HHV-7, and HHV-8 constitute a diverse group in terms of their biology, pathogenesis, and the diseases they produce; HHV-6 and HHV-7 are able to infect a broader array of cell types than HHV-8. Clinical presentation ranges from asymptomatic infection or mild illnesses, such as febrile exanthems, in the case of HHV-6 and HHV-7, extending to life-threatening disease in the immune compromised host. Selected clinical and virologic characteristics are summarized in Table 188.1 and limited antiviral treatment information is presented in Table 188.2.

HUMAN HERPESVIRUS 6

HHV-6 is a member of the *Betaherpesvirinae* group of the genus *Roseolovirus*, of which cytomegalovirus (CMV) was the only previously recognized human pathogen. HHV-6 consists of two related variants, HHV-6A and HHV-6B, that have 90% DNA homology and cannot be distinguished by serologic tests, but have distinctive molecular, cell culture, and clinical features. Infection is ubiquitous; 70% to 100% of adults worldwide have serologic evidence of HHV-6 infection. Infection follows a 2-week incubation period and most often occurs between the ages of 6 and 15 months.

Shedding and tissue tropism

HHV-6B is shed in saliva, which is an important vehicle of transmission (perhaps most often from mother to child). The virus is not found in breast milk. After primary infection, viral replication occurs in salivary glands and recurs during periodic episodes of reactivation and shedding, which decrease in frequency over time. Both variants are lymphotropic; primarily infect CD4-positive T cells; the A variant also infects CD8 cells. HHV-6 infects other lymphocytes, monocytes, macrophages, and epithelial and endothelial cells utilizing the CD46 molecule as its receptor. The virus is highly neurotropic with a central nervous system (CNS) site of latency. HHV-6 is unique among human herpesviruses in that its DNA can integrate into specific locations on chromosomes 1, 17, and 22. HHV-6 DNA integration into germ cells can result in inheritance of HHV-6 genetic elements and when it occurs, is associated with persistent high-level viremia. High-level viremia suggestive of chromosomal integration is uncommon but not rare; it was reported in 3% of blood donors in a recent British study but the prevalence may vary significantly by population group. One percent of newborns have congenital HHV-6 infection, the majority of instances of which occur in the setting of maternal chromosomal integration. Unlike CMV, transplacental transmission of HHV-6 only rarely results in clinical sequelae.

Infection in immunocompetent hosts

When detected, primary infection with HHV-6 is associated with fever $\geq 40^{\circ}C$, lasts 3 to 7 days, and then suddenly resolves. Infection with HHV-6B is characterized by fever followed by a maculopapular rash (exanthema subitum [ES] or roseola infantum or sixth disease) on the trunk, face, and neck; HHV-6 is a leading cause of skin rash and fever in children under 2 years of age. Malaise, otitis media, and gastrointestinal and respiratory symptoms are also common. It is estimated that HHV-6 may account for 20% to 25% of all emergency room visits for children 6 to 12 months of age and one-third of all febrile seizures in children <2 years of age in the United States. Encephalomeningitis is a rare complication; both HHV-6 variants can be recovered from cerebrospinal fluid (CSF), though the "A" variant is thought to be more neurotropic.

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Table 188.1 Clinical features of human herpesviruses 6, 7, and 8

Virus	Age of first infection	Sites of shedding	Unique attribute	Clinical features of primary infection	Clinical features of infection in compromised hosts
HHV-6A	Most before 2 years	Serum, CSF	Chromosomal integration and germ cell transmission occurs	Not known	? pneumonitis, ? disseminated infections
HHV-6B	Most before 2 years, congenital and perinatal transmission is possible	Saliva, cervical secretions, stool, serum	Chromosomal integration and germ cell transmission occurs and is associated with persistent high-grade viremia	Pityriasis rosea, exanthem subitum, fever, febrile seizures, respiratory and GI symptoms	Pneumonitis, hepatitis, hemorrhagic cystitis, colitis, bronchiolitis obliterans, encephalitis, allograft rejection, suppression of bone marrow engraftment, retinitis, role in GVHD, optic neuritis, hemophagocytosis, dissemination, rash
HHV-7	Early childhood	Saliva, breast milk		Less frequent cause of exanthem subitum and other exanthems	Unknown
HHV-8	Childhood to puberty	Saliva, semen (rare)	Cancer-producing virus	Most often asymptomatic, febrile illness of infancy	Kaposi's sarcoma, multicentric Castleman's disease, body cavity-based lymphoma

Abbreviations: CSF = cerebrospinal fluid; GI = gastrointestinal; GVHD = graft-versus-host disease.

Table 188.2 Summary of in-vivo and in-vitro information regarding antiviral treatment of HHV-6, HHV-7, and HHV-8

Virus	Treatment indication	Drug	Comment
HHV-6B	Treatment of documented (direct detection of virus) bone marrow, lung, brain infection in transplant recipient	Ganciclovir, foscarnet, cidofovir	No proven efficacy in clinical trials, CMV dosing presumed to be required
HHV-7	None known	None known	
HHV-8	KS, MCD in AIDS patient KS in solid organ transplant recipient	1. cART regimen 2. Cidofovir, or ganciclovir, or foscarnet Withdraw as much immunosuppressive therapy as possible	Potent antiretroviral combination treatment CMV dosing, duration not known Proven efficacy Presumed CMV dosing, no clinical data, theoretical efficacy at best

Abbreviations: CMV = cytomegalovirus; KS = Kaposi's sarcoma; MCD = multicentric Castleman's disease; AIDS = acquired immunodeficiency syndrome; cART = complete antiretroviral therapy.

As in many other viral illnesses, the severe complications are more common in adults with primary infection; these include a mononucleosis-like syndrome, hepatitis, hemophagocytosis, thrombocytopenia, encephalitis, and/or fatal dissemination. HHV-6 may influence the occurrence of demyelinating diseases such as multiple sclerosis and Guillain–Barré syndrome, but a causal role has not been proven and research findings are often contradictory.

Infection in immunocompromised hosts

Active HHV-6B replication is frequently detected in immunocompromised hosts, such as bone marrow and solid organ transplant recipients. Most infections are identified 2 to 4 weeks post-transplantation. Serious infections can occur with a pattern that mimics CMV, including pneumonitis, colitis, hemorrhagic cystitis, encephalitis (most often involving the temporal lobe), hepatitis, bone marrow suppression, and graft-versus-host disease. HHV-6 contributes to the frequent occurrence of skin rash after bone marrow grafting and lesion histology can demonstrate lymphocytic basophilic inclusions and viral DNA. HHV-6 is associated with bronchiolitis obliterans among lung transplant recipients, and linked with eventual graft failure. HHV-6 activity may occur concurrently with CMV or HHV-7, making distinction of the clinical manifestations due to each virus difficult. Viremia may be particularly common after cord blood grafts. The intensity of HHV-6 viremia is related to the

occurrence of clinical manifestations and graft-versus-host disease in allogeneic bone marrow transplant recipients. Similarly, extent of viremia is linked to graft failure after solid organ transplantation.

HHV-6 can function as an opportunistic pathogen in acquired immunodeficiency syndrome (AIDS) patients with reported cases of encephalitis, pneumonitis, and retinitis. HHV-6 or-7 reactivation has been associated with DRESS syndrome (drug reaction with eosinophilia and systemic symptoms) which may respond to antiherpes treatment, though definitive studies have not been performed. As is the case for CMV, combination antiretroviral therapy (cART) appears to have reduced the incidence of serious HHV-6 infections in AIDS.

Detection of infection

The very high prevalence of infection, intermittent reactivation, and the occurrence of chromosomal integration must be considered in the interpretation of diagnostic tests for HHV-6; detection of virus does not necessarily indicate disease. Viral culture from peripheral blood mononuclear cells may be the gold standard for viral detection but it is not routinely available. Detection of HHV-6 DNA in either cellular or acellular specimens using polymerase chain reaction (PCR) is suggestive of active HHV-6 replication and occurs in children with ES and a variety of immunocompromised individuals. In classic childhood ES, etiologic diagnosis is seldom necessary. Immunohistochemistry can detect cells with active infection in biopsy or cytologic specimens. Serologic tests include indirect immunofluorescence assay (IFA), anticomplement immunofluorescence assay, competitive radioimmunoassay, neutralization, and enzyme immunoassays (EIA). The EIA tests are more easily quantified and are less subjective. Primary infection can be demonstrated by serologic conversion in children and adults or with the presence of immunoglobulin (Ig)M in children. The presence of IgM in adults may indicate either primary infection or reactivation from latency. A 4-fold increase in serum IgG by IFA or a 1.6-fold increase by EIA indicates recent infection.

Treatment of HHV-6 infection

In culture, gancyclovir, cidofovir, and foscarnet are active against both HHV-6 variants. Case reports describe clinical responses to gancyclovir, cidofovir, or foscarnet in transplant recipients with encephalitis, though treatment failures are also reported. Treatment is recommended for virologically confirmed infection in the setting of post-transplant bone marrow suppression, encephalitis, or pneumonitis. Analogous to CMV, bone marrow transplant recipients who receive high-dose acyclovir, despite lack of efficacy in vitro, appear to have fewer HHV-6 infections. Reduction in the intensity of immunosuppression is recommended when possible. Immunotherapies, such as transfer of HHV-6-specific T cells may, in the future, prove useful in life-threatening infections among bone marrow transplant recipients.

HUMAN HERPESVIRUS 7

HHV-7 is similar in terms of morphology and genome sequence to HHV-6; the viruses resemble each other more than CMV. HHV-7 is also a member of the *Betaherpesvirinae* group, genus *Roseolovirus*, infects CD4-positive T lymphocytes, and produces latent infection. Primary infection occurs during childhood, and is probably most often asymptomatic. Some evidence indicates that asymmetric periflexural exanthem (APE), a unilateral maculopapular eruption mostly of children, is associated with HHV-7 infection. Cross-reactivity between HHV-6 and HHV-7 in some assay systems may have complicated early studies of the viruses. Infection is ubiquitous; serum antibodies can be identified in >85% of adults. Salivary shedding occurs even more frequently than in the case of HHV-6 (can be found in saliva from 75% of adults) and exposure to oral secretions is likely the major mode of transmission. The virus can be detected in breast milk, CSF, cervical tissue, and peripheral blood lymphocytes. Congenital infection is rare, if it occurs at all.

HHV-7 infrequently causes ES; far less often than does HHV-6B. Other febrile illnesses of childhood have been reported in association with development of serum antibodies to HHV-7. The detection of HHV-7 DNA in blood from transplant recipients is reported variably, and the role of this virus in post-transplant morbidity is not clear. While HHV-7-related disease in transplant recipients is considered rare, the virus has been implicated in fever, rash, bone marrow suppression, and organ involvement. Few research data are available to guide treatment, but reduction in immune suppression, or foscarnet or cidofovir are recommended for clinically evident disease.

Table 188.3 Clinical characteristics of conditions associated with HHV-8 infection

Condition	Setting	Clinical characteristics
Classic KS	A rare condition seen among elderly men of Mediterranean or Ashkenazi Jewish descent. No known environmental etiologic precipitator	Indolent condition that typically involves lower extremities, slowly progressive, primarily cutaneous, often not cause of death
Endemic KS	A relatively common cause of cancer (or a cancer-like condition) in children and adults residing in central Africa. No known environmental etiologic precipitator	Variable from mild (like classic) to locally aggressive disease
Iatrogenic KS	Seen in solid organ transplant recipients and other recipients of medication-induced immunologic suppression	Aggressive condition that often improves or resolves with withdrawal of immunosuppressive therapy, and may recur with reinstitution
AIDS KS	AIDS-defining illness in HIV-infected patients, most often homosexual men (in developed countries). One of the most common HIV-associated malignancies, the incidence is falling	Often aggressive condition that progressively involves metastatic mucosal or cutaneous foci (often the mouth, face, and genitalia), and then may extend to lymphatic, pulmonary, and gastrointestinal tract disease. Paradoxical worsening may occur after immune reconstitution with antiretroviral therapy
Multicentric Castleman's disease (MCD)	HHV-8-associated MCD is a distinct entity characterized by systemic inflammation, episodic flares that are potentially fatal. Incidence has not declined in era of effective HIV treatment	Intermittent symptoms of systemic inflammation: fever, fatigue, loss of appetite, cough, nausea, diarrhea, and edema. Lymphadenopathy and splenomegaly are common. Flares are associated with anemia and thrombocytopenia, elevated C-reactive protein, hyponatremia, and hypoalbuminemia. May progress to non-Hodgkin's lymphoma
Body cavity-based lymphoma	Most common in AIDS patients, most cases reported in men, but occurs in women. Has been reported in recipients of solid organ transplants	Aggressive lymphoma which typically presents with ascites or pleural effusion and no solid tumor mass

HUMAN HERPESVIRUS 8

HHV-8 is a member of the *Gammaherpesvirinae* group with Epstein–Barr virus (EBV). In central Africa, a region in which Kaposi's sarcoma (KS) was common before the human immunodeficiency virus (HIV) epidemic, HHV-8 infection is a common cause of febrile illness in infants and may be associated with respiratory symptoms in some cases. In these areas the prevalence of HHV-8 infection increases with age, reaching 39% to 48% in adolescence. In immunocompromised hosts, particularly those with loss of T-cell function, primary HHV-8 infection may be associated with the transient development of KS and related conditions. In the absence of deficiencies of T-lymphocyte function, HHV-8 infection is clinically unremarkable. HHV-8 infects a variety of cell types, including B lymphocytes and vascular endothelial cells. Lytic and latent infections occur; relatively few viral gene products are expressed in latently infected cells. Lytic infection is characterized by the transcription of a wide array of viral genes, producing gene products with immunomodulatory functions that participate in the pathogenesis of HHV-8-related malignancies. A viral version of interleukin-6 (*v*IL-6) appears to play a particularly important role in the inflammatory nature of HHV-8-related malignancies. The clinical characteristics of conditions associated with HHV-8 infection are summarized in Table 188.3.

Kaposi's sarcoma

Moritz Kaposi first described classic KS in 1872 as a rare skin tumor seen primarily in elderly men of Mediterranean or Ashkenazi Jewish origin. While KS is somewhat unique as a malignancy by involving multiple types of cells, HHV-8 infection of its characteristic spindle cell, and a clear relationship between intensity of HHV-8 replication and risk of KS supports the conclusion that the virus is causative. The occurrence of KS is associated with impaired natural killer lymphocyte responses characterized by altered surface receptor expression; resolution of this immune impairment can result in clinical regression. Early KS lesions appear as faint red-violet or brown macules that increase in size, become papular, and can ulcerate. Typically, untreated KS evolves from skin to mucosal, lymphatics (often with lymphedema), and then internal organs. Genital and/or oral lesions are not uncommon.

The endemic or African form of KS was recognized in the early part of this century, and is confined to equatorial areas where, until the AIDS era, it accounted for up to 10% of all malignancies. In a 1990 study, the risk of KS was at least 20 000 times greater among AIDS patients than the general population and 300 times greater among AIDS patients than other immunosuppressed groups. AIDS KS is more prevalent among men who have sex with men than in other HIV exposure groups (such as injection drug users). AIDS KS has a variable course, which can range from isolated skin lesions to more aggressive disease with rapid dissemination. An immune reconstitution phenomenon, as occurs paradoxically with AIDS opportunistic infections, occurs with KS and is characterized by the onset of KS or worsening of existing KS lesions after initiation of cART. Generally cART can be continued through immune reconstitutional KS, but fatal disease has been reported, particularly in resource-poor settings. The incidence of KS among HIV-infected persons has greatly decreased among recipients of cART. An iatrogenic form of KS occurs primarily in solid organ transplant recipients and tends to be an aggressive illness with rapid dissemination, unless immunosuppressive therapies are discontinued or modified.

Multicentric Castleman's disease (MCD and MCD-associated plasmablastic lymphoma)

MCD is a rare lymphoproliferative condition involving B cells characterized by multicentric angiofollicular hyperplasia associated with fever, adenopathy, and splenomegaly. Several clinical variations exist; HHV-8-related MCD appears to be distinct from forms that are not linked to the virus, and almost always occurs with HIV infection. Contrasting with KS, the occurrence of MCD has not declined in the present era of potent antiretroviral treatment. HHV-8 DNA sequences are found in the polyclonal plasmacytoid cells within lymph nodes that are diagnostic for HHV-8-associated MCD. HHV-8 sequences of patients with MCD may have unique microRNA signatures which may contribute to viral pathogenesis. Survival with MCD is variable and the clinical course is remissive with severe flares that are associated with intensity of HHV-8 viremia. No standard therapy exists for HHV-8 MCD, though responses to antiretroviral and antiherpes drugs, cytotoxic chemotherapies, anti-CD20 monoclonal antibody (rituximab), and/or glucocorticoids do occur. MCD can transition to a large B-cell non-Hodgkin's lymphoma.

Primary effusion lymphomas (PEL) or body cavity-based lymphoma (BCBL)

This is a rare non-Hodgkin's lymphoma of B-cell origin occurring among persons with marked immunologic dysfunction, most commonly due to HIV infection. PEL presents as a neoplastic effusion of the pleural, pericardial, and peritoneal cavities in the absence of a solid tumor mass. PEL diagnoses require typical body cavity malignant effusions and the presence of HHV-8 and EBV; no other lymphomatous effusion expresses HHV-8. Solid lymphomas have been reported prior to and subsequent to PEL. In general, prognosis of PEL is poor, though some HIV-infected patients demonstrate improvement after initiation of cART. In addition, noncurative but significant responses have been reported after the intracavitary administration of cidofovir, an antiviral drug with broad efficacy.

Detection of infection

Standardized methods for detection of HHV-8 infections have not yet been established. Prevalence rates depend on testing method as well as the population being evaluated. DNA detection techniques such as PCR may be of limited value in studying the epidemiology of HHV-8 since infected tissue must be directly sampled and the technique is cumbersome and sensitive to laboratory error. Indirect IFA and EIA have been developed for the detection of antibodies to lytic and latent HHV-8 antigens. Antibody assays range from 80% to 98% sensitivity in KS patients (when compared with PCR). The pattern of reactivity to lytic versus latent antigens does not appear to impart much clinical information.

Epidemiology and modes of transmission

HHV-8 antibodies are highly prevalent among patients with KS and in homosexual men. The prevalence of serologic reactivity is also relatively high among persons in regions where KS was endemic prior to the AIDS epidemic. The prevalence of HHV-8 infections in various populations is summarized in Table 188.4. As is true of many herpes simplex virus infections and other sexually transmitted diseases (STDs), prevalence rates

Table 188.4 Estimated prevalence of HHV-8 infection in various populations

Population	% Prevalence[a]
Homosexual men in industrialized countries	21–67
Injection drug users in industrialized countries	5–50
HIV-uninfected heterosexual patients	<1–64
US women with HIV infection	4–15
Solid organ donors	4–10

[a] Prevalence rates depend on type of diagnostic test, are higher with lytic antigen.

tend to increase with age and incidence peaks during years of greatest sexual activity.

HHV-8 is likely transmitted via oral contact with infected saliva in a manner analogous to that of EBV. Among body fluids, HHV-8 is most often shed in oral sections. HHV-8 has a far lower prevalence rate and later age of infection than occurs with HHV-6, HHV-7, and EBV, infections in which saliva is also a likely vehicle for transmission. HHV-8 can also be transmitted via blood products and tissue grafts.

Transmission via allografts and blood products

HHV-8 is transmitted to 25% to 33% of previously uninfected recipients of solid organ grafts taken from a HHV-8-seropositive donor. While KS is a relatively common form of cancer among solid organ transplant recipients, it occurs infrequently. BCBL and MCD have also been reported in allograft recipients. Since HHV-8 can be identified in blood from healthy donors, transmission from blood products is possible but does not appear to occur commonly.

Treatment of HHV-8 infection

At present treatment of HHV-8 infection in immunosuppressed patients, in the absence of disease, is not generally recommended but may be considered in regions of high prevalence. Traditional treatment for KS, MCD, and BCBL includes reduction or elimination of any immunosuppressive treatment, chemotherapy, and/or radiation therapy. The clinical course of AIDS KS has improved greatly in the years since the introduction of cART. Ganciclovir, cidofovir, and foscarnet effectively inhibit HHV-8 and may be used with modifications of immune suppression. Systemic administration of cidofovir, foscarnet, ganciclovir, and α-interferon can induce response or remission in patients with AIDS KS, often in conjunction with antiretroviral therapy and/or chemotherapy. Foscarnet has been successfully used to treat MCD. Foscarnet or ganciclovir may be effective in preventing KS among HIV-infected men, though this approach has been largely displaced by cART. Dosage of the antiviral drugs is based on anti-CMV therapy; specific dosing recommendations for HHV-8 are not available.

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189. Influenza

Ramin Sedaghat Herati and Harvey M. Friedman

Influenza infections have caused significant morbidity and mortality throughout recorded human history. Each year, seasonal influenza is estimated to cause around 500 000 excess deaths worldwide. At least 32 pandemics have occurred since 1580 in addition to the seasonal waves of influenza infection. In 1918, a particularly severe pandemic, dubbed the "Spanish flu," led to the rapid spread of influenza and resulted in at least 20 million deaths worldwide. Recently, the possibility of a worldwide pandemic due to pathogenic avian influenza viruses has become of great concern. Significant resources worldwide have been dedicated to the detection and containment of influenza outbreaks and the development of response plans to influenza epidemics at international, national, and local levels.

INFLUENZA VIRAL STRUCTURE

Influenza viruses are enveloped, single-stranded, negative-sense RNA viruses in the family Orthomyxoviridae, which include the genera *Influenzavirus* types A, B, and C. Influenza tends to be spherical and 80 to 120 nm in diameter. Influenza A and B viruses cause the majority of human infections with influenza, whereas influenza C virus causes only sporadic upper respiratory infections. Influenza A viruses can cause infections in birds as well as humans, swine, and other mammals.

Influenza virus has an envelope composed of a lipid bilayer, with a layer of matrix protein on the inner surface and spike-like surface projections of glycoproteins on the outer surface. These glycoproteins include hemagglutinin and neuraminidase. Hemagglutinin is responsible for binding to cells of the respiratory tract expressing sialic acid. Once phagocytosed, hemagglutinin then fuses with the endosome membrane and releases viral ribonucleoproteins into the cytoplasm, which leads to viral replication. In contrast, neuraminidase primarily functions in the last stage of cellular infection by enzymatic cleavage of sialic acid and release of mature virions from the cell surface. Within the envelope of influenza A and B are eight segments of viral RNA encoding polymerase proteins A, B1, and B2, hemagglutinin, neuraminidase, matrix proteins M1 and M2, nucleocapsid protein, and nonstructural proteins NS1 and NS2.

EPIDEMIOLOGY

Antigenic shift and drift

One of the most remarkable features of influenza virus is the frequency of its antigenic change. Therefore, immunity to the influenza viruses is often incomplete. Antigenic shift and antigenic drift are two types of antigenic variation that have been described, principally involving the two external glycoproteins of the virus, hemagglutinin and neuraminidase. Antigenic shift is less common but more dramatic and results from genetic reassortments between human and animal viral strains. Antigenic drift, on the other hand, is produced by single point mutations in the hemagglutinin or neuraminidase genes that result in changes of one or a few amino acids. Antigenic drift is primarily seen in influenza A viruses but can be seen in influenza B viruses as well. Three subtypes of hemagglutinin, H1 (variants H0, H1, Hsw1), H2, and H3, and two subtypes of neuraminidase, N1 and N2, are recognized among human influenza A viruses. Only a few strains of influenza A or B virus tend to dominate during each annual influenza season.

Antigenic shifts can produce immunologically novel strains of influenza A that herald the epidemics and worldwide pandemics. In 2009, infections with a novel H1N1 virus, thought to derive from reassortment of avian, swine, and human influenza viruses, resulted in a pandemic. First recognized as a major threat in April 2009, the virus spread rapidly and may have resulted in

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over 300 000 deaths within 15 months worldwide. Another influenza virus, avian H5N1, is under close surveillance due to its pandemic potential. It was originally thought to be endemic in many wild bird populations and not pathogenic in humans. However, beginning in 1997, approximately 50 cases of laboratory-confirmed human H5N1 infection have been reported annually. Unfortunately, humans have little pre-existing immunity to H5N1 and an overall case-fatality rate of 60% has been observed. Isolated human-to-human transmission has been observed, but the vast majority of cases have occurred after close contact with infected birds.

The World Health Organization (WHO) is currently leading a global effort to detect and characterize influenza outbreaks before they become pandemics. In 2013, another avian-origin virus, H7N9, was identified in China as a cause of severe respiratory tract infections with numerous case fatalities. In contrast to H5N1, infected birds are asymptomatic and thus environmental surveillance has been challenging. The true incidence and prevalence of H7N9 infections are not yet known.

Transmission

Most influenza infections are acquired through human-to-human transmission of small-particle aerosols. Localized clusters of infection begin rather abruptly, reach a sharp peak in 2 to 3 weeks, and wane in incidence over the subsequent 5 to 6 weeks. Attack rates during such outbreaks can approach 10% to 40%. Although influenza is virtually always active somewhere in the world, seasonal influenza is most common during the winter months. The peak influenza season typically extends from December through April in the Northern Hemisphere. Influenza season is defined by viral isolation, whereas an epidemic is defined by a rise in pneumonia and influenza deaths above the epidemic threshold in the Centers for Disease Control and Prevention (CDC)'s nationwide mortality surveillance system. Although influenza can affect all individuals in a population, severe infections resulting in hospitalization during most influenza seasons generally occur among adults over age 65 and children aged 0 to 4 years.

Immunology

Influenza infection results in activation of the innate and adaptive arms of the immune system. Upon initial infection, innate pattern-recognition receptors including Toll-like receptor 7 (TLR7) "sense" the infection and lead to proinflammatory cytokine production. Dendritic cells acquire and present influenza antigens to T cells, which leads to stimulation of the adaptive immune system. Naïve and memory T cells, including CD4 and CD8 subsets, then mediate a variety of responses including recruitment of additional immune effectors, direct killing of infected cells, and B-cell help. Neutralizing antibodies are produced by B cells and block the ability of free influenza virions from infecting additional cells. After a successful immune response, tissue repair takes place and inflammation returns to baseline, along with the death or egress of most of the responding immune cells. Memory T and B cells are established which respond much more quickly to subsequent infections. For many decades, neutralizing antibody titers have been used as a strain-specific correlate of protection against future infections. A titer of 1:40 or higher indicates that an individual is likely protected. However, this correlate has limitations. Some with low titers are resistant to infection in experimental challenge models, whereas some with very high titers become infected. Work to develop better correlates of protection is ongoing.

CLINICAL MANIFESTATIONS

Uncomplicated influenza

Classic influenza is characterized by the abrupt onset of symptoms including fever, headaches, and myalgias after a short incubation period. Systemic symptoms predominate initially, including chills or rigors, malaise, and anorexia. Severe intraocular muscle pain can often be elicited on lateral gaze. Calf muscle myalgia may be particularly prominent in children. The systemic symptoms usually persist for approximately 7 days and then wane. Respiratory symptoms, such as dry cough and nasal discharge, emerge early during the illness and begin to dominate the clinical presentation as fever resolves. Cough is the most common and troublesome of these later complaints and can take several weeks to resolve.

Complications of influenza

The complications of influenza can be classified as pulmonary and nonpulmonary and result either from progression of the viral process itself or from secondary bacterial infections. Influenza can be associated with a primary influenza viral

Table 189.1 Pulmonary complications of influenza

Feature	Primary viral pneumonia	Secondary bacterial pneumonia
Setting	Cardiovascular disease Pregnancy Young adults (in large outbreaks)	Age >65 years Chronic pulmonary, cardiac, or metabolic disease
History	Rapid progression after typical onset	Biphasic illness, with worsening after clinical improvement
Physical examination	Diffuse crackles	Consolidation
Sputum culture	Normal oral flora	*Streptococcus pneumoniae* *Staphylococcus aureus* *Haemophilus influenzae*
Isolation of influenza virus	Yes	No
Chest radiograph	Diffuse bilateral interstitial disease	Consolidation
Response to antibiotics	No	Yes
Mortality	Variable, high during some pandemics	Variable, generally low

pneumonia and/or a secondary bacterial pneumonia (Table 189.1). Nonpulmonary complications of influenza occur less often and are most prevalent during large outbreaks. These include myositis (more common with influenza B infection), myocarditis, pericarditis, transverse myelitis, encephalitis, and Guillain–Barré syndrome. A toxic shock-like syndrome has occurred in previously healthy children and adults during outbreaks of influenza A or B. This syndrome has been attributed to the effects of the viral infection on the colonization and replication characteristics of toxin-producing staphylococci. Reye's syndrome has also been described in children treated with aspirin during influenza outbreaks. The major causes of death are pneumonia and exacerbation of chronic cardiopulmonary conditions. Of those who die, 80% to 90% are age 65 years or older.

H5N1 infection

Most cases of H5N1 have occurred in healthy young adults, approximately 2 to 4 days after exposure to infected birds. Initial symptoms include high fever and an influenza-like illness. In contrast to infection with human influenza viruses, lower respiratory tract involvement and clinically apparent pneumonia are almost universal. Watery diarrhea may be present before the development of respiratory symptoms. Progression to multiorgan failure, including respiratory failure, renal dysfunction, and cardiac compromise, is common. Atypical presentations, such as encephalopathy, gastroenteritis, and mild respiratory disease, have been reported, but frequencies of such presentations are unknown. Death occurs on average 9 to 10 days after the onset of illness. Asymptomatic infection likely occurs as well, as indicated by antibody screens in populations at risk, but the true incidence is unknown.

DIAGNOSIS

Reverse transcriptase–polymerase chain reaction (RT–PCR) assays are extremely sensitive, specific, and rapid, which has made them the standard for diagnosis. Other rapid assays include immunofluorescence, which requires skilled expertise and has lower sensitivity than RT–PCR. Viral culture is utilized in some areas but takes days to give a result. Serologic tests to measure hemagglutinin neutralizing antibody titers in acute and convalescent sera are not recommended by the CDC for diagnosis due to the delay required to establish the diagnosis. A clinical diagnosis based on fever, headache, myalgias, and cough during influenza season has an accuracy of 60% to 85%. However, influenza cannot be distinguished from other respiratory viruses by symptoms alone, and testing is necessary to know if a patient would benefit from influenza antiviral treatment.

THERAPY

Two classes of antiviral drugs are available for treatment of influenza, including neuraminidase inhibitors (NI) and M2 inhibitors. Zanamivir (Relenza) and oseltamivir (Tamiflu) are two NI approved for treatment of both influenza A and B infection. These agents inhibit neuraminidase activity and prevent viral particle release from infected cells. Zanamivir has poor oral bioavailability and is formulated for oral inhalation using a disk inhaler. Oseltamivir is the ethyl-ester prodrug of the active compound and is well absorbed orally. When given within 48 hours after the onset of symptoms, NI decrease the duration of symptoms by about 1 day. Meta-analyses

indicate a reduction in the incidence of influenza-related complications including pneumonia and bronchitis when administered early during the course of an infection. There are insufficient data as to whether NI are effective treatment of these complications once they occur, but they may have some modest benefit. These agents are generally well tolerated, although zanamivir can cause bronchospasm and respiratory compromise in patients with chronic respiratory diseases. Infection with NI-resistant virus occurs sporadically but likely has only a limited impact on public health. Despite resistance developing during treatment with oseltamivir in up to 25% of individuals, transmission of resistant strains is uncommon. New agents under active development include peramivir (intravenous) and laninamivir (inhaled), which are long-acting NI. They are effective against viruses resistant to oseltamivir and can be administered as a single dose.

The M2 inhibitors, amantadine and rimantadine, are an older class of drugs approved for the treatment of influenza. The M2 inhibitors prevent viral replication by blocking the M2 protein ion channel, thus preventing fusion of the virus and host cell membranes. Both drugs have been shown to reduce the duration of symptoms of clinical influenza and decrease the severity of fever and other symptoms in randomized trials. However, they have been associated with several adverse effects. For example, amantadine causes reversible central nervous system (CNS) toxicities, including insomnia, dizziness, nervousness, and difficulty concentrating, especially in the elderly. Viral resistance to M2 inhibitors has increased over time among influenza A isolates, and their use has not been recommended during recent influenza seasons. These agents are not active against influenza B.

PREVENTION

Vaccine

Vaccination is the mainstay of influenza prevention. Because influenza viruses undergo frequent antigenic alterations, a new vaccine containing antigens predicted to predominate in the upcoming winter epidemic is prepared each year. The CDC, in conjunction with the WHO, tracks influenza activity throughout the world to predict the components of the annual influenza vaccine. The majority of administered vaccines target two strains of influenza A and one strain of influenza B. The inactivated influenza intramuscular vaccine (IIV) is the most commonly administered version and is more immunogenic in adults, whereas the live attenuated intranasal vaccine (LAIV) is less frequently used and is more immunogenic in children. The latter has the potential to produce mild signs and symptoms of influenza infection because it contains live virus.

The protective efficacy of influenza vaccination depends on the similarity between the viruses used in the vaccine and those in circulation, as well as an individual's age and immune status. In healthy adults younger than 65 years, a well-matched vaccine is 70% effective at preventing influenza illness. During poorly matched seasons, efficacy is 30% to 50% among healthy persons. In older adults, efficacy is even lower and the number of vaccine nonresponders increases. However, vaccination is nonetheless effective at decreasing hospitalization, secondary complications, and death due to influenza. A high-dose IIV vaccine has been approved for use in older adults but efficacy data are lacking. A recombinant IIV has been developed which reduces vaccine production time and eliminates the need for eggs. Among human immunodeficiency virus (HIV)-infected individuals, efficacy is lowest among those with low CD4 counts ($\leq 200/mm^3$) and uncontrolled HIV viremia. Individuals receiving antiretroviral therapy probably derive protection from vaccination but not as effectively as HIV-uninfected adults. Regardless, all HIV-infected patients should be vaccinated against influenza to prevent morbidity and mortality. Similarly, solid organ transplant recipients also derive less benefit from vaccination but should be vaccinated annually.

Contraindications to influenza vaccination are few. Individuals who have a severe allergic reaction to influenza vaccination should not be vaccinated, although such cases are exceedingly rare. Individuals with moderate or severe acute febrile illnesses usually should not be vaccinated until their symptoms have abated. However, minor illnesses with or without fever are not a contraindication. The LAIV is approved only for healthy, nonpregnant individuals between ages 2 and 49 years. Although a history of Guillain–Barré syndrome after vaccination and egg allergies are not formal contraindications to vaccination, extra precautions should be taken when vaccinating these individuals. The optimal time for organized vaccination campaigns for persons in high-risk groups is typically October through December. Recommendations for the use of influenza vaccine are listed in Table 189.2.

Table 189.2 Available seasonal influenza vaccines.

Vaccine	Recommended recipients	Contraindications
Inactivated influenza vaccine (IIV)	All individuals over 6 months of age	History of severe allergic reaction to this vaccine[a]
Inactivated influenza vaccine (IIV), high dose	All adults over age 65	History of severe allergic reaction to this vaccine[a]
Live attenuated influenza vaccine (LAIV)	Healthy, nonpregnant, ages 2–49 years	History of severe allergic reaction to this vaccine[a] Immunosuppressed patients, healthcare personnel in close contact with immunosuppressed populations, children with history of asthma or severe wheezing
Recombinant influenza vaccine, trivalent	Adults ages 18–49	History of severe allergic reaction to this vaccine[a]

[a] *Note*: Individuals with active moderate or severe febrile illness usually should not be vaccinated until symptoms have abated. Individuals with a history of egg allergy may receive these vaccines if administered with additional observation and safety measures. History of Guillain–Barré syndrome within 6 months of receipt of an influenza vaccine is considered to be a precaution for future vaccinations.

Adapted from Interim Recommendations: Prevention and Control of Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2013.

Chemoprophylaxis

Chemoprophylaxis is an important adjunct to vaccination. Vaccination-induced neutralizing antibodies to influenza peak at 2 to 3 weeks after vaccination. Thus chemoprophylaxis may be considered in high-risk individuals until immunity develops. Some high-risk individuals, such as organ transplant recipients, have poor responses to vaccination and should be considered for additional protection with chemoprophylaxis. Chemoprophylaxis may also be effective at controlling outbreaks in chronic care settings.

The NI, oseltamivir and zanamivir, are approved for prophylaxis of influenza A and B. When given to healthy adult volunteers, both zanamivir, at a dosage of 10 mg/day over a 4-week period, and oseltamivir, at 75 mg/day over a 6-week period, reduced laboratory-confirmed cases by 82% and 84%, respectively. Both drugs are effective at decreasing secondary spread of influenza. Lower rates of influenza among household contacts of suspected cases of influenza were documented in patients who took zanamivir for 10 days or oseltamivir for 7 days compared with placebo. Amantadine and rimantadine are approved for use as prophylactic agents against influenza A virus, but high rates of drug resistance in circulating influenza strains from recent years have rendered these agents unreliable.

PANDEMIC PREPAREDNESS

The emergence of the avian influenza virus, H5N1, has raised awareness of the possibility of a severe, worldwide influenza pandemic. By some estimates, 30% or more of individuals could become ill during a pandemic. Healthcare systems will likely become overwhelmed, and supplies such as vaccines, antivirals, antibiotics, ventilators, and personal protective equipment will be in short supply. Very likely, there will not be adequate hospital beds to meet healthcare needs. Public health measures, including school closings, travel bans, and individual quarantine, may cause significant social disruption. Absenteeism could exceed 40% and have profound effects on commerce, the economy, and the supply of goods and services.

Proper planning could lessen the effects of a pandemic on society. Preparedness on federal, state, and local levels is crucial, but business and healthcare sectors as well as individuals must also prepare. Hospitals, clinics, and long-term care facilities are encouraged to develop pandemic preparedness plans that include the development of surveillance systems for identifying potential outbreaks, plans for communication (i.e., with public officials, employees, and patients), strategies for dealing with surges in patient volume (including triage, admissions, cohorting, and facility access), and protocols for dealing with sick and exposed employees and the reassignment of worker duties. Other important issues include developing guidelines for the distribution of antivirals, vaccine, and medical supplies that may be limited. Healthcare workers should also encourage patients to develop their own pandemic preparedness plans with their families.

The CDC provides checklists, guidelines, and suggestions for pandemic planning in health care,

family, school, business, and community, state, and local government settings. Given the likely limited availability of vaccine and antiviral medication during the initial waves of a pandemic, the CDC is also promoting nonpharmacologic interventions to limit transmission of the virus. This strategy has been termed *targeted layered containment* and includes isolation of ill persons and voluntary quarantine of household contacts, social distancing measures (i.e., school closure, increased use of telecommuting in the workplace), cancellation of public events and public gatherings (including closure of houses of worship), and individual infection control measures (such as hand hygiene and cough etiquette).

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190. Papillomavirus in oro-genital infection

Lawrence J. Eron

Human papillomaviruses (HPV) cause 10 000 cases of squamous cell carcinoma (SCC) of the cervix each year in the United States, as well as 3700 deaths annually. It is the third most common cancer in women worldwide. The virus also causes genital warts, the most common sexually transmitted disease in the United States with an annual incidence of 5.5 million cases and a prevalence of 20 million infections (Figure 190.1). Peak prevalence of infection occurs during the first 10 years following sexual debut, between 15 and 25 years of age. The National Health and Nutrition Examination Survey (NHANES) study found a 25% prevalence of HPV DNA from vaginal swabs of 20- to 24-year-olds. Because HPV produces persistent infection that in most cases is subclinical (and therefore undetected) and because the virus is easily transmitted via intercourse, 80% of sexually active people are infected during their lifetime.

Rates of transmission differ according to body site: Transmission from penis to cervix is 58.8 cases per 100 patient years; from cervix to penis is 208.8 cases per 100 patient years. Nonpenetrative intercourse transmits HPV from the anus to the scrotum and from the hand to the penis.

GENITAL HPV INFECTION

Of the more than 100 different DNA types of HPV, distinguished on the basis of relatedness of their genomes, 40 infect the genital area. These 40 genital types fall into two groups, distinguished by the type of disease that they produce. The first group, which includes the two most common HPV types, 6 and 11, causes exophytic condylomata, referred to as genital warts (Figure 190.2), as well as low-grade dysplasia of the vulva, vagina, and cervix.

The second group, typified by types 16 and 18, causes SCC as well as high-grade dysplasia of the cervix, vagina, vulva, and penis, which appears as white areas of skin after the application of acetic acid (Figure 190.3). Low-grade dysplasia is referred to as squamous intraepithelial lesions (SIL) grade I, moderate dysplasia as SIL grade II,

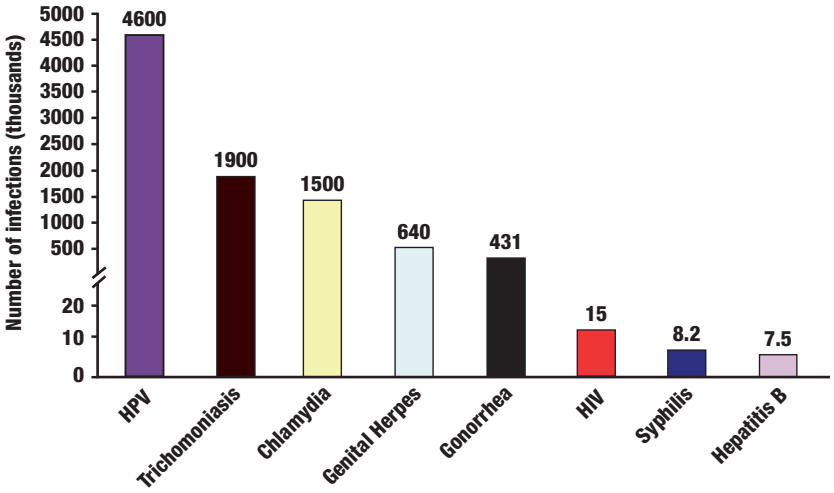

Figure 190.1 Human papillomaviruses (HPV) are the cause of the most common sexually transmitted disease, genital warts, with an annual incidence of 6.2 million and a prevalence of 20 million infections. HIV = human immunodeficiency virus.

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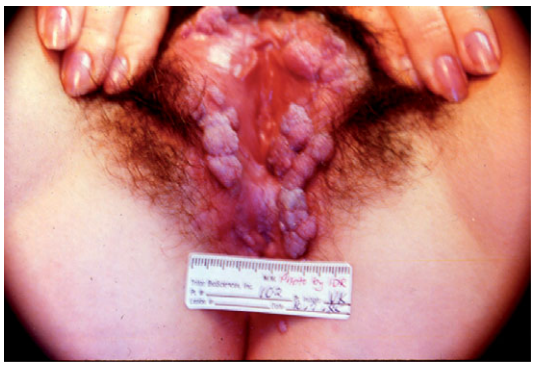

Figure 190.2 Exophytic condylomata, also referred to as genital warts.

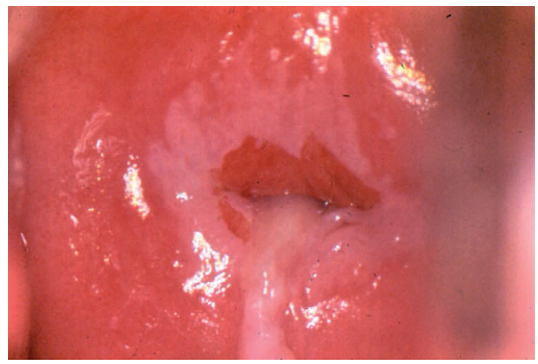

Figure 190.3 High-grade dysplasia of the cervix, vagina, and vulva, appears as white areas after the application of acetic acid.

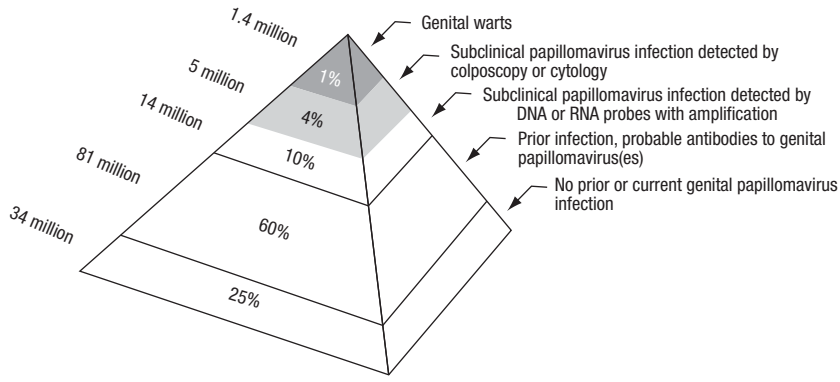

Figure 190.4 Human papillomaviruses may produce asymptomatic infection, subclinical disease, or clinically apparent disease.

and severe dysplasia as SIL grade III. When the cervix is affected, it is termed cervical intraepithelial neoplasia (CIN) with similar grading as SILs. Both groups of HPV viruses may produce asymptomatic infection, subclinical disease, or clinically apparent disease (Figure 190.4).

HPV may also infect the perianal region and the distal rectum above the dentate line. In people infected with human immunodeficiency virus (HIV), HPV may produce small, innocent-appearing ulcers that on biopsy are proven to be SCC. HIV infection, as well as other immunodeficiency states, increases the likelihood that dysplastic lesions of the cervix may evolve into invasive carcinomas. Recurrent or refractory genital warts may be surrogate markers for concomitant infection by HIV, and it is important to test for HIV in patients with HPV infection.

Despite the enormous prevalence, HPV infections in the majority of woman usually resolve in 6 to 12 months. Up to 30% of infections by low-grade HPV types 6 and 11 may be transient. and will not evolve into a malignant state. Although moderate or severe dysplasia may also remit without treatment, women with these lesions should be evaluated by colposcopy to detect the development of carcinoma *in situ*. Women with persistent infection by the oncogenic HPV types are at risk for developing precancerous and cancerous lesions (Figure 190.5).

HPV CAUSES MOST CANCERS OF THE OROPHARYNX

SCC of the oropharynx are associated with either tobacco/alcohol/betel nut use or HPV infection. HPV type 16 and, less commonly, types 18, 31, and 33 are found in 80% of these tumors. In SCC of the tobacco/alcohol/betel nut type, the host p53 and retinoblastoma oncogenes (pRb) are altered by the virus, while p16, a tumor suppressor, is decreased. In contrast, HPV-associated SCC of the oropharynx contains no mutations of the p53 oncogene and expression of pRb is down-regulated, while p16 is upregulated. HPV+

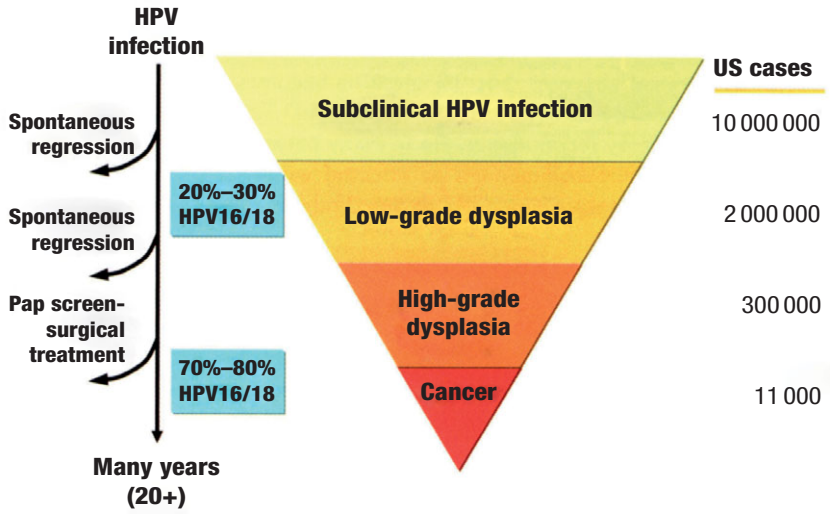

Figure 190.5 Infection by low-grade human papillomavirus (HPV) types may be transient.

tumors arise in the base of the tongue and tonsillar region, and show a much better response to chemotherapy than the other type.

HPV may be transmitted through open-mouthed kissing as well as oral sex. Among men with no oral sexual contacts, the risk of oral HPV transmission varies with the number of kissing partners. While the overwhelming majority of oral HPV infection clears with no intervention, the increasing prevalence of HPV-positive SCC of the oropharynx raises the question as to the benefit of vaccinating boys as well as girls, and at even earlier ages, to prevent oral, as well as sexual, transmission of HPV.

DIAGNOSIS OF HPV INFECTION

The methods used to diagnose HPV infection include cytologic exam via the Pap smear, colposcopy and biopsy, and tests for HPV DNA. Colposcopy of the cervix is useful when there is moderate to severe dysplasia. While HPV DNA testing improves the sensitivity of detecting infection, it lacks specificity, leading to unnecessary colposcopy. HPV DNA testing for primary screening is only recommended for women >30 years old, as younger women very often have self-limited infection.

PRINCIPLES OF THERAPY

The main problem with treatments that extirpate clinically evident disease is that they do not eliminate the underlying HPV infection. The epithelium of healthy-appearing skin around a genital wart may be subclinically infected with HPV up to 1.0 cm from the actual lesion. Because the virus can be shed asymptomatically from apparently normal tissue adjacent to the treated areas, and removal of a wart or dysplastic tissue has not been shown to decrease transmissibility of HPV infection, this shedding may be the mechanism of recurrence following treatment. Because many external genital warts resolve spontaneously and there is little likelihood that the viral reservoir can be eliminated by treatment, the primary goal of treatment of external genital warts is to ameliorate symptoms. Although infections are often asymptomatic and many cases will resolve spontaneously, patients with genital warts often experience depression and a sense of social isolation.

Topical treatments may be either cytotoxic (e.g., podophyllotoxin) or immune-mediated (e.g., imiquimod), both of which may be self-applied. These treatments are recommended for exophytic condylomata. Both types of treatments have similar efficacy (~60%) and recurrence rates (~30%).

For moderate to severe dysplasia of the cervix, vagina, vulva, and the penis cytodestructive procedures such as surgical excision and cryotherapy using liquid nitrogen may be effective.

Both surgical excision and cryotherapy are equally effective (~80%) and have similar relapse rates. Loop electrical excisional procedure (LEEP) and laser ablation of dysplastic tissue of the cervix may be more effective (~90%) than surgical excision or cryotherapy. However, recurrences still occur (~29%). Modulating the immune

response to decrease persistent infection and recurrence rates following treatment is the "holy grail" of HPV treatment.

IMMUNITY TO HPV INFECTION

Although the prevalence of HPV infection is high in young women, only a minority (≤5%) of infected women develop persistent infection and progress to SIL. In most cases, infection may be transient if the individual develops a sufficient immune response to the virus. When infection of the cervix by HPV 16 or 18 becomes persistent, SILs and CIN may evolve to SCC usually several decades later.

Seroconversion following HPV infection occurs in only 60% of infected females and far less frequently in males. HPV may evade the immune system since its replication does not induce cytolysis, necrosis, or viremia. Viral proteins are released only in terminally differentiated epithelial cells, which are programmed for apoptosis and thus evade immune surveillance. Furthermore, HPV inhibits the synthesis of interferon and other cytokines.

Viral, environmental, and host factors play a role in the evolution of infection to the development of SIL/CIN and thence to SCC. Polymorphisms among HPV type 16 variants are associated with longer persistence, more aggressive infection, and higher frequency of SCC. Environmental factors that are associated with progression of SIL to SCC include smoking, long-term oral contraceptive use, high parity, and coinfection with other sexually transmitted diseases (STDs). Host factors associated with increased susceptibility to SCC include genetic polymorphisms in the major histocompatibility complex (MHC) genes which decrease class I MHC cell surface expression and in TAP proteins associated with antigen processing, thereby interfering with host immune response.

THE HPV GENOME AND CARCINOGENESIS

HPV contains a circular, double-stranded DNA genome, consisting of eight structural genes in two distinct regions (Figure 190.6). The early region is composed of six genes (E1–E2 and E4–E7) that control viral replication, transcription, and cell transformation. The late region is composed of two genes (L1 and L2) that encode the viral coat proteins. The "long control region" regulates the expression of these eight genes. In productive infection, as is the case for types 6 and

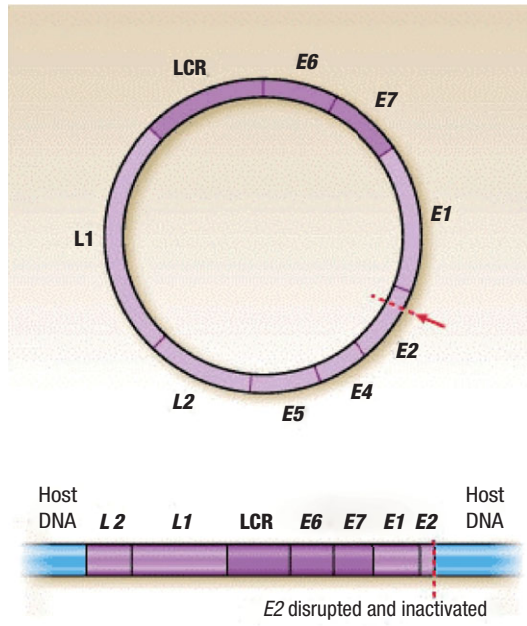

Figure 190.6 Human papillomavirus contains a circular, double-stranded DNA genome, consisting of eight structural genes in two distinct regions.

11, both early and late regions of the virus are transcribed into messenger RNA (mRNA), which codes for proteins essential for viral DNA replication and for coat proteins. Many copies of HPV DNA are produced in each infected cell as circular, extrachromosomal plasmids. The net result is mature infectious virions.

In contrast to productive infection, when type 16 or 18 infects a cell, late genes are not transcribed, viral coat proteins are not synthesized, and no mature virions are produced. Instead the circular HPV genome inserts itself into the host chromosome, disrupting its E2 gene, resulting in the loss of E1 and E2 gene functions (Figure 190.6). Normally E1 and E2 downregulate E6 and E7 expression, but with the loss of E1 and E2 control, E6 and E7 functions are upregulated. The E6 and E7 gene products then alter host oncogenes (p53 and pRb, respectively) that normally control cell growth and differentiation by arresting host cell division in the G1 phase. This normally allows the cell time to repair damaged DNA before progressing to the S (DNA replication) phase. The loss of this repair mechanism results in cell transformation, which renders the host genome susceptible to other carcinogens, such as smoking. The time between initial HPV infection and the development of SCC is between 10 and >20 years.

HPV PREVENTION

Because the viral genome is highly conserved and because HPV uses cellular enzymes to replicate (and thus cannot easily develop resistance in contrast to HIV for example), effective vaccines (Gardasil and Cervarix) have been developed that produce neutralizing antibodies that protect against viral infection. In addition the vaccines also produce cytotoxic CD8 lymphocytes that eliminate nascent HPV-infected cells. The vaccines are ~95% effective in the prevention of infection by HPV types 16 and 18 (which represent 70% of oncogenic HPV types). The Gardasil vaccine is also highly effective (90%) against HPV types 6 and 11 that produce condylomata.

Vaccine administration is recommended for females, ages 11 to 26, to induce immunity prior to the female sexual debut, which in 77% occurs by age 19. Following the sexual debut, the incidence of HPV infection rises to 40% within 2 years and to >50% within 4 years, at which point the vaccine is likely to be ineffective. Widespread vaccination of males would induce herd immunity in females and would prevent oropharyngeal cancers caused by HPV 16 and 18 in 93% and 100% of males, respectively. The vaccines offer durable protection against HPV types contained in the vaccines for at least 5 years, but are woefully underutilized in the United States as compared to Australia where an 80% vaccination rate of young girls has very nearly eliminated condylomata from not only females but also males <21 years of age, indicating herd immunity. Furthermore, high-grade lesions have also decreased in girls <18 years old.

In addition to vaccines, the most cost-effective strategy for reducing HPV infection is the consistent use of condoms. In a well-designed and executed study, condoms reduced the incidence of genital HPV infection from 89.3 per 100 patient-years to 37.8. In those women whose partners used condoms 100% of the time, there were no cervical SILs observed in 32.1 patient-years, whereas 14 SILs were detected in 96.8 patient-years among women whose partners used condoms less than 100% of the time.

Because the HPV genome contains two oncogenes, E6 and E7, that are involved in the production of SCC, vaccines against the products of these genes could be used theoretically to prevent or treat cervical cancer. While in animals such a vaccine can protect against challenge with tumors expressing E6 and E7 antigens, no such results have been reported in humans.

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191. Acute and chronic parvovirus infection

Neal S. Young

Parvoviruses are small viruses with unenveloped icosahedral capsids that contain a single-stranded DNA genome. These physical properties contribute to viral resistance to heat, solvents, and extreme chemical conditions. Because of their limited genome, parvoviral propagation depends on infection of mitotically active cells. B19 parvovirus is the only member of the Parvoviridae family known to cause diseases in humans (although other parvoviruses recently have been isolated from human blood and tissue, their pathogenicity remains uncertain). In the taxonomy of the parvovirus family, B19 and closely related simian parvoviruses constitute the *Erythrovirus* genus, separated from autonomous animal parvoviruses, dependoviruses (which require coinfection with a second virus for efficient propagation in cell culture), and insect parvoviruses called densoviruses.

B19 parvovirus has a peculiar and extreme tropism for human erythroid progenitor cells, which are responsible for the generation of circulating erythrocytes. In tissue culture, B19 has been propagated in hematopoietic cells: bone marrow, fetal liver, peripheral blood, and (rather inefficiently) in a few leukemic cell lines. B19 viral DNA replication in patients has been detected in blood and marrow. Specificity for erythroid cells follows from the cellular receptor for the virus, globoside or P antigen, a tetrahexose ceramide present on erythroid cells, megakaryocytes, endothelial cells, and some placental cell types, as well as fetal liver and heart. Parvovirus infection is terminated by host production of neutralizing antibodies. Failure to produce neutralizing antibodies can result in persistent infection. Cellular immune responses to parvoviruses have been measured and some CD4 and CD8 T-cell epitopes defined.

B19 DISEASES

Serologic studies have shown that more than half of the adult population has antibodies to B19 parvovirus; although most infection occurs during childhood, the seropositivity rate continues to rise with age. Probably the majority of infections are asymptomatic. Reliable diagnostic assays are now widely available. The presence of immunoglobulin G (IgG) to virus only signifies past infection. Immunoglobulin M (IgM) or virus DNA detected by direct hybridization testing indicates recent infection. The interpretation of a positive DNA study obtained by gene amplification (polymerase chain reaction) is more problematic, as individuals may not clear small amounts of virus for many months after an acute infection, and laboratory contamination can produce false positives.

Fifth disease

This common childhood exanthem is caused by acute parvovirus infection. The slapped-cheek rash and the evanescent maculopapular eruption over the trunk and proximal extremities are typical (Figure 191.1). Children may be febrile but usually have few symptoms. Meningitis and encephalitis have been reported as very rare complications. The blood of children with fifth disease contains IgM antibody to B19 but little if any virus; because the syndrome is due to immune-complex formation between virus and antibodies, affected individuals are not considered infectious. Reassurance and antipyretics as needed are sufficient for this self-limited illness.

In adults, acute parvovirus infection may be more serious. Adults have more rheumatic complaints than do children, and there may be frank joint inflammation and a pattern of distribution and chronicity mimicking rheumatoid arthritis; occasionally rheumatoid factor will be present. In most cases, symptoms resolve within a few days or weeks, but in some individuals the arthropathy and systemic symptoms become chronic and debilitating, although there is no joint destruction. The pathophysiology of the rheumatic manifestations after B19 infections is not well

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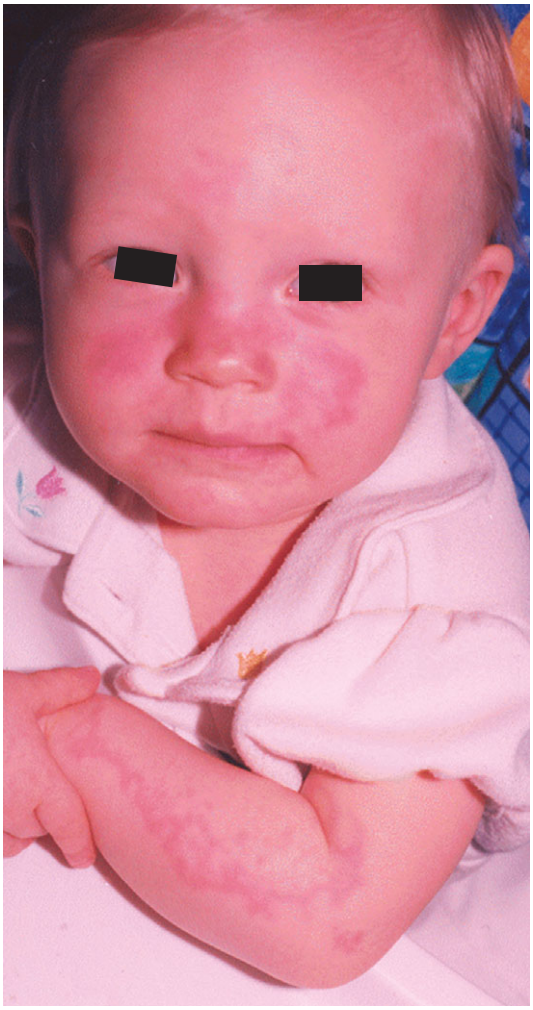

Figure 191.1 Fifth disease; note characteristic maculopapular rash with "slapped cheek" appearance.

understood, but symptoms usually can be addressed with conventional anti-inflammatory drug therapy. Parvovirus is not a cause of rheumatoid arthritis.

Transient aplastic crisis and other hematologic syndromes

Transient aplastic crisis is caused by parvovirus infection in patients who have hemolytic anemia, compensated hemolysis (as in many cases of hereditary spherocytosis), or an increased demand for red cell production (iron deficiency, acute hemorrhage). B19 briefly interrupts erythropoiesis in most persons infected but without consequence because of the long survival of circulating red blood cells. Transient aplastic crisis is manifested by anemia, reticulocytopenia, and red cell aplasia in the marrow. There may be moderate thrombocytopenia and neutropenia in addition to the severe anemia, especially in patients with functioning spleens. The syndrome may be accompanied by marrow necrosis and has been fatal, especially in young children. As the anemia is self-limited, transfusion is adequate therapy. Specific antibody production terminates the episode and likely prevents recurrence.

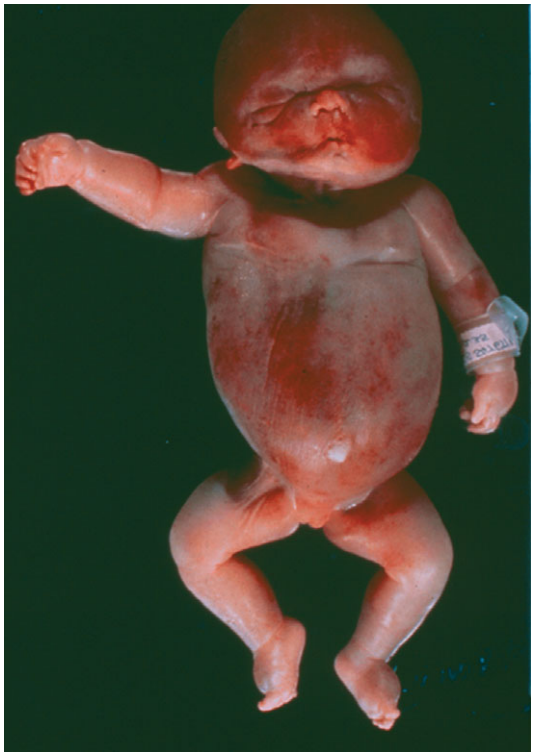

Figure 191.2 Hydrops fetalis (see text).

Hydrops fetalis and congenital infection

Parvovirus infection of the pregnant woman may be transmitted to the fetus. Midtrimester events have been best characterized; first trimester infection may result in abortion, and third trimester infection has not been associated with adverse outcomes. Infection of the fetus is predominantly in the liver, the site of red cell production; the heart may also be affected (fetal myocardial cells express P antigen). Untreated, the fetus develops severe anemia and heart failure leading to the massive edema of hydrops and death at birth or shortly afterward (Figure 191.2). In utero blood transfusions have apparently been successful in a

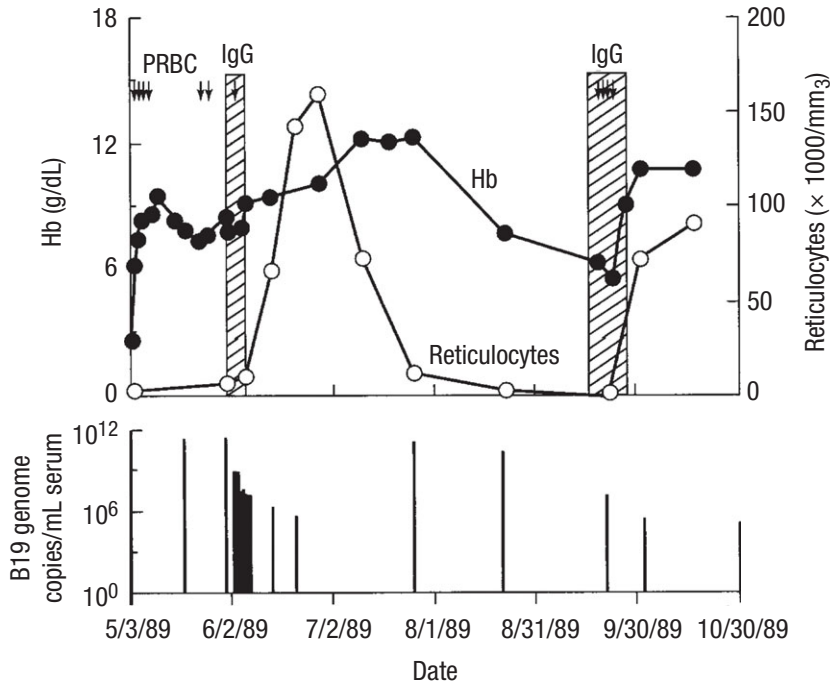

Figure 191.3 Immunoglobulin G (IgG) treatment of B19 persistence in acquired immunodeficiency syndrome (AIDS), illustrating recurrence predicted by molecular studies and the effectiveness of repeated treatment. PRBC = packed red blood cells.

few instances; however, untreated fetal infection need not result in mortality or morbidity. As ultrasound diagnosis may not be definitive, a conservative recommendation is to document progressive hydrops on serial testing before intervention.

Congenital parvovirus infection after transfusion treatment of hydrops can produce chronic anemia from birth. Only a few infants have been described: In all, virus was localized to the marrow and did not circulate, and gene amplification was required to detect the low levels of B19 DNA. The pathology of the marrow was erythroid hypoplasia (Diamond–Blackfan anemia) or erythroid dysplasia resembling congenital dyserythropoietic states. Immunoglobulin therapy has not been effective.

Persistent infection

In the absence of an appropriate immune response, B19 infection can become chronic. Persistent infection has been observed in congenital immunodeficiency (Nezelof syndrome), acquired immunodeficiency syndrome (AIDS) secondary to human immunodeficiency virus (HIV) 1 infection, and during therapy with cytotoxic or immunosuppressive drugs. The deficit in the immune response may be subtle; B19 infection may be the only evidence of constitutional immunodeficiency and the first sign of AIDS. Clinically, the patients have typical pure red cell aplasia with severe anemia, absent reticulocytes in the blood, and a paucity of red cell precursors in the marrow. Scattered giant pronormoblasts, a morphologic feature of B19 infection, may signal the diagnosis, which is established by DNA hybridization studies of serum.

Persistent infection results from inability to mount an effective humoral immune response, measured either as neutralizing antibodies in functional tissue culture experiments or by immunoblot binding of viral capsid proteins. Most AIDS patients lack any antibodies to B19; some congenital cases may have circulating IgM to B19 suggestive of a class-switch abnormality. Fortunately, commercial immunoglobulin preparations are a good source of effective antibodies to parvovirus. Administration of IgG 0.4 g/kg/day intravenously for 5 to 10 days terminates infection. The reticulocyte count dramatically increases after the first week, the marrow shows healthy normoblastic erythroid proliferation, and the hemoglobin rises to a level appropriate for the patient. Treatment can be curative, and the virus may no longer be detectable in some patients who have congenital immunodeficiency or whose immunosuppressive therapy is discontinued. AIDS patients have intense chronic parvoviremia, and IgG treatment appears to reduce but not eliminate the virus (Figure 191.3). Although

relapse after some months is common, recurrent anemia responds to a second course of IgG. Monthly maintenance injections of IgG have been used in a few patients.

OTHER POSSIBLE ASSOCIATIONS

Accumulated case reports are suggestive of a link between B19 and neonatal and childhood myocarditis (P antigen is present on fetal heart cells), a variety of pediatric neurologic syndromes, and some cases of acute, self-limited hepatitis. The association of B19 parvovirus with other clinical syndromes is less secure. Apparent links to childhood neutropenia, idiopathic thrombocytopenic purpura, vasculitis, and juvenile rheumatoid arthritis have not been reproducible. A major technical problem has been the use of gene amplification methods, which not only are susceptible to false-positive results but also are positive in a high proportion of normal individuals: Viral DNA has been found in almost half of knee joints biopsied for trauma and in 20% of normal bone marrows using this sensitive method. Polymerase chain reaction-derived data that are reported without other clinical or serologic evidence of recent infection should be especially suspect. In addition, paroxysmal cold hemoglobinuria, a severe childhood hemolytic anemia that usually follows a viral illness, is a good candidate as a B19 parvovirus syndrome because of the presence of the pathogenic Donath–Landsteiner antibody, directed against erythrocyte P antigen, the virus's cellular receptor.

VACCINE DEVELOPMENT

Effective vaccines to prevent parvovirus infection in animals have been produced by tissue culture modification of virus. For B19, which resists conventional cell culture, recombinant empty capsids have been produced in a baculovirus system by expression of a portion of the parvovirus genome; they contain no viral DNA. Capsids enriched for the highly immunogenic VP1 protein elicit strong neutralizing antibody responses in test animals and, with the appropriate adjuvant, in normal volunteers. The limitation to development of a vaccine is commercial – the perceived market – rather than scientific.

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192. Rabies

Gloria von Geldern, Anita Mahadevan, Susarla K. Shankar, and Avindra Nath

HISTORY

The first clear reference to rabies was from writings by Aristotle in circa 380 BC in which he described the symptoms and transmission of rabies in dogs. Despite centuries of observations on the transmission, symptoms, and a myriad of unsuccessful remedies, the disease remained invariably fatal until approximately 1885, when Louis Pasteur developed the first rabies vaccine in Paris. Unable to identify the organism – indeed unaware of even the difference between bacteria and viruses – he cultured it in the spinal cords of rabbits and, ultimately, injected it into Joseph Meister, a young boy attacked by a rabid dog on his way home from school. Given the severity of his wounds on his face, hands, and legs he undoubtedly would have died; however, he received a series of 13 injections, survived, and subsequently spent his life working as a guard at the Pasteur Institute.

EPIDEMIOLOGY

In 2010, the Centers for Disease Control and Prevention (CDC) reported that there were 6153 cases of rabies in animals and 2 human cases in the United States. Hawaii has been the only state free of rabies infection in humans and animals. Ninety-two percent of cases were in wild animals. In Europe, the World Health Organization (WHO) reported 6065 cases of animal rabies and 9 human cases in 2012. Most of these occurred in Eastern Europe. In Latin America, there were 111 cases of human rabies reported between 2010 and 2012. The highest prevalence of rabies worldwide is still in developing countries, with India being in the lead followed by China, Nepal, and Myanmar. A rising incidence has also been seen in some African countries such as Malawi. In the United States the largest reservoirs remain in raccoons followed by skunks, bats, foxes, and coyotes. Raccoon and fox reservoirs are mainly from the eastern states; bat and skunk cases were also found in parts of the south, Pacific Northwest, and California. Domestic animals only accounted for about 6.8% of rabies. Interestingly, cats are found to be infected with rabies almost double the infections of dogs. The cases of rabid cats continue to rise, whereas the cases in other animals are declining yearly. This paradox may be due to administration of vaccines in certain animals, especially dogs. In Europe, the rabies reservoir is mainly the fox, whereas the bat is the main reservoir in Australia, Mexico, and parts of South America. Worldwide, death from rabies is usually from a rabid dog.

PATHOGENESIS AND PATHOLOGY

Rabies is caused by a number of different species of neurotropic viruses in the Rhabdoviridae family, genus *Lyssavirus*. The virus replicates at the wound site for a period of days and then, via retrograde axoplasmic flow, moves up the peripheral nerves to the anterior horn cells in the spinal cord and then trans-synaptically to the brain. Both sensory and motor nerves can propagate the infection. Once the central nervous system (CNS) is seeded with the virus, it then centrifugally spreads back to the periphery. This process involves infection of non-neural tissues, especially the salivary glands, whereby the viral transmission occurs.

Histologic examination of the brain shows perivascular inflammation of the gray matter, neuronal degeneration, and the characteristic cytoplasmic inclusions called the Negri bodies (Figure 192.1A). Renal tubular necrosis has also been demonstrated at autopsy. In 2005 and in 2012, cases of rabies were also reported from organ transplant recipients. Neuropathologic features in the latter showed Duret hemorrhages, widespread neuronal loss, perivascular lymphocytic infiltration, and extensive spinal cord pathology. The case in 2012 was unusual in that rabies occurred 18 months after the kidney transplant

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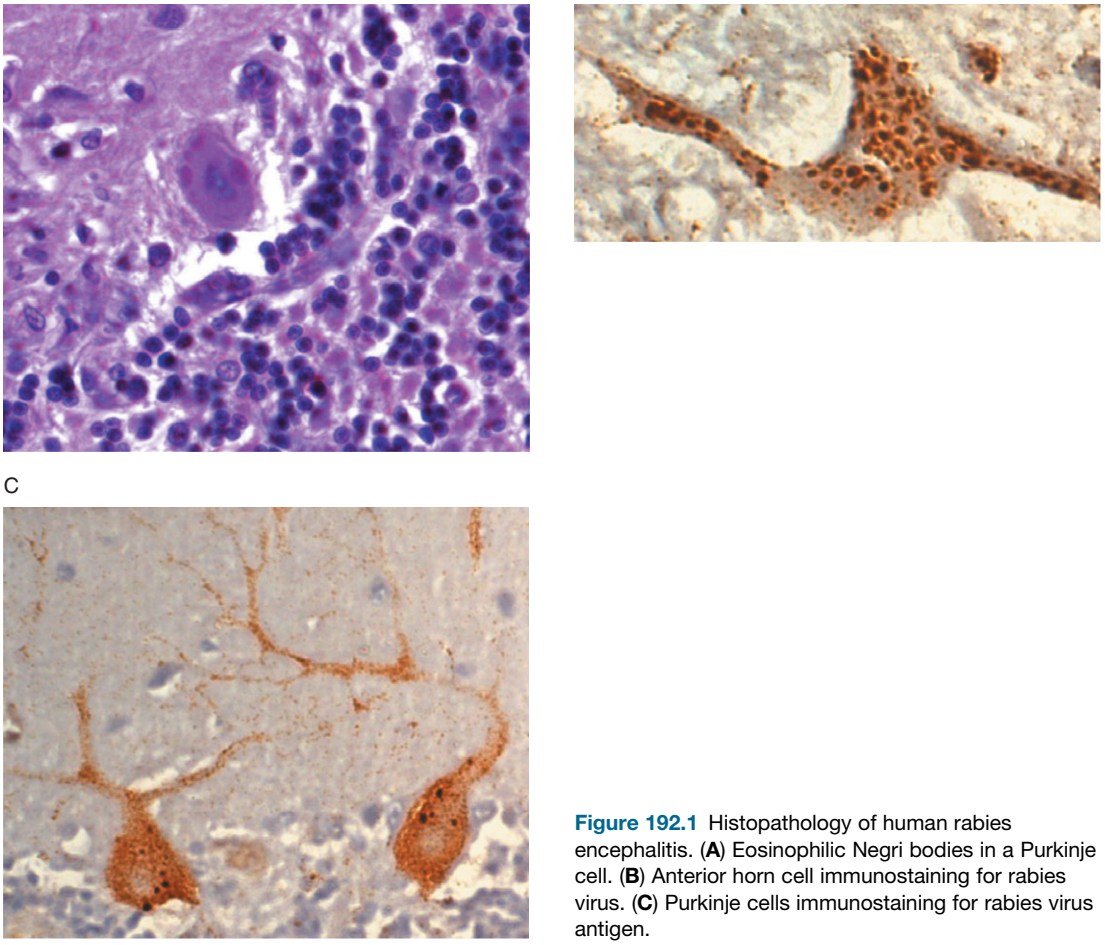

Figure 192.1 Histopathology of human rabies encephalitis. (**A**) Eosinophilic Negri bodies in a Purkinje cell. (**B**) Anterior horn cell immunostaining for rabies virus. (**C**) Purkinje cells immunostaining for rabies virus antigen.

and three others who received organs from the same donor remained asymptomatic likely due to a low dose of the inoculum.

CLINICAL SYMPTOMS

The clinical course in humans is acute, usually progressing from initial symptoms to death within 2 to 3 weeks, even with intensive supportive care. The incubation period of rabies can vary from a few days to several years with an average of 1 to 2 months. The length of the incubation period varies with the infecting strain and is thought to be inversely related to the size of the inoculum and the proximity of the bite to the CNS. Approximately half of the patients develop pain or paresthesias at the wound site. A diagnosis of rabies should not always depend on a history of an animal bite. Exposure may not be obvious in bat-acquired rabies, which often gets misdiagnosed. The prodrome includes low-grade fevers, loss of appetite, and anxiety. Most patients have "furious rabies" characterized by marked hyperactivity, disorientation, hallucination, or bizarre behavior, which lead to an initial psychiatric evaluation. This hyperactivity later becomes intermittent and may be spontaneous or precipitated by tactile, auditory, or visual stimuli. Hydrophobia (spasm of the pharynx and larynx provoked by drinking or the sight of water) and aerophobia (similar effect produced by blowing air on the face of the patient) are considered hallmarks of the disease. The inability to swallow from paralysis of bulbar muscles may also result in hypersalivation. Seizures, which are more common in children, may also occur during this stage, as can dysfunction of the autonomic nervous system. Rarely, there may be respiratory

distress with medullary involvement. A few patients die during this stage, but most go on to develop progressive paralysis and eventually coma. Abnormal cranial nerve, motor, and sensory examinations; tremor; myoclonus; and local sensory symptoms at the exposure site are more common in bat-acquired rabies. In some patients, the paralytic state dominates the entire clinical picture; hence, it is termed *paralytic rabies*. Paralysis or paresis involves the proximal muscles and can be accompanied by constipation, urinary retention, and respiratory failure. Alternatively, inflammation with demyelination and axonal dysfunction of the peripheral nerve causes an ascending lower motor neuron weakness without anterior horn cell involvement. Physical exam shows a motor weakness involving the respiratory muscles and loss of deep tendon reflexes with maintained consciousness which may mimic an acute axonal Guillain-Barré syndrome. This lack of involvement of spinal cord motor neurons and brainstem is called an "escape phenomenon." In some patients, however, the clinical manifestations can be nonspecific; hence, in all patients with unknown cause of progressive encephalitis, the possibility of rabies should be considered. In patients receiving intensive supportive care, the average duration of illness between onset of paralysis and death is 7 days. Once neurologic symptoms have developed, survival is rare.

DIAGNOSIS

Prior to available accurate laboratory tests, a potentially infected animal was placed in isolation for observation. If it died a characteristic rabies death, the diagnosis was established. With the advent of the microscope in 1903, intracytoplasmic inclusion bodies were discovered in infected brain tissue by Aldelchi Negri, who at the time was an assistant of Camillo Golgi. These structures were subsequently called Negri bodies. In the 1980s the direct fluorescent antibody (DFA) test was formed, which remains to this day the diagnostic gold standard (Figure 192.1). For postmortem diagnosis in animals, fresh unfixed brain tissue is necessary for DFA testing as fixed tissue with agents such as formalin may yield inaccurate results. Brain tissue is the only sample tissue type for diagnosis as saliva and salivary gland excretion of the virus can be intermittent. The predictive value of a negative brain DFA test is 100%.

Routine laboratory tests and diagnostic studies are of little value in the diagnosis of rabies. Examination of the cerebrospinal fluid (CSF) may show leukocytosis, but protein and glucose assays are often normal. Antibodies to the virus in an unvaccinated patient with encephalitis confirms the diagnosis. In addition, saliva samples can be cultured and then tested for viral nucleic acid. A tissue diagnosis can be made in premortem humans using the DFA test on a skin sample from the back of the neck. Polymerase chain reaction (PCR) can also be used in diagnosis, but DFA is still considered the gold standard as PCR is hampered by obtaining universal *Lyssavirus* primers. Due to the ability to detect low copy numbers of viral nucleic acid, rapid turnaround time, and falling costs, it is likely that PCR-based techniques may become a viable diagnostic test in the near future.

In 2006, the CDC reported a case of encephalitis in a 15-year-old girl from Wisconsin who was bitten by a bat. Antibody titers to rabies virus were found in CSF and serum. She survived the infection. Another young boy developed encephalitis of undetermined etiology that progressed rapidly. He developed rabies-specific immunoglobulin G antibodies in increasing titers. Rabies virus could not be detected in the CSF by PCR; however, antibodies to the rabies virus were present.

Magnetic resonance imaging (MRI) changes most likely occur in the early stages of the infection. More extensive involvement of various regions of the brain has been shown in advanced stages on serial imaging. There are no specific features that are attributable to the rabies virus. Patients with acute rabies encephalitis have T2 hyperintense lesions in the brainstem, thalami, temporal cortex, hippocampus, and subcortical white matter. Mild signal changes can also be seen in the spinal cord and nerve roots corresponding to the site of injury of some patients. Enhancement with gadolinium contrast is not present until the patient is comatose.

TREATMENT

Treatment efforts are concentrated on preventing and treating complications of established infection and protecting those who come in contact with the patient from virus exposure. Neither vaccine nor rabies immunoglobulin increases survival in symptomatic patients and should be avoided. Attempts to treat symptomatic patients infected with dog rabies with therapeutics and intensive care support are usually unsuccessful.

A few patients who survived infection with good functional recovery had evidence of an early immune response to rabies virus in blood and CSF, with absence of virus in biologic fluids or hair follicles. Thus, a good outcome likely depends on a prompt host response in eradication of virus. Steroids should also be avoided in the treatment of cerebral edema if it develops. Universal precautions should be followed by hospital staff, and respiratory precautions are recommended for suctioning. Postexposure prophylaxis is recommended for contacts who were bitten or had clear contamination of mucous membranes to the patient's saliva, urine, or other body tissue.

Symptomatic treatment

Benzodiazepines, barbiturates, ketamine, or intravenous morphine may be used for treatment of the pharyngeal spasms. However, impairment of consciousness to the extent that ventilatory support is needed should be avoided. Autonomic symptoms should be monitored and treated.

Postexposure prophylaxis

Once an individual is bitten by an animal presumed to have rabies, it is vital to immediately begin the immunization. Raccoons, skunks, foxes, and coyotes are most often infected with the rabies virus. Patients exposed to these animals should receive postexposure prophylaxis as soon as possible. Transmission of rabies virus can occur from minor, even unrecognized, bites from bats. Therefore, rabies postexposure prophylaxis is recommended for all persons with bite, scratch, or mucous membrane exposure to a bat and should be considered if the history indicates that a bat was physically present, even if the person is unable to reliably report contact that could have resulted in a bite. An unprovoked attack by a domestic animal is more likely than a provoked attack to indicate that the animal is rabid. If the animal has been vaccinated, it is unlikely to be infected; if not vaccinated but otherwise healthy, the animal should be confined and observed for 10 days. Any illness during this time should be evaluated by a veterinarian and the public health department. Vaccination can be withheld if the animal remains healthy during this time. Small rodents (e.g., squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice) and lagomorphs (including rabbits and hares) are almost never infected with the virus and have not been known to transmit rabies to humans. Large rodents such as woodchucks are sometimes infected. Therefore, in cases involving rodent exposure, the state or local health department should be consulted before initiating prophylaxis. Postexposure therapy for rabies is highly effective, and no failures have been recorded in patients who have received all three arms of treatment. Failures have occurred only on deviation from the recommended protocol.

Local wound care

The abraded skin after a bite must be cleaned by soap and water or povidone-iodine solution. Even scratches or contaminated skin from saliva should be cleaned the same way. It has been found that cleaning the wound would help reduce the chances of developing rabies. There are no areas that are deemed more susceptible after a bite. All bites in any area should be treated with the same level of care. Tetanus prophylaxis and antibiotics may be necessary to prevent secondary infection.

Vaccination

Postexposure therapy includes both passive immunization with rabies immune globulin (RIG) and active immunization with the vaccine in those who have not been vaccinated previously. RIG is administered as a one-time dose and should be given within the first 7 days of the vaccine because after this time period the vaccine production of antibody is thought to have occurred. The recommended dose of RIG is 20 IU/kg body weight for any age group. It is typically administered around the bite wound. The RIG and vaccine should not be given at the same site. Vaccine alone is indicated in persons who have had pre-exposure prophylaxis with a cell culture vaccine series or who had been vaccinated with other types of rabies vaccine with a documented neutralizing antibody response.

In the United States, there are currently two Food and Drug Administration (FDA)-approved vaccines. The human diploid cell vaccine (HDCV), trade name Imovax, and the purified chick embryo cell vaccine (PCEC), trade name RabAvert, which are both administered intramuscularly (IM). Outside the United States, there are a purified vero cell rabies vaccine (PVRV) and a purified duck embryo vaccine available in addition to the HDCV and PCEC vaccines.

The vaccine should be given as a 1.0 mL IM injection in the deltoid area (the outer thigh may be used in younger children, but vaccine should not be given in the gluteal area) on days 0, 3, 7, and 14 according to CDC guidelines. All of these vaccines are used for both pre-exposure and post-exposure prophylaxis. The WHO still recommends a five-dose immunization (with an additional dose on day 28) in cases of higher exposure and both the WHO and CDC recommend five doses in immunocompromised individuals.

HDCV is the most expensive rabies vaccine but PCEC and PVRV are just as efficacious and safe and can be administered at lower doses intradermally in resource-limited settings. Older vaccines that are produced in sheep, goat, or mouse nervous tissue have unreliable potency and a high incidence of neurologic complications but are still used in some developing countries as they are cheaper.

Pre-exposure vaccination

Pre-exposure prophylaxis should be offered to persons at high risk for exposure to rabies. Persons who work with rabies virus in research laboratories or vaccine-production facilities are at highest risk for exposure and should have rabies antibody titers checked every 6 months. Other laboratory workers (e.g., those performing rabies diagnostic testing), spelunkers, veterinarians and staff, and animal-control and wildlife officers in areas where animal rabies is enzootic should also have antibody measurements done every 2 years. Booster doses (IM or ID) of vaccine should be administered to maintain an adequate serum titer. The immunization practices advisory committee (ACIP) recommends three pre-exposure doses of the HDCV given IM at 0, 7, and 21 or 28 days. This ensures both seroconversion and adequate duration of protective antibody. Routine serologic testing after vaccination is not needed as seroconversion has been uniform. Patients who are immunosuppressed or taking medications such as chloroquine, which may interfere with antibody response to the vaccine, should postpone pre-exposure vaccinations and consider avoiding activities for which rabies pre-exposure prophylaxis is indicated. When this is not possible, they should be vaccinated and their antibody titers checked.

EDUCATION

Prevention is the best cure. Knowledge is extremely vital in this disease. People should be informed of preventative measures if they are considered to be a high-risk group. The CDC has immensely resourceful web-based information for individuals who have concerns or common questions related to a dog bite. They have recommendations for people who would like to have a dog or cat as a household pet. Casual handshaking or standing next to someone who may be infected are not considered to be risks for acquiring the infection. Changing bed linen from an infected individual does not pose a threat, either. Certain risks seen in the domestic setting, barring animal bites, would also be from sexual activity, sharing utensils or cigarettes, and saliva contact from an infected source (CDC). A healthy person undergoing postexposure prophylaxis (PEP) does not constitute a potential threat for infecting others. If a person is found to be infected, the local health department should be notified once the infection is documented. In an unknown case of encephalitis, especially in children, a history must be ascertained about recent animal bites. Patients may not recognize that certain animals can be a threat for a rabies virus infection.

As there is currently no cure for rabies infection once it has reached the CNS, determining a definitive, positive diagnosis does not aid the patient directly. However, it is an important part of the workup and differential for acute encephalitis in that a negative result points toward a different cause for the encephalitis. Alternatively, a positive result is important from a public health perspective and garners patient isolation a necessity. It also aids in establishing a more detailed history for possible exposure in other family members.

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193. Varicella-zoster virus

Jeffrey M. Weinberg

Varicella-zoster virus (VZV) is a member of the herpesviruses family, and is the etiogic agent of varicella and varicella zoster. Varicella, the exanthem caused by primary infection with VZV, generally occurs in childhood. Shingles, the clinical syndrome of segmental, unilateral, exanthem, and neuralgic pain due to reactivation of latent VZV infection, usually occurs many years after the primary infection. In the immunodeficient person, both primary and reactivated VZV infection can lead to severe generalized virus dissemination, the life-threatening form of VZV infection. The availability of antiviral agents for management of VZV infection has raised the importance of recognizing this infection in high-risk groups. Prior to the introduction of the VZV vaccine in the United States in 1995, approximately 4 million cases of chickenpox occurred each year, 83% in children younger than 9 years. The association between aging and VZV vulnerability is apparent in the epidemiology of the disease: of the estimated 1 million cases of herpes zoster in the United States each year, approximately 50% occur in individuals aged 50 years or older. A VZV vaccine was approved in 2006 for the prevention of shingles.

CLINICAL PRESENTATION

Varicella (chickenpox)

In healthy unvaccinated children, VZV infection manifests as a vesicular exanthem often associated with prodromal malaise, pharyngitis, rhinitis, and abdominal pain. The rash generally appears 15 days after VZV exposure; the range is 10 to 21 days. The vesicular eruption emerges in successive crops over the first 3 to 4 days of illness, usually with concomitant enanthem. Each skin vesicle appears on an erythematous base, resulting in the descriptive image of a dewdrop on a rose petal.

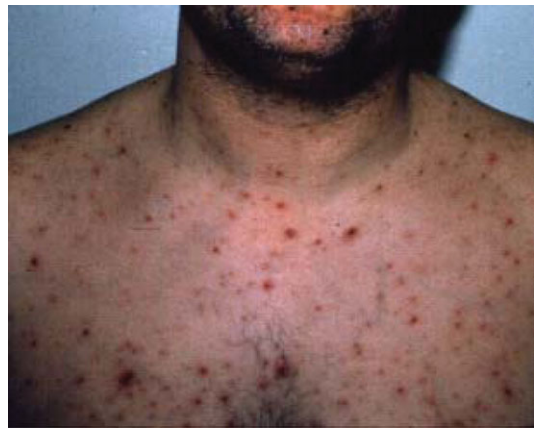

Figure 193.1 Varicella. Note various stages of lesions in each area of eruption. (Courtesy of David Schlossberg, MD.)

The eruption most commonly originates on the head and quickly progresses to the trunk, arms, and, finally, the legs. It is common to observe all cutaneous stages, including macules, vesicles, papules, and crusts, in the same area of the skin (Figure 193.1). Varicella often is associated with fever, headache, sore throat, or stomach ache. These symptoms may last for a few days, with fever in the 101°F to 102°F (38.3°C to 38.8°C) range. Primary VZV infection may involve the mucosal surfaces of respiratory, alimentary, and genitourinary systems, therefore those with varicella can have severe laryngitis, laryngotracheobronchitis, vaginitis, urethritis, pancreatitis, and enteritis. In immunocompromised individuals, severe abdominal pain or back pain can be an indicator of progressive VZV infection.

Varicella vaccine was licensed in the United States in 1995 for individuals ≥12 months of age. A second dose was recommended in the United States in June 2006. Since the introduction of the vaccine, the age-unadjusted incidence of

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chickenpox has been approximately 3 cases per 1000 population, and the hospitalization rate for complications of varicella has decreased dramatically. Complications of varicella occur most frequently in those younger than 1 year and older than 15 years. These complications include bacterial superinfection of skin, dehydration, pneumonia, encephalitis, and hepatitis. With the availability of the vaccine, hospitalizations for chickenpox have significantly decreased and VZV-associated mortality is at an all-time low of less than 0.1 per million population.

Varicella zoster (shingles)

Although 10% to 20% of Americans overall will develop zoster in their lifetimes, 50% of persons reaching age 85 can be expected to do so; the incidence of herpes zoster rises dramatically, from a low of between 1.1 and 2.9 per 1000 person-years in people younger than 50 to 4.6 and 6.9 per 1000 person-years, respectively, in the age groups 50–59 and 60–69. The age groups 70–79 and $\geq$80 years old have the highest incidence, with 9.5 and 10.9 per 1000 person-years, respectively.

The principal risk factor for herpes zoster is prior history of VZV exposure. Any person who has had chickenpox or received the varicella vaccine as a child, which includes more than 90% of the US adult population, is at risk for herpes zoster. The association with advancing years, as previously described, is due to the age-related decline in VZV-specific cell-mediated immunity. Childhood zoster is rare but not unheard of, with cases reported in children as young as 4 months. The incidence of zoster in children younger than 10, however, is only 0.74 per 1000 person-years.

Immunocompromised people or those receiving immunosuppressive drugs are also at increased risk for zoster. Thus, human immunodeficiency virus (HIV) patients have a higher incidence of zoster disease than individuals with a healthy immune system, reported in one longitudinal study as 29.4 cases per 1000 patient-years. Patients undergoing bone marrow or organ transplant and treated with immunosuppressives are known to develop zoster with increased frequency.

Genetics may play a role in the development of herpes zoster, as suggested by the finding that elderly white men are four times more likely to develop zoster than elderly black men. Some reports have suggested that systemic steroid therapy can incite VZV reactivation as well, placing persons with conditions such as rheumatoid arthritis or lupus at increased risk. Finally, both trauma and stressful life circumstances have been suggested to play a role in development of herpes zoster, further increasing the population at risk.

The characteristic feature of herpes zoster is a vesicular rash of unilateral distribution limited to one to three adjacent dermatomes. The onset of the rash, however, often is preceded by a prodromal phase. Beginning 4 days to 2 weeks before lesions appear, patients often note pain and paresthesia in what will become the zoster-affected dermatome. The pain can be intermittent or continuous, and has been described by patients variously as throbbing, sharp, stabbing, burning, or shooting pain. Malaise, dysesthesia, and itching are frequent elements of the prodrome, as well.

The most common site of infection is the trigeminal nerve. Most patients exhibit thoracic distribution of zoster rash, with more than 50% of cases presenting with cutaneous lesions of the trunk. The rash generally appears proximally, then spreads distally along the affected dermatome. The initial lesions appear as erythematous maculopapules, which turn into vesicles within 12 to 24 hours. The vesicles become pustules in about 3 days, and form scabs 7 to 10 days later. New lesions generally appear over no more than 3 to 7 days, but the duration of the rash has been correlated with patient age (advancing age associated with longer duration) and site of infection (face healing more rapidly than other loci).

Zoster affecting the first division of the trigeminal nerve, as occurs in 10% to 15% of cases, can lead to herpes zoster ophthalmicus (HZO), which produces the characteristic zoster rash on the forehead, periocular area, and nose and can be accompanied by local pain. Ocular complications of HZO are among the most dangerous morbidity of zoster disease, placing patients at risk for sight impairment or vision loss due to nerve damage or ocular pathology.

Approximately 60% to 90% of zoster patients experience local neuritic pain and hypersensitivity in association with the acute herpetic rash. This pain is likely due to an immediate nociceptive response: local inflammation and tissue damage stimulate the primary afferent neurons of the skin and subcutaneous tissue, which neurologically manifests as pain. In addition, allodynia and hyperalgesia may be present, adding to patient discomfort during acute herpes zoster.

Pain associated with zoster disease resolves within several days for many patients, although

the degree of pain can be variable; one report has suggested that more extensive pain during the acute phase might predict the prolonged pain of postherpetic neuralgia (PHN), and another indicates that early pain therapy might limit the central development of chronic PHN pain following herpes zoster.

DIAGNOSIS

The features of varicella and varicella zoster are so characteristic that a diagnosis is generally made clinically. In chickenpox, lesions in all stages of development (macules, vesicles, pustules, and crusted lesions) may be a suggestive finding. The differential diagnosis of varicella includes the following: herpes simplex virus, Coxsackie and other enteroviruses, mycoplasma, streptococcal impetigo, rickettsialpox, insect bites, and allergic contact dermatitis.

For herpes zoster, the diagnosis can be made based on the presence of prodromal pain and/or itching, and the defining zoster rash. For patients presenting in the prodromal period, the pain and dysesthesia may require differentiation from other pain sources, such as trauma, myocardial ischemia, renal colic, gallbladder disease, or dental pain. Atypical lesions, furthermore, may require laboratory confirmation, which sometimes is obtained from viral culture (often difficult to recover from swabs) or more readily from direct immunofluorescence assay. Recently, nested and real-time polymerase chain reaction (PCR) testing of samples from skin lesions have proved valuable for identifying VZV, with more rapid amplification than other methods and high sensitivity. These laboratory techniques are most valuable for differentiating VZV from zosteriform herpes simplex, a herpes simplex viral infection that mimics zoster disease.

PREVENTION AND THERAPY

Varicella vaccine

The live, attenuated varicella vaccine (Varivax) was approved in the United States in 1995 and is recommended for persons older than 12 months. Every person in the United States who does not have indicators for VZV immunity should have two doses of varicella vaccine. The first dose should be administered at the age of 12 to 15 months. The second dose should be given between the ages of 4 and 6 years. People 13 years of age and older who have never had chickenpox or received chickenpox vaccine should get two doses, at least 28 days apart.

Each dose, for infants and adults, is 0.5 mL administered subcutaneously.

Other populations may benefit from varicella vaccine, including eligible healthcare and day-care workers, college students, prisoners, military recruits, nonpregnant women of childbearing age, and international travelers.

Prior to the introduction of the vaccine, about 11 000 people were hospitalized for chickenpox each year in the United States, and about 100 people died each year as a result of chickenpox in the United States. As noted previously, since the introduction of the vaccine, the incidence of chickenpox and the hospitalization rate for complications of varicella has decreased dramatically.

The vaccine is not recommended for infants <1 year old, for those on salicylate therapy, for pregnant women, or those allergic to components of the vaccine, including neomycin, gelatin, and monosodium glutamate. Immunosuppressed individuals should confer with their physician about the risks and benefits of vaccination.

Zoster vaccine

The herpes zoster vaccine is a live attenuated preparation of the Oka/Merck strain of VZV that boosts the recipient's immunity to VZV, thus increasing the chance that their latent VZV will remain dormant and that they will not develop herpes zoster. Its efficacy and safety in reducing the risk of herpes zoster disease in adults over age 60 were established in a pivotal trial, on the basis of which the US Food and Drug Administration (FDA) approved the vaccine in May 2006 for clinical use. On March 24, 2011, the FDA approved Zostavax for individuals 50 to 59 years of age.

Chickenpox

OVERALL ASSESSMENT

The goal in management is to treat the symptoms of primary VZV infection and to prevent complications if possible. The three stages of management are (1) establishing the likelihood of the diagnosis, (2) determining whether antiviral therapy is indicated, and (3) ruling out secondary bacterial infection, other complications, and failure of previous antiviral treatment.

SYMPTOMATIC THERAPY

Itching is the major symptom of chickenpox, and antipyretic management is important. Warm baths containing baking soda (1/3 cup per bathtub) or emulsified oatmeal (Aveno) can temporarily relieve pruritus. This can be combined with the oral administration of either diphenhydramine (Benadryl), 1.25 mg/kg every 6 hours, or hydroxyzine (Atarax, Vistaril), 0.5 mg/kg every 6 hours. In older children, cold pramoxine HCl 1% lotion with calamine 8% (Caladryl) can be used, but this should be avoided in infants because of the risk of excessive surface exposure and absorption of drug or vehicle (alcohol 2.2%). Fever should be controlled with acetaminophen, but salicylates should not be used because administration of certain salicylates to children with chickenpox increases the risk of subsequent Reye's syndrome. For severe dysuria, a cold compress on the genital area during urination will ease the pain and minimize the likelihood of a functional bladder obstruction.

ANTIVIRAL THERAPY

Acyclovir (Zovirax) is the only agent licensed in the United States for the treatment of chickenpox. It is indicated for treatment of chickenpox in certain normal persons, for disseminated VZV infection in immunosuppressed persons, and for treatment of shingles. Oral acyclovir should be used in otherwise healthy persons with chickenpox who are at risk for moderate to severe disease, such as those older than 12 years, those with chronic cutaneous or pulmonary disorders, those receiving chronic salicylate therapy, and those receiving short, intermittent, or aerosolized courses of corticosteroids or aerosolized corticosteroids (Table 193.1). The American Academy of Pediatrics (AAP) does not recommend that otherwise normal children younger than 12 years receive oral acyclovir for chickenpox.

All adults with chickenpox should receive oral acyclovir, and those with rapidly progressive infection should be treated with intravenous acyclovir. Valacyclovir (Valtrex) and famciclovir (Famvir), both of which are approved for treatment of shingles, are not approved in the United States for treatment of chickenpox. All immunosuppressed persons with chickenpox should be treated with intravenous acyclovir until the course of infection is defined. However, as noted by the AAP, some experts have used oral acyclovir in highly selected immunocompromised persons who are at relatively low risk for developing complications and in whom follow-up is assured. Case-by-case evaluation of risks versus benefits is necessary, but for many groups the risk of disseminating infection is sufficiently high and so unpredictable that intravenous treatment should be recommended in nearly all cases. Intravenous acyclovir should be used for the pregnant patient with serious complications of varicella, but, if acyclovir is used routinely for the pregnant woman with uncomplicated chickenpox, it should be recognized that the risk and benefits to the fetus and mother are mostly unknown. Varicella-zoster immune globulin (VZIG) is licensed for use in high-risk individuals at the time of exposure to VZV infection but is not recommended for treatment of chickenpox.

COMPLICATIONS

Pyoderma is the most frequently observed bacterial complication of varicella. It can be minimized by attention to good hygiene, including daily bathing with bacteriostatic soap or dilute bleach baths. Streptococcal and staphylococcal bacterial infections can be associated with bacteremia and subsequent osteomyelitis, with scarlet fever, and with bacterial synergetic gangrene.

Bacterial superinfection can affect the lower respiratory tract, producing pneumonia and bronchitis. Viral pneumonia is more likely to be a problem in older persons with chickenpox. Therefore, it is important to monitor pulmonary status during treatment.

It is important to monitor for gastrointestinal tract involvement, including bleeding and vomiting. Mild asymptomatic hepatitis is observed in a majority of children with varicella, usually asymptomatic elevation of hepatic enzymes for which no treatment is necessary. However, elevation of serum or urinary amylase may indicate pancreatitis, which may require supportive treatment. Although rare today, Reye's syndrome and other metabolic diseases must be considered in any child with varicella in whom there is vomiting and changes in mental status.

Neurologic complications include cerebral or cerebellar abnormalities; the latter is a more benign disease. Cerebellar ataxia, the most common syndrome associated with varicella encephalitis, is most often a benign entity due to postinfectious demyelination. There is no evidence that acyclovir treatment is necessary in postchickenpox cerebellitis, but it is prudent to include antiviral therapy in any cerebral presentation of VZV infection, especially if it may be

Table 193.1 Antiviral treatment of varicella-zoster virus (VZV) infection[a]

Agent	Indication	Creatinine clearance (mL/min/1.73 M^2)	Dose	Dosing interval	Duration (days)
Oral acyclovir	Chickenpox >age 12 yr	>25	20 mg/kg up to 800 mg	4 times/d	5
		10–25	Same	q8h	5
		0–10[b]	Same	q12h	5
	Shingles	>25	20 mg/kg up to 800 mg	5 times/d	5–7
		10–25	Same	q8h	5–7
		0–10[b]	Same	q12h	5–7
IV acyclovir	Life-threatening VZV infection	>50	500 mg/M^2 or 10 mg/kg[c,d]	q8h	7
		25–50	Same	q12h	7
		10–25	Same	q24h	7
		0–10[b]	250 mg/M^2	q24h	7
Famciclovir	Shingles >age 18 yr	>60	500 mg	q8h	7
		40–59	500 mg	q12h	7
		20–39	500 mg	q24h	7
		≤20	250 mg	q24h	7
Valacyclovir	Shingles >age 18 yr	>50	1000 mg	q8h	7
		30–49	1000 mg	q12h	7
		10–29	1000 mg	q24h	7
		≤10	500 mg	q24h	7
Foscarnet	Acyclovir-resistant VZV[e]	>100[f]	60 mg/kg	q8h	7–10

[a] See package insert for recommended dose adjustment of all drugs.

[b] An additional dose is recommended after each hemodialysis treatment.

[c] To minimize renal toxicity an adequate urine output is required. This can be assured if the acyclovir is infused at a concentration of approximately 4 mg/mL over 1 hour and the same volume of fluid is given over the next hour.

[d] Use ideal body weight for height to calculate dose in obese person: M^2, square meter of body surface area.

[e] Foscarnet is recommended by experts for treatment of life-threatening acyclovir-resistant VZV infection, but this is not an US Food and Drug Administration (FDA)-approved indication for foscarnet use. Appropriate informed consent should be obtained before such use.

[f] Foscarnet is nephrotoxic, and dosage should be based on creatinine clearance. Guidelines for dosage adjustment are listed in the package information.

associated with continued viral replication such as in acquired immunodeficiency syndrome (AIDS) or other immunosuppressive states.

Bleeding disorders associated with varicella include disseminated intravascular coagulation, vasculitis, and idiopathic thrombocytopenic purpura (ITP). These should be managed according to conventional treatment, and there is no VZV-specific management regimen.

IMMUNOSUPPRESSED PATIENTS

As noted, acyclovir is the only indicated drug for the treatment of VZV infections in the immunosuppressed patient. These infections include disseminated chickenpox, disseminated shingles, or localized shingles. Three other antiviral medications, valacyclovir, famciclovir, and foscarnet (Foscavir), have activity against VZV. Valacyclovir and famciclovir are indicated for the treatment of shingles as described below (see Table 193.1). Foscarnet is recommended for the treatment of acyclovir-resistant VZV.

Shingles

OVERALL ASSESSMENT

The development of shingles in and of itself does not produce substantial morbidity; rather, it is the potential for neurologic and inflammatory complications of zoster disease that cause patients – and physicians – the greatest difficulty. The relationship between zoster infection and destruction of neurons and satellite cells has been well established, with neurologic damage beginning even before the characteristic zoster rash appears. PHN (Table 193.2), the most frequent complication of VZV, can cause debilitating pain and impaired quality of life among the otherwise healthy elderly. The associated pain, furthermore, can continue long after the rash resolves, despite aggressive antiviral and/or pain therapy.

SYMPTOMATIC THERAPY

Individuals with zoster should be instructed to keep the cutaneous lesions clean and dry to

Table 193.2 PHN can present with a range of neurologic features

- Pain can be intermittent or continuous, deep or superficial
- Pain described as throbbing or stabbing
- Spontaneous aching or burning
- Paroxysmal shooting pain
- Allodynia
- Hyperalgesia
- Intense itching

Adapted from Johnson and Whitton. *Expert Opin Pharmacother.* 2004;5:551–558.

reduce the risk of bacterial superinfection. A sterile, nonocclusive, nonadherent dressing placed over the involved dermatome will protect the lesions from contact with clothing. Acute pain can be very severe and refractory to therapy. Sympathetic-nerve blockade can provide rapid, temporary relief of severe pain. Scheduled short-acting narcotic analgesics can be prescribed. For persistent pain, long-acting, controlled-release are preferred. If the eye is involved, an ophthalmologist should be consulted for use of topical anti-inflammatory or antiviral medication and for long-term evaluation.

Treatment with corticosteroids may in the short term reduce herpes-related pain intensity, but it is associated with a risk of serious adverse effects. Longer-term studies have demonstrated that corticosteroids, administered orally or intrathecally, offer acute benefits but fail to prevent PHN. Corticosteroids may reduce pain intensity, but the high prevalence of diabetes, hypertension, and glaucoma among adults aged 50 years and older, those most likely to develop herpes zoster, severely limits the number of patients for whom corticosteroids would be helpful.

ANTIVIRAL THERAPY

Antiviral drugs have been consistently found to effectively reduce the severity and duration of herpes zoster, and are safe and well tolerated with minimal adverse effects. They do not, however, reliably prevent the development of PHN. Nearly all study protocols require initiation of antiviral therapy within 72 hours of rash onset. Although 72 hours is frequently mentioned as a cutoff for therapy, there are no data showing that antiviral therapy initiated more than 72 hours after rash onset is not helpful, and there are observational data to suggest that it is quite helpful.

Acyclovir, valacyclovir, and famciclovir are licensed in the United States for the treatment of shingles in otherwise normal persons (see Table 193.1). Acyclovir is the agent of choice for immunocompromised persons and is the only intravenous agent available for treatment of shingles. Valacyclovir is the prodrug of acyclovir and, because of better bioavailability, is preferred over acyclovir for oral therapy of shingles. Famciclovir is an oral prodrug of the antiviral agent penciclovir, which has potent activity against VZV, and famciclovir undergoes rapid biotransformation to the active antiviral compound. Safety and efficacy in children has not been established for either valacyclovir or famciclovir. Also, because of the potential for tumorigenicity in rats, famciclovir should not be given to pregnant or nursing mothers unless nursing is discontinued.

MANAGEMENT OF EXPOSURE TO VZV

The spread of infectious VZV from a person with chickenpox is by air droplets from nasopharyngeal secretions, which usually requires face-to-face exposure indoors for an hour but can also be via air currents to susceptible individuals without direct contact. The period of respiratory infectivity is generally considered to begin 48 hours prior to the onset of exanthem and to continue for 4 days after onset. In addition, the vesicular fluid can spread the virus by direct contact, so infectivity by contact with skin lesions is possible until they are crusted. Shingles can also spread by direct contact or by exposure to airborne infectious material. The incubation period for chickenpox following exposure to shingles is the same as for exposure to chickenpox – 15 days with a range of 10 to 21 days. The varicella attack rate in susceptible children on household exposure to chickenpox is approximately 90% and is 25% on exposure to household shingles.

IMMUNOCOMPROMISED HOST EXPOSED TO VZV

Prior to the introduction of the varicella vaccine, the only protection from VZV infection was passive immunization at the time of exposure. Families and school personnel must continue to be aware of exposure to VZV in high-risk persons so that VZIG can be administered within 96 hours. Any susceptible person at risk for complications of VZV (Table 193.3) should receive passive immunization if exposure was adequate to communicate disease and occurred within approximately 4 days.

Individuals receiving immunosuppressive therapy should have this discontinued during the incubation period, although this precaution

Table 193.3 Groups at risk for complications of VZV infection[a]

Susceptible persons on immunosuppressive therapy[b]
Persons with congenital cellular immunodeficiency
Person with an acquired immunodeficiency, including AIDS
Persons older than 20 years
Newborn infants exposed to onset of maternal varicella less than 5 days before or 2 to 7 days after birth
Premature infants weighing <1 kg[c]

[a] Susceptible (antibody negative) persons exposed to VZV by indoor face-to-face contact with an infected person less than 2 days before or anytime during vesiculopustular stage of chickenpox are at highest risk and should receive VZIG.

[b] All cytoreductive chemotherapy and radiotherapy is considered immunosuppressive. The immunosuppressive dose of prednisone equivalent can vary in individual cases but is in the range of 1 to 2 mg/kg/d.

[c] The risk of complications of VZV infection in this group, which is poorly defined, is based on the likelihood of protective maternal antibody versus gestational age at birth.

Abbreviations: VZV = varicella-zoster virus; AIDS = acquired immunodeficiency syndrome; VZIG = varicella-zoster immune globulin.

is waived if the underlying disease requires continued treatment. Although not approved for such use, especially in children ≤12 years, valacyclovir, given at a dose of 1000 mg orally three times daily or 500 mg in those weighing less than 40 kg, can be effective in settings of acute exposure to VZV to prevent the development of chickenpox.

NORMAL ADULTS EXPOSED TO VZV

More than 90% of adults have had VZV. Susceptible adults are at risk for life-threatening chickenpox, and they are the source of unexpected epidemics. The decision to use VZIG in susceptible healthy adults following close exposure to VZV should be made on an individual basis, taking into consideration the person's health, the type of exposure, and the likelihood of previous chickenpox.

NOSOCOMIAL VZV

Control of nosocomial infections requires three actions: (1) routine continuous surveillance of VZV susceptibility among hospital staff, with VZV vaccination as indicated; (2) adequate isolation of contagious VZV infections; and (3) rapid evaluation of and response to exposure. Hospitals that care for immunodeficient children should screen staff at the time of employment for susceptibility. This can be done efficiently by performing antibody tests on those who have a negative or unknown history of chickenpox. Susceptible employees should be vaccinated and excluded from care of patients with VZV infection until approximately 1 month after the second dose of vaccine. Exposed susceptible healthcare workers should be furloughed from the eighth day after initial exposure until 21 days after the last exposure.

If the VZV exposure is from a patient, he or she should be discharged if possible. If not possible, the patient should be placed in isolation designed to prevent spread of infection by both air and direct contact. Isolation should remain in effect until skin lesions are crusted.

After control of the source of infection comes quick assessment of three types of information: (1) the nature of the exposure and whether it is likely to result in secondary infections, (2) the susceptibility to VZV of the exposed patients or staff, and (3) the risk for complications in these exposed patients. Thus, the initial step is to define the hospital areas in which a definitive VZV exposure has occurred and then to focus on which patients in these areas are at risk for infection. Those patients remaining in the hospital should be placed in respiratory isolation between days 8 and 21 postexposure or for 8 to 28 days for those receiving VZIG.

MANAGEMENT OF THE PREGNANT WOMAN

A syndrome of congenital varicella consisting of low birth weight, cutaneous scarring, limb hypoplasia, microcephaly, and other brain and eye abnormalities can occur in the baby of a pregnant woman who has chickenpox. Teratogenic damage results only from first- and second-trimester infection, and clinically apparent disease occurs only in approximately 2% of infants born after maternal varicella in early pregnancy. For this reason, experts advise that maternal chickenpox is not a medical indication for abortion. There is no reliable diagnostic method, including amniocentesis and ultrasound, for determining teratogenic intrauterine infection. VZIG should be offered to pregnant, varicella-seronegative women with significant exposure to VZV infection. Oral antiviral prophylaxis should be considered for susceptible pregnant women exposed to VZV who did not receive VZIG or have risk factors for severe disease. Intravenous acyclovir should be given to pregnant women who develop complicated varicella at any stage of pregnancy. However, it is generally recommended that these agents be used only if the benefit to the pregnant woman clearly exceeds the potential risk to the fetus.

ACKNOWLEDGMENT

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194. Viral hemorrhagic fevers

Daniel G. Bausch

INTRODUCTION

The term *viral hemorrhagic fever* (VHF) refers to an acute systemic illness classically involving fever, a constellation of initially nonspecific signs and symptoms, and a propensity for bleeding and shock. VHFs are caused by small, single-stranded, lipid-enveloped RNA viruses from four families (Table 194.1).

EPIDEMIOLOGY

Natural maintenance and transmission to humans

With the exception of dengue virus (see Chapter 183, Dengue), for which humans can now be considered to be the reservoir, hemorrhagic fever viruses are zoonotic and maintained in nature in mammals (Table 194.1). The endemic area of any given VHF is thus restricted by the distribution of its natural reservoir and/or arthropod vector, although the distribution of the virus and disease are often less vast than that of the reservoir. Infection is presumed to most often result from inadvertent inoculation of virus-contaminated reservoir excreta into mucous membranes or broken skin or, in the case of the arbovirus VHFs, mosquito or tick bite. Aerosol transmission has been suggested but there are few data to confirm or refute this route of exposure and empiric field observations suggest that aerosol transmission is not a predominant mode of spread, if it occurs at all. Nevertheless, artificially produced aerosols can infect laboratory animals, with obvious implications for potential use as bioweapons.

Human-to-human transmission

Secondary human-to-human transmission occurs in many VHFs, usually through direct contact with contaminated blood or body fluids (Table 194.1), although secondary attack rates are generally low (15%–20%). Infection probably occurs most often through oral or mucous membrane exposure. Again, there are few data on aerosol spread. Large outbreaks are almost always the result of amplification in healthcare settings in which basic infection control measures have broken down, usually in areas of extreme poverty or civil strife. The risk of transmission during the incubation period or from asymptomatic persons is negligible, although a case of Argentine hemorrhagic fever was reported due to blood transfusion from a donor who was asymptomatic. Although rare, sexual transmission during early convalescence has been suspected, best documented for Ebola, Marburg, Lassa, and Junín viruses. Despite the ease of modern-day travel, imported VHF cases remain extremely rare.

PATHOLOGY AND PATHOGENESIS

Microvascular instability, increased vascular permeability, and impaired hemostasis are the pathophysiologic hallmarks of VHF, although the mechanisms vary with each virus. Mortality usually results not from exsanguination but from a process akin to septic shock, with insufficient effective circulating intravascular volume leading to cellular dysfunction and multiorgan system failure. In fact, external bleeding is seen in a minority of cases of some VHFs (Table 194.2).

After inoculation, virus typically replicates in dendritic cells before disseminating to regional lymph nodes and then through the lymph and blood monocytes to a broad array of organs, including liver, spleen, lymph node, adrenal gland, lung, and endothelium. The particular organs most affected vary with the VHF (Table 194.2). Virus interaction with immune cells, especially macrophages and endothelial cells, results in cell activation and the unleashing of an inflammatory vasoactive process consistent with the systemic inflammatory response syndrome. Impaired hemostasis may entail endothelial cell, platelet, and/or coagulation factor

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Table 194.1 Principal viruses causing hemorrhagic fever

Virus	Disease	Geographic distribution of disease	Principal reservoir/vector	Annual cases	Case: infection ratio	Human-to-human transmissibility
Filoviridae						
Ebolavirus[a]	Ebola HF	Sub-Saharan Africa	Fruit bat?	–[b]	1:1	High
Marburgvirus	Marburg HF	Sub-Saharan Africa	Fruit bat: Egyptian fruit bat (*Rousettus aegyptiacus*)	–[b]	1:1	High
Arenaviridae[c, d]						
Old World Group						
Lassa	Lassa fever	West Africa	Rodent: natal mastomys or multimammate rat (*Mastomys natalensis*)	50 000–100 000	1:5–10	Moderate
Lujo[e]	Lujo HF	Zambia	Unknown, presumed rodent	Unknown	Unknown	Moderate-to-high
New World Group						
Junín	Argentine HF	Argentine pampas	Rodent: corn mouse (*Calomys musculinus*)	~100	1:1.5	Low
Machupo	Bolivian HF	Beni department, Bolivia	Rodent: large vesper mouse (*Calomys callosus*)	≤50	1:1.5	Low
Guanarito	Venezuelan HF	Portuguesa state, Venezuela	Rodent: cane mouse (*Zygodontomys brevicauda*)	≤50	1:1.5	Low
Sabiá[f]	Proposed name: Brazilian HF	Rural area near Sao Paulo, Brazil?	Unknown, presumed rodent	Unknown	1:1.5	Low?
Chapare[g]	Chapare HF	Cochabamba, Bolivia	Unknown, presumed rodent	Unknown	Unknown	Unknown
Bunyaviridae[c]						
Old World Group						
Hantaan, Seoul, Puumala, Dobrava-Belgrade, others	HF with renal syndrome	Hantaan: northeast Asia; Seoul: urban areas worldwide; Puumala and Dobrava-Belgrade: Europe	Rodent: Hantaan – striped field mouse (*Apodemus agrarius*); Seoul – Brown or Norway rat (*Rattus norvegicus*); Puumala – bank vole (*Clethrionomys glareolus*); Dobrava-Belgrade – yellow-necked field mouse (*Apodemus flavicollis*)	50 000–150 000	Hantaan: 1:1.5 Others: 1:20	None
New World Group						
Sin Nombre, Andes, Laguna Negra, others (see also Chapter 186, Hantavirus cardiopulmonary syndrome in the Americas)	Hantavirus cardiopulmonary syndrome	Americas	Rodent: Sin Nombre – deer mouse (*Peromyscus maniculatus*); Andes – long-tailed colilargo (*Oligoryzomys longicaudatus*); Laguna Negra – little laucha or small vesper mouse (*Calomys laucha*)	50 000–150 000	Sin Nombre: 1:1; others up to 1:20	None, except for Andes virus

Table 194.1 *(continued)*

Virus	Disease	Geographic distribution of disease	Principal reservoir/vector	Annual cases	Case: infection ratio	Human-to-human transmissibility
Rift Valley fever	Rift Valley fever	Sub-Saharan Africa, Madagascar, Saudi Arabia, Yemen	Domestic livestock/mosquitoes (sylvatic *Aedes* and others)	100–100 000[b,h]	1:100	None
Crimean-Congo HF	Crimean-Congo HF	Africa, Balkans, southern Russia, Middle East, India, Pakistan, Afghanistan, western China	Wild and domestic vertebrates/tick (primarily *Hyalomma* species)	~500	1:1–2	High
Flaviviridae						
Yellow fever	Yellow fever	Sub-Saharan Africa, South America up to Panama	Monkey/mosquito (*Aedes aegypti*, other *Aedes* and *Hemagogus* species)	5000–200 000[i]	1:2–20	None
Dengue	Dengue HF	Tropics and subtropics worldwide	Human/mosquito (*Ae. aegypti* and *Ae. albopictus*)	100 000–200 000[i]	1:10–100 depending on age, previous infection, genetic background, and infecting serotype	None
Omsk HF	Omsk HF	Western Siberia	Rodent/tick (primarily *Dermacentor* and *Ixodes* species)	100–200	Unknown	Not reported
Kyasanur Forest disease	Kyasanur Forest disease	Karnataka state, India; Yunnan Province, China; Saudi Arabia	Vertebrate (rodents, bats, birds, monkeys, others)/tick (*Haemophysalis* species and others)	~500	Unknown	Not reported, but laboratory infections have occurred
Alkhumra HF[j]	Proposed name: Alkhumra HF	Saudi Arabia, Egypt	Ticks?	≤50	Unknown	Not reported

Abbreviation: HF = hemorrhagic fever.

[a] Six species or subtypes of Ebolavirus are recognized with varying associated case-fatality ratios (see Table 194.2). All are endemic to sub-Saharan Africa, with the exceptions of Reston ebolavirus that is found in the Philippines and Lloviu ebolavirus which was detected in bats in Spain.

[b] Although some endemic transmission of the filoviruses (Ebolavirus>Marburgvirus) and Rift Valley fever virus occurs, these viruses have most often been associated with outbreaks. Filovirus outbreaks are typically less than 100 cases and have never been greater than 500.

[c] The virus families Arenaviridae and Bunyaviridae are serologically, phylogenetically, and geographically divided into Old World (i.e., Africa) and New World (i.e., the Americas) complexes.

[d] In addition to the arenaviruses listed in the table, Flexal and Tacaribe viruses have caused human disease as a result of laboratory accidents. Another arenavirus, Whitewater Arroyo, has been noted in sick persons in California but its role as a pathogen has not been clearly established.

[e] Discovered in 2008. Only 5 cases (4 of them fatal) from one outbreak have been noted. The index case came to South Africa from Zambia.

[f] Discovered in 1990. Only 3 cases (1 fatal) have been noted, 2 of them from laboratory accidents.

[g] Discovered in 2003 from a small outbreak from which blood was obtained from one fatal case and Chapare virus isolated. Few other details have been reported.

[h] Although Rift Valley fever virus can be found throughout sub-Saharan Africa, large outbreaks usually occur in East Africa's Rift Valley region.

[i] Based on estimates from the World Health Organization. Significant underreporting occurs. Incidence may fluctuate widely in place and time.

[j] Alkhumra is considered by some to be a variant of Kyasanur Forest disease virus. Disagreement exists over the proper spelling of the virus, written as "Alkhurma" in some publications.

Table 194.2 Clinical aspects of the viral hemorrhagic fevers

Disease	Incubation period (days)	Onset	Bleeding	Rash	Jaundice	Heart	Lung	Kidney	Central nervous system	Eye	Case fatality ratio	Clinical management
Filoviridae												
Ebola HF	3–21	Variable	++	+++	+	++?	+	+	+	+	40%–85%[a]	Supportive
Marburg HF	3–21	Abrupt	++	+++	+	++?	+	+	+	+	22%–85%[b]	Supportive
Arenaviridae												
Lassa fever	5–16	Gradual	+	+[c]	0	++	+	0	+	0	20%	Ribavirin
Lujo HF	9–13	Abrupt	++	+	0	?	+	+	+	0	80%	Ribavirin
South American HFs[d]	4–14	Gradual	+++	+	0	++	+	0	+++	0	15%–40%	Ribavirin, convalescent plasma
Bunyaviridae												
Hemorrhagic fever with renal syndrome	9–35	Abrupt	+++	0	0	++	+	+++	+	0	<1–50% depending on specific virus	Ribavirin
Hantavirus pulmonary syndrome	7–35	Gradual	0 (except for Andes virus infection)	0	0	+++	+++	+	+	0	<1–50% depending on specific virus	Supportive, ECMO?
Rift Valley fever[e]	2–5	Abrupt	++	+	++	+?	0	+	++	++	Up to 50% in severe forms	Ribavirin?
Crimean-Congo HF	1–12[f]	Abrupt	+++	0	++	+?	+	0	+	0	15%–30%	Ribavirin
Flaviviridae												
Yellow fever	3–6	Abrupt	+++	0	+++	++	+	++	++	0	20%–50%	Supportive
Dengue HF	3–15	Abrupt	++	+++	+	++	+	0	+	0	Untreated: 10–15% Treated: ≤1%	Supportive
Omsk HF	3–8	Abrupt	++	0	0	+	++	0	+++	+	1%–3%	Supportive
Kyasanur Forest disease	3–8	Abrupt	++	0	0	+	++	0	+++	+	3%–5%	Supportive
Alkhumra HF[g]	3–8	Abrupt	++	+	+	+	+	0	++	+	20%–25%	Supportive

Abbreviations: ECMO = extracorporeal membrane oxygenation; HF = hemorrhagic fever.

[a] Six species or subtypes of Ebolavirus are recognized with varying associated case-fatality ratios: Zaire – 85%, Sudan – 55%, Bundibugyo – 40%, Tai Forest (also called Cote d'Ivoire) – 0 (only one recognized case, who survived), Reston – 0 (not pathogenic to humans), Lloviu – no human infections recognized.

[b] The case fatality ratio was 22% in the first recognized outbreak of Marburg HF in Germany and Yugoslavia in 1967 but has been consistently over 80% in outbreaks in central Africa where the virus is endemic. Possible reasons for this discrepancy include differences in quality of care, strain pathogenicity, route and dose of infection, underlying prevalence of immunodeficiency and comorbid illnesses, and genetic susceptibility.

[c] A morbilliform or maculopapular skin rash almost always occurs in persons with lighter skin, who are usually expatriates, but, for unclear reasons, is rarely present in darker-skinned Africans from the endemic area.

[d] Data are insufficient to distinguish between the syndromes produced by the various arenaviruses found in the Americas. They are thus frequently grouped as the "South American hemorrhagic fevers."

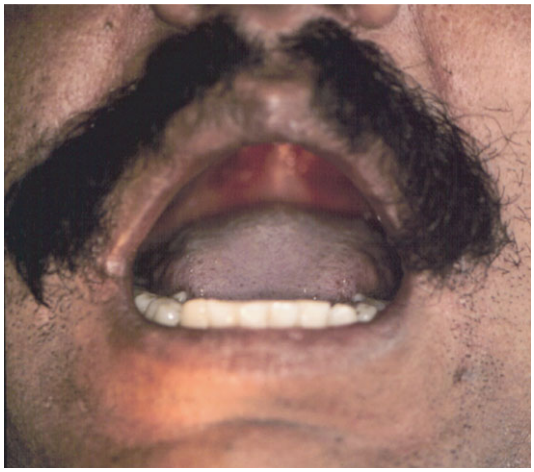
[e] HF, encephalitis, and retinitis may be seen in Rift Valley fever independently of each other.

[f] The incubation period of Crimean-Congo HF varies with the mode of transmission: typically 1–3 days after tick bite and 5–6 days after contact with infected animal blood or tissues.

[g] Based on preliminary observations. Fewer than 100 cases have been reported.

Key: 0 = sign not typically noted/organ not typically affected, + = sign occasionally noted/organ occasionally affected, ++ = sign commonly noted/organ commonly affected, +++ = sign characteristic/organ involvement severe.

A



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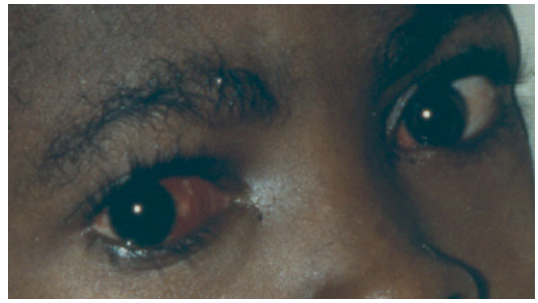

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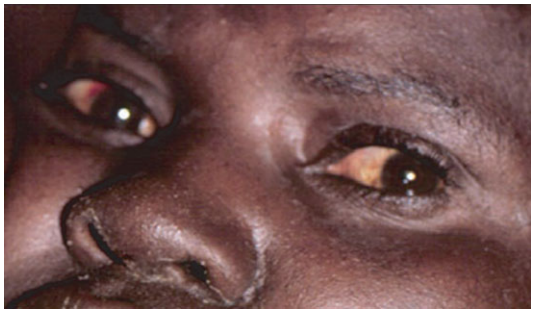

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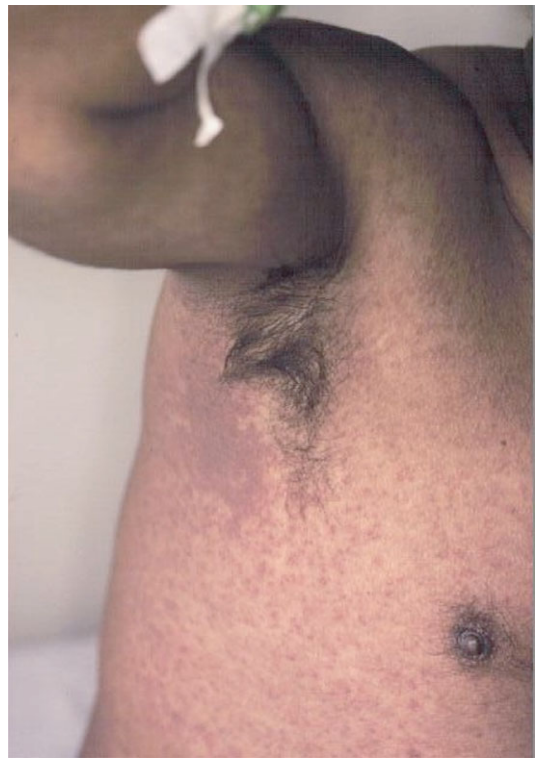

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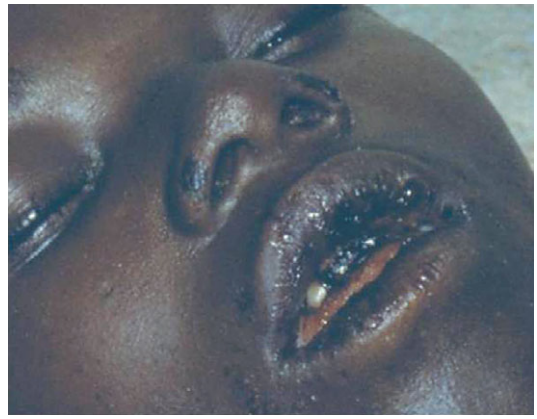

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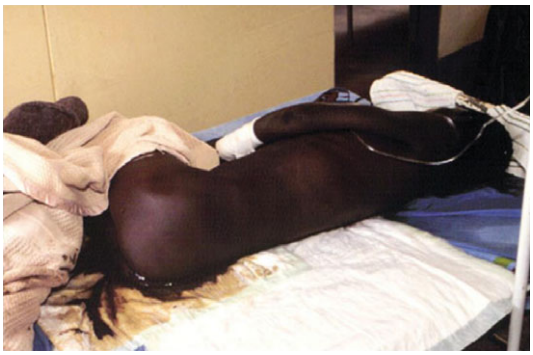

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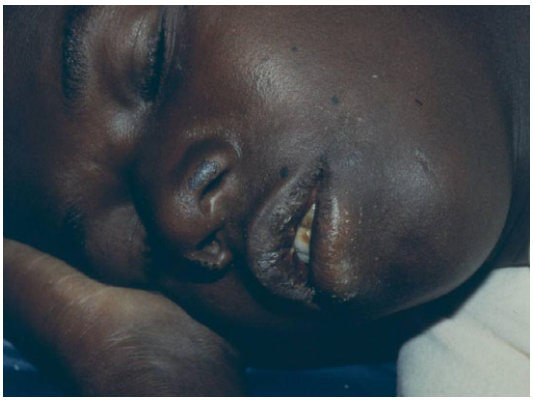

Figure 194.1 Clinical manifestations of viral hemorrhagic fever. **(A)** Soft and hard palate erythema in Lassa fever. **(B)** Subconjunctival hemorrhage in Lassa fever. **(C)** Subconjunctival hemorrhage in Ebola hemorrhagic fever. **(D)** Maculopapular skin rash in Lassa fever. **(E)** Severe oral and nasal mucosal bleeding in Ebola hemorrhagic fever. **(F)** Mild oral and nasal mucosal bleeding in Lassa fever. **(G)** Rectal bleeding in Ebola hemorrhagic fever. **(H)** Facial edema in Lassa fever.

dysfunction. Disseminated intravascular coagulation (DIC) is frequent in some VHFs (Table 194.2). The degree of tissue damage varies with the VHF and may be mediated either through necrosis or apoptosis. Cardiac inotropy may be inhibited in some VHFs, further impairing organ perfusion. Adrenal or pituitary gland necrosis with consequent vascular collapse has been postulated but not specifically demonstrated. Virus is cleared rapidly from the blood in survivors but may remain for weeks or months in a few immunologically protected sites, such as the chambers of the eye, central nervous system, and gonads, the latter resulting in the aforementioned sexual transmission during convalescence.

The pathogenesis of most VHFs appears to be related to unchecked viremia, with most fatal cases failing to mount a significant antibody response, in some cases due to virus-induced suppression of the host adaptive immune response. Virus can be found in a wide variety of body fluids during the acute illness, including blood, saliva, stool, and breast milk. Inflammatory cell infiltration is usually mild, consisting of a mix of mononuclear cells and neutrophils. However, in dengue, yellow fever, and hantavirus infections (see Chapter 186, Hantavirus cardiopulmonary syndrome in the Americas), in which viremia is usually cleared prior to the most severe phase of the disease, the host immune response may play a detrimental role. The unique process of antibody-mediated enhancement may facilitate the development of dengue hemorrhagic fever (see Chapter 183, Dengue).

CLINICAL PRESENTATION

VHF is seen in both genders and all ages. Although the clinical manifestations of each VHF may differ as disease progresses, distinction in the early phases is rarely possible. Most patients present with nonspecific signs and symptoms difficult to distinguish from other common febrile illnesses, including fever, general malaise, anorexia, headache, chest or retrosternal pain, sore throat, myalgia, arthralgia, and lumbosacral pain (Table 194.2). The pharynx may be erythematous or even exudative, especially in Lassa fever, resulting in misdiagnosis of streptococcal pharyngitis or mononucleosis (Figure 194.1A). Conjunctival injection or hemorrhage is frequent but not typically accompanied by itching, discharge, or rhinitis (Figures 194.1B and C). Hiccups may be seen early in Ebola hemorrhagic fever. Gastrointestinal signs and symptoms ensue in the first few days, including nausea and vomiting, epigastric and abdominal pain and tenderness (especially in the right upper quadrant in Ebola hemorrhagic fever), and non-bloody diarrhea. Appendicitis or other acute abdominal emergencies are sometimes suspected, prompting potentially hazardous (in terms of risk of bleeding and nosocomial spread) surgical interventions. Morbilliform, maculopapular, petechial, or

ecchymotic skin rashes may be seen, depending on the specific VHF (Table 194.2 and Figure 194.1D). Hepatosplenomegaly is frequently noted but may simply represent high underlying prevalence in populations in sub-Saharan Africa where most clinical observations have been made. Relative bradycardia (Faget's sign) and orthostatic hypotension may be noted, especially in yellow fever and dengue virus infections. Biphasic illnesses are described with a quiescent period of days (yellow fever, dengue hemorrhagic fever, and Rift Valley fever) to weeks (Kyasanur Forest disease and Omsk hemorrhagic fever) after which the most severe manifestations may set in, but not uniformly noted. Distinct progressive phases of prodrome, hypotension, oliguria/renal failure, diuresis, and convalescence are classically described for hemorrhagic fever with renal syndrome (HFRS), but again not uniformly seen. Neck pain and stiffness, retro-orbital pain, and photophobia and other meningeal signs are common in Rift Valley fever, Kyasanur Forest disease, and Omsk hemorrhagic fever.

In severe cases, patients progress towards the end of the first week of illness to vascular instability that may be manifested by facial flushing, edema, bleeding, hypotension, shock, and proteinuria (Figures 194.1E–H). The likelihood of hemorrhage varies with the VHF (Table 194.2) and may be manifested as hematemesis, melena, hematochezia, menometrorrhagia, petechiae, purpura, epistaxis, and bleeding from the gums and venipuncture sites (Figures 194.1E–G). Hemoptysis and hematuria are infrequent. Hemorrhage is almost never present in the first 48 hours of illness. Facial and neck swelling are classic signs of severe Lassa and Lujo virus infection. Central nervous system manifestations, including delirium, tremor, gait anomalies, convulsions, and hiccups may be noted in end-stage disease. Renal insufficiency or failure may occur, especially in HFRS. Pregnant women often present with spontaneous abortion and vaginal bleeding. A dry cough, sometimes with a few scattered rales on auscultation, is frequently noted, but prominent pulmonary symptoms early in the course of disease are uncommon, with the exception of with hantavirus pulmonary syndrome. With the exception of yellow fever, jaundice is not typical in the absence of underlying Gilbert's syndrome, drug reaction, or coinfection. Radiographic and electrocardiographic findings are generally nonspecific.

Disease usually progresses rapidly, with death 7 to 14 days after symptom onset in fatal cases. Common indicators of a poor prognosis include shock, bleeding, neurologic manifestations, high viremia (or surrogate measurements of antigen or genome copies), and elevated levels of aspartate aminotransferase (>150 IU/L). Maternal and fetal mortality are elevated in pregnancy, especially during the third trimester, where they approach 100%. However, mild and even asymptomatic cases have been reported even for what are considered the most virulent VHFs, possibly related to differences in route and dose of infection, underlying comorbid illness, and host genetic predisposition. Specific human genotypes or histocompatibility markers have been associated with risk of Lassa fever and hantavirus infection.

DIFFERENTIAL DIAGNOSIS

The nonspecific early clinical presentation makes clinical diagnosis difficult, with a long differential diagnosis (Table 194.3). Recognition of case clusters, often involving healthcare workers, is a common first clue. A detailed epidemiologic history and physical exam and preliminary laboratory results (Table 194.4) are critical, including details of travel, exposures, occupational risks, and disease progression (for example, timing of hemorrhage relative to onset of illness). VHF should be considered in patients who (1) reside in or traveled to an endemic area (Table 194.1); (2) had potential direct contact with blood or body fluids of someone with a VHF during their acute illness (this group most often is composed of healthcare workers, persons caring for family members at home or preparing bodies for burial, and laboratory personnel); (3) had contact with live or recently killed wild animals (especially nonhuman primates) in or recently arriving from an endemic area, including veterinarians, hunters, farm and abattoir workers, and taxidermists. Food potentially recently contaminated by these animals could also be a source of infection, although this remains to be clearly documented; (4) worked in a VHF research laboratory or animal facility; or (5) had sexual relations with someone recovering from a VHF in the last 3 months. Most VHFs are rare even in persons meeting the above criteria so alternative diagnoses, especially malaria and typhoid fever, should always be aggressively sought. Acts of bioterrorism must be considered if VHF is strongly suspected in a patient without any of the above criteria, especially if clusters of cases occur.

Table 194.3 Differential diagnosis of the viral hemorrhagic fevers

Disease	Distinguishing characteristics and comments
Parasites	
Malaria	Classically shows paroxysms of fever and chills; hemorrhagic manifestations less common; malaria smears or rapid test usually positive; coinfection (or baseline asymptomatic parasitemia) common; responds to antimalarials
Amebiasis	Hemorrhagic manifestations other than bloody diarrhea generally not seen; amebic trophozoites identified in the stool by microscopy and/or antigen assays; responds to antiparasitics
Giardiasis	Positive stool antigen test and/or identification of trophozoites or cysts in stool; responds to antiparasitics
African trypanosomiasis (acute stages)	Especially the east African form. Examination of peripheral blood smear/buffy coat may show trypanosomes
Bacteria (including Spirochetes, *Rickettsia*, *Ehrlichia*, and *Coxiella*)	
Typhoid fever	Hemorrhagic manifestations other than bloody diarrhea generally not seen; responds to antibiotics
Bacillary dysentery (including shigellosis, campylobacteriosis, salmonellosis, and enterohemorrhagic *Escherichia coli* and others)	Hemorrhagic manifestations other than bloody diarrhea generally not seen; respond to antibiotics
Capnocytophaga canimorsus	Associated with dog and cat bites, typically in persons with underlying immunodeficiency, notably asplenic patients; responds to antibiotics
Meningococcemia	Bacterial-induced DIC may mimic the bleeding diathesis of VHF; bleeding within the first 24–48 hours after onset of illness and rapidly progressive illness typical; large ecchymoses typical of meningococcemia are unusual in the VHFs except for Crimean-Congo HF; rapid serum latex agglutination tests can be used to detect bacterial antigen in meningococcal septicemia; may respond to antibiotics (critical to administer early)
Staphylococcemia	Bacterial-induced DIC may mimic the bleeding diathesis of VHF; may respond to antibiotics
Septic abortion	History of pregnancy and positive pregnancy test
Septicemic or pneumonic plague	Bacterial-induced DIC may mimic the bleeding diathesis of VHF; large ecchymoses typical of plague are unusual in the VHFs except for Crimean-Congo HF; pneumonic plague may mimic hantavirus pulmonary syndrome; may respond to antibiotics
Streptococcal or Epstein–Barr virus pharyngitis	May mimic the exudative pharyngitis sometimes seen in Lassa fever
Tuberculosis	Hemoptysis of advanced pulmonary tuberculosis may suggest VHF, but tuberculosis generally has a much slower disease evolution
Tularemia	Ulceroglandular and pneumonic forms more common; responds to antibiotics
Acute abdominal emergencies	Appendicitis, peritonitis, and bleeding upper gastrointestinal ulcer
Pyelonephritis and poststreptococcal glomerulonephritis	May mimic HF with renal syndrome
Anthrax (inhalation or gastrointestinal)	Prominent pulmonary manifestations and widened mediastinum on chest x-ray in inhalation form; responds to antibiotics
Atypical bacterial pneumonia (*Legionella*, *Mycoplasma*, *Chlamydia pneumoniae* and *Chlamydia psittaci*, others)	May mimic hantavirus pulmonary syndrome; exposure to birds; symptoms often not present until late in the illness in psittacosis; respond to antibiotics
Relapsing fever	Recurrent fevers and flu-like symptoms, with direct neurologic involvement and splenomegaly; spirochetes visible in blood while febrile; responds to antibiotics
Leptospirosis	Jaundice, renal failure, and myocarditis in severe cases; responds to antibiotics
Spotted fever group rickettsia (including African tick-bite fever, Boutonneuse fever, Rocky Mountain spotted fever)	Incubation period of 7–10 days after tick bite, compared with 1–3 days in Crimean-Congo HF; necrotic lesions (eschar) typically seen at site of tick bite in some rickettsial diseases while there may only be slight bruising at the bite site in Crimean-Congo HF; rash (if present) of rickettsial infection classically involves palms and soles

Table 194.3 *(continued)*

Disease	Distinguishing characteristics and comments
Q fever *(Coxiella burnetii)*	Broad spectrum of illness, including hepatitis, pneumonitis, encephalitis, and multisystem disease with bleeding; responds to antibiotics
Ehrlichiosis	Diagnosis by serology and PCR; blood film may be useful; responds to antibiotics
Viruses	
Influenza	Prominent respiratory component to clinical presentation; no hemorrhagic manifestations; influenza rapid test may be positive; may respond to anti-influenza drugs
Arbovirus infection (including dengue and West Nile fever)	Encephalitis unusual, but when present may mimic the VHFs with significant neurologic involvement (Kyasanur Forest disease, Omsk HF); usually less severe than VHF; hemorrhage not reported
Viral hepatitis (including hepatitis A, B, and E, Epstein–Barr, and cytomegalovirus)	Jaundice atypical in HF except yellow fever; tests for hepatitis antigens positive; fulminant infection resembling VHF may be seen in persons with underlying immune deficiencies
Herpes simplex or varicella-zoster	Fulminant infection with hepatitis (with/without vesicular rash); elevated transaminases and leukopenia typical; disseminated disease may be noted in otherwise healthy persons; poor response to acyclovir drugs unless recognized early
HIV/AIDS	Seroconversion syndrome or HIV/AIDS with secondary infections, especially septicemia
Measles	Rash may mimic that seen in early stages of some VHFs and may sometimes be hemorrhagic; prominence of coryza and upper respiratory symptoms in measles should help differentiate; vaccine preventable
Rubella	Rash may mimic that seen in early stages of some VHFs; usually a mild disease; vaccine preventable
Hemorrhagic or flat smallpox	Diffuse hemorrhagic or macular lesions; in contrast to the VHFs, the rash may involve the oral mucosa, palms, and soles; smallpox in the wild has been eradicated
Alphavirus infection (including chikungunya and o'nyong-nyong)	Joint pain typically a predominant feature
Fungi	
Histoplasmosis	Pulmonary disease may mimic hantavirus pulmonary syndrome; recent entry into mines or caves
Noninfectious etiologies	
Heat stroke	History for extreme heat exposure; absence of sweating; bleeding not typical but DIC may occur
Idiopathic and thrombotic thrombocytopenic purpura (ITP/TTP)	Presentation usually less acute than VHF; may have prominent neurologic symptoms in TTP; coagulation factors normal and DIC absent; often respond to corticosteroids (ITP) or plasma exchange (TTP)
Acute glaucoma	May mimic the acute ocular manifestations of Rift Valley fever
Hematologic malignancies (leukemia, lymphoma)	May resemble leukemoid reaction occasionally seen in HF with renal syndrome
Drug sensitivity or overdose	Stevens–Johnson syndrome and anticoagulant (warfarin) overdose
Industrial and agricultural chemical poisoning	Especially anticoagulants, although other symptoms of VHF absent
Hematoxic snake bite envenomation	History of snake bite

Abbreviations: AIDS = acquired immunodeficiency syndrome; DIC = disseminated intravascular coagulopathy; HF = hemorrhagic fever; HIV = human immunodeficiency virus; PCR = polymerase chain reaction; VHF = viral hemorrhagic fever.

LABORATORY DIAGNOSIS

Prompt laboratory confirmation of VHF is imperative but testing is unfortunately only available in a few specialized laboratories since no commercial assays exist, with the exception of various kits for dengue fever and hantavirus pulmonary syndrome. In the United States, testing can be arranged through the Centers for Disease Control and Prevention (phone 404–639–1115, after hours 770–488–7100; e-mail dvd-1spath@cdc.gov). Commonly used diagnostic assays include enzyme-linked immunosorbent assay (ELISA) for viral antigen and IgM antibody, polymerase chain reaction, virus culture, immunofluorescent antibody assay, and

Table 194.4 Indicated laboratory tests and characteristic findings in the viral hemorrhagic fevers

Test	Characteristic findings and comments
Leukocyte count	Early: moderate leukopenia (except for hantavirus infection, in which early leukocytosis with immunoblasts are classically noted); later: leukocytosis with left shift; granulocytosis more suggestive of bacterial infection
Hemoglobin and hematocrit	Hemoconcentration (especially noted in hemorrhagic fever with renal syndrome and hantavirus pulmonary syndrome)
Platelet count	Mild-to-moderate thrombocytopenia
Electrolytes	Sodium, potassium, and acid–base perturbations, depending upon fluid balance and stage of disease Often increased
BUN/creatinine	Renal failure may occur late in disease
Serum chemistries (AST, ALT, amylase, gamma-glutamyl transferase, alkaline phosphatase, creatinine kinase, lactate dehydrogenase, lactic acid)	Usually increased, especially in severe disease; AST > ALT; a lactate level greater than 4 mmol/L (36 mg/dL) may indicate persistent hypoperfusion and sepsis. Lactate dehydrogenase is typically markedly increased in hantavirus pulmonary syndrome
Sedimentation rate	Normal or decreased
Blood gas	Metabolic acidosis may be indicative of shock and hypoperfusion
Coagulation studies (PT, PTT, fibrinogen, fibrin split products, platelets, D-dimer)	DIC common in Ebola, Marburg, Lujo virus, Crimean-Congo HF, and New World arenavirus infections. D-dimers appear to be an especially early and sensitive indicator
Urinalysis	Proteinuria common; hematuria may be occasionally noted; sediment may show hyaline-granular casts, and round cells with cytoplasmic inclusions
Blood culture	Useful early to exclude VHF and later to evaluate for secondary bacterial infection; blood should be drawn before antibiotic therapy is instituted
Stool culture	Useful to exclude VHF (in favor of hemorrhagic bacillary dysentery)
Thick and thin blood smears	May aid in the diagnosis of blood parasites (malaria and trypanosomes), bacterial sepsis (meningococcus, capnocytophaga, and anthrax) and ehrlichiosis; all negative in VHF unless coinfection
Rapid test, PCR, or other assay for malaria	Negative in VHF unless coinfection with malaria

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; DIC = disseminated intravascular coagulation; VHF = viral hemorrhagic fever; BUN = blood urea nitrogen; PT = prothrombin time; PTT = partial thromboplastin time; PCR = polymerase chain reaction.

immunohistochemistry on postmortem tissues. Research is underway on a variety of new diagnostic approaches.

CLINICAL MANAGEMENT

Patients should generally be treated in an intensive care unit. For most VHFs, only supportive therapy is available. Treatment guidelines generally follow those recommended for septic shock, given the overlap in the pathogenesis of that condition and severe VHF, and considering that results from controlled trials on VHF are rare. Consultation with infectious disease specialists with experience treating VHF should be sought as soon as the diagnosis is considered. The process of performing a workup for non-VHF etiologies while assuring staff and patient safety and avoiding undue panic is a delicate one. Knowledge that most VHFs are rare and that routinely practiced universal and contact precautions are protective in the vast majority of cases should offer reassurance. Confirmed cases of VHF should be reported immediately to government health authorities.

Fluid management

Fluid management in VHF poses a particular challenge. Severe microvascular instability, often complicated by vomiting, diarrhea, decreased fluid intake, and third-spacing, often dictates aggressive fluid replacement, which may prevent shock and DIC. However, overaggressive and unmonitored rehydration may lead to pulmonary edema, especially given the impaired cardiac

function present in some VHFs, particularly hantavirus pulmonary syndrome. Although invasive hemodynamic monitoring would seem to be in order, with the exception of peripheral intravenous lines, indwelling vascular devices are contraindicated due to the risk of bleeding at the site, although they have been occasionally placed without reported complications. Intramuscular and subcutaneous injections should be avoided due to the risk of hematoma. It is probably best to rely on frequent sphygmomanometer readings and fluid balance assessment from capillary refill and urine output.

Early goal-directed therapies have been shown to mitigate both mortality and organ dysfunction in shock. Crystalloids (normal saline or Ringer's lactate), blood products (see below), and, if necessary, vasopressors (norepinephrine, adding epinephrine when warranted) should be infused to maintain mean arterial blood pressure above 65 mm Hg in adults. Vasopressin (0.03 U/min) can be added to decrease the norepinephrine dose but should not be used as the initial vasopressor. Dobutamine should be considered if there is evidence of myocardial dysfunction but dopamine is not recommended. Peritoneal and hemodialysis have been employed extensively in patients with HFRS without frequent complications, but there is little published experience with the other VHFs. Specific World Health Organization (WHO) guidelines exist for the fluid management of dengue shock syndrome (see Chapter 183).

Blood products and management of DIC

Despite profuse bleeding in some VHFs (Table 194.2), blood products should not be given empirically but rather only to meet defined clinical and laboratory parameters in the face of clinically significant hemorrhage. Transfusions, preferably with packed red blood cells, should be used to maintain a hemoglobin over 7.0 g/dL while avoiding volume overload, taking into account that chronic anemia due to malaria and malnutrition may be frequent in patients in certain geographic areas. Whole blood may be substituted if packed cells are not available. Transfusion of platelet concentrate (1–2 U/10 kg) and/or fresh frozen plasma (FFP) (15–20 mL/kg) may be required if DIC is present (Table 194.2). Treatment should not be based on laboratory results alone except in preparation for an invasive procedure or when platelet levels fall to dangerously low levels (<50 000/mm^3 in a bleeding patient or 20 000/mm^3 without bleeding). The platelet count should generally rise by at least 2000/mm^3 per unit of platelets transfused, although the response will be less if there is ongoing DIC and platelet consumption. Impaired platelet aggregation may promote hemorrhage in some VHFs, especially Lassa fever, even when platelet counts are not drastically low. Fibrinogen concentrate (total dose 2–3 g) or cryoprecipitate (1 U/10 kg) may be administered instead of FFP, although FFP has the theoretical advantage of containing all coagulation factors and inhibitors deficient in DIC but no activated coagulation factors. Vitamin K (10 mg intravenous or orally for 3 days) and folic acid may be given, especially if underlying malnutrition or liver disease is suspected, although their efficacy is unknown.

Oxygenation and ventilation

With the exception of hantavirus pulmonary syndrome, for which early mechanical ventilation is often lifesaving, impaired gas exchange is not typically a prominent feature of VHF, especially in the early phases of disease and in the absence of iatrogenic pulmonary edema. Most patients can be supported with oxygen administered via a nasal cannula or face mask. In neurologically intact patients, noninvasive positive pressure ventilation may be a useful adjunct to forestall intubation. When mechanical ventilation is required, lung-protective tidal volumes (6–8 mL/kg of ideal body weight) should be employed to avoid ventilator-induced lung injury (i.e., barotrauma) and pulmonary hemorrhage. Extracorporeal membrane oxygenation has been used with apparent benefit in hantavirus pulmonary syndrome. Due to the risk of bleeding, arterial puncture for blood gas determination should be minimized, relying on respiratory rate and pulse oximetry if possible.

Antiviral drugs

The guanosine analog ribavirin is the only currently available antiviral therapy for any VHF (Table 194.2). Early treatment is imperative for maximum benefit. The best data are for the arenaviruses, especially Lassa fever, and HFRS (Table 194.2). Ribavirin also appears to be efficacious in Crimean-Congo HF, although few randomized controlled clinical trials have been performed. A prospective trial of ribavirin in

Rift Valley fever in Saudi Arabia in 2000 was stopped after an increase in encephalitis was noted in the treatment group, but significant baseline discrepancies between the treatment and control groups make definitive conclusions difficult. In vitro data generally show activity of ribavirin against dengue, yellow fever, and Omsk hemorrhagic fever viruses, but clinical studies have not been performed. Ribavirin is not efficacious against Ebola or Marburg viruses. The main side effects of intravenous ribavirin are a mild-to-moderate hemolytic anemia, which infrequently necessitates transfusion and disappears with cessation of treatment, and rigors when the drug is infused too rapidly. A number of experimental therapies have shown in vitro activity and therapeutic benefit in animal studies and have been used on a compassionate-use basis in humans, but are not yet approved or widely available.

Convalescent plasma and antibody therapy

Although cellular immunity is thought to be the primary arm of protection in most VHFs, treatment with convalescent immune plasma has often been tried, especially for arenavirus infections. Transfusion of appropriately titered convalescent plasma within the first 8 days of illness reduces the case fatality of Argentine hemorrhagic fever to less than 1%. However, this therapy has been associated with a convalescent-phase neurologic syndrome characterized by fever, cerebellar signs, and cranial nerve palsies in 10% of those treated 7 to 80 days (mean 20 days) after initial symptom resolution. Animal studies show convalescent plasma to be efficacious in Lassa fever as well, but only if it contains a high titer of neutralizing antibody (which is not automatically the case) and there is a close antigenic match between the infecting viruses of the donor and recipient. Convalescent plasma or blood has been given to numerous patients with Ebola hemorrhagic fever, but their efficacy is still unknown. Risk of concomitant transmission of other bloodborne pathogens and lack of an existing bank of immune plasma for VHF treatment are significant impediments to this approach in most countries. With the exception of for Argentine hemorrhagic fever, this therapy should be reserved for severe and refractory cases when ribavirin is not an option. Numerous mono- and polyclonal antibody preparations show promise in VHF animal models.

Coagulation modulators

A growing body of literature suggests that disturbances in the procoagulant–anticoagulant balance play an important role in the mediation of septic shock. Coagulation-modifying drugs that have been explored anecdotally in humans or in animal models of sepsis and/or VHF, with varying degrees of efficacy, included rNAPc2 (a potent experimental recombinant inhibitor of the tissue factor/factor VIIa coagulation pathway), recombinant factor VIIa itself (paradoxically, since it would have the opposite effect of rNAPc2), heparin sulfate, and antithrombin III. Lower mortality was recently noted in heparin-treated patients with severe sepsis in a phase III clinical trial. Nevertheless, use of coagulation modulators for VHF should still be considered experimental. Despite early promise, recombinant activated protein C is no longer recommended for septic shock or VHF.

Immune modulators

Trials of various immune modulators in septic shock or VHF, including ibuprofen, corticosteroids, anti-tumor necrosis factor-α (TNF-α), nitric oxide inhibitors, statins (HMG-CoA reductase inhibitors), and interleukins, have not shown conclusive benefit. Ribavirin combined with interferon (IFN) alfacon-1, a consensus IFN, diminished mortality in a hamster arenavirus model. Although approved for clinical use in humans, IFN alfacon-1 has not been tested in human VHF. In a small study, recombinant interleukin-2 reduced renal insufficiency in HFRS, but confirmation is needed before this can be considered the standard of care. There has been renewed interest in the use of corticosteroids for possible adrenal insufficiency in septic shock. Interestingly, viral infection of the adrenal cortex and adrenal gland necrosis have been reported in various VHFs. Results of a few clinical trials of corticosteroids in shock as well as in HFRS have been mixed. Furthermore, their use might exacerbate the immunosuppression common in some VHFs. Until more conclusive studies are conducted, corticosteroids should probably not be administered unless adrenal insufficiency is strongly suspected, the target blood pressure is not maintained despite adequate fluid repletion and vasopressors, or if cerebral edema is suspected. If necessary, a dose of 200 mg intravenous hydrocortisone per day in adults should be used, divided into two to

four daily doses or administer by continuous infusion.

Antibiotics and secondary infection

Patients should be immediately covered with appropriate antibacterial and/or antiparasitic therapy, with specific consideration of malaria and rickettsial disease, until VHF can be confirmed (Table 194.3). These drugs should then be stopped unless there is evidence of coinfection. Secondary bacterial infection should be suspected when patients have persistent or new fever after about 2 weeks of illness, when most VHFs have either resulted in death or are resolving.

Pain control, gastrointestinal stress ulcer prophylaxis, and management of seizures and other central nervous system manifestations

Oral or parenteral acetaminophen, tramadol, opiates, or other analgesics should be used as needed for pain control, adjusting as necessary for hepatic insufficiency. Avoid salicylates and nonsteroidal anti-inflammatory drugs because of the risk of bleeding. Prophylactic therapy for gastrointestinal stress ulcers with proton pump inhibitors or histamine-2 receptor antagonists is recommended. Antiemetics, such as the phenothiazines, are frequently warranted. Seizures can usually be managed with standard use of benzodiazepines, phenytoins, or levetiracetam, with careful attention to possible respiratory depression and hypotension. These drugs should not be given prophylactically.

Clinical laboratory testing

A broad range of clinical laboratory parameters should be monitored in patients with VHF (Table 194.4). Laboratory tests for DIC should be performed. Third-spacing, vomiting, diarrhea, decreased fluid intake, and the administration of intravenous fluids may result in significant electrolyte imbalance, especially hypokalemia, so regular potassium supplementation may be needed, keeping a close eye on renal function, which is often compromised in late disease. Although hyperglycemia has not been reported frequently in VHF, glucose should be monitored and levels kept <180 mg/dL via the use of intravenous insulin.

Nutrition

Gut feeding is preferable to parenteral alimentation when possible. Nasogastric tubes may be theoretically indicated for patients unable to eat, but there is little practical experience with their use in the VHFs. Exacerbation of gastrointestinal bleeding and heightened risk of transmission to healthcare workers during tube placement are concerns.

Management of pregnancy

Uterine evacuation in pregnant patients appears to lower maternal mortality and should be considered given the extremely high maternal and fetal mortality associated with VHF. However, this procedure must be performed with extreme caution, since it can be considered high risk with regard to nosocomial transmission. Although technically contraindicated in pregnancy (US Food and Drug Administration [FDA] Category X), ribavirin should nevertheless be considered, in consultation with the patient, as a lifesaving measure for the mother in VHFs for which the drug is efficacious (Table 194.2).

CONVALESCENCE AND SEQUELAE

Since patient clinical status and infectivity generally correlate with the level of viremia, patients who have recovered from their acute illness can safely be assumed to have cleared their viremia and discharged without concern of subsequent transmission at home. RT-PCR testing of blood and other body fluids has sometimes revealed residual nucleic acids, but the significance of this is unclear without cell culture confirming the presence of infectious virus. Sexual abstinence or condom use is recommended for 3 months because of the delayed virus clearance in the urine and semen, as well as simple precautions to avoid contact with excretions, including separate toilet facilities and regular hand washing, although transmission through toilet facilities has not been noted. Breastfeeding should be avoided unless there is no other way to support the baby.

Survivors usually suffer no obvious long-term sequelae, with the exceptions of deafness in Lassa fever and optic retinopathy with vision loss in Rift Valley fever, both of which appear during early convalescence and may persist for life to varying degrees. Nevertheless, convalescence may be prolonged, with persistent myalgia, arthralgia, anorexia, weight loss, alopecia, pancreatitis, uveitis, and orchitis up to a year after

infection. The psychological effects may also be significant, with some patients experiencing irritability, depression, post-traumatic stress disorder, or social stigmatization. Clinical management during convalescence is supportive.

INFECTION CONTROL

Patient isolation, personal protective equipment, and nursing precautions

Although normal barrier nursing and precautions to prevent parenteral and droplet exposure to blood and body fluids suffice in most instances, for added safety these should be upgraded to "VHF precautions" once the diagnosis is suspected, which includes patient isolation and the use of surgical masks, face shields, double gloves, gowns, head and shoe covers, and protective aprons. It is prudent to place the patient in a negative airflow room if available. Hermetically sealed isolation chambers are not required and may have profound negative psychological effects. Patient access should be limited to essential designated trained staff and family members. Use of sharps should be minimized. Small particle aerosol precautions, such as the use of high-efficiency particulate air filter masks, should be employed when performing procedures which may generate aerosols, including endotracheal intubation. The hospital laboratory should be alerted before sending specimens so that appropriate precautions can be implemented. Blood samples can be inactivated by the addition of detergents, such as Triton X-100, although their effect on the various laboratory parameters to be measured has not been firmly established. Use of point-of-care diagnostic assays at the bedside can further limit exposure to laboratory personnel. Disinfection of items coming into direct contact with the patient is advised, including chemical or heat inactivation of human waste.

Contact tracing

Given the generally low secondary attack rates, widespread contact tracing, laboratory testing, or postexposure prophylaxis are not indicated for casual contacts. Contacts should be defined as persons with unprotected direct contact with someone during the symptomatic phase of a human-to-human communicable VHF. Contacts should be monitored daily for the duration of the longest possible incubation period starting after their last contact (Table 194.2), checking and recording their temperature daily. It is usually recommended that exposed persons avoid intimate contact and sharing of utensils with household members for the duration of the incubation. Confinement of asymptomatic persons is not warranted. Persons who develop signs and symptoms suggestive of VHF should be immediately isolated and tested.

Postexposure prophylaxis

Postexposure prophylaxis should be considered in persons with distinct high-risk exposure defined as one of the following: (1) penetration of skin by a contaminated sharp instrument (e.g., needlestick injury), (2) exposure of mucous membranes or broken skin to blood or body secretions (e.g., blood splashing in the eyes or mouth), (3) participation in emergency procedures without appropriate personal protective equipment (e.g., resuscitation after cardiac arrest, intubation, or suctioning), and (4) prolonged (i.e., hours) and continuous contact in an enclosed space without appropriate personal protective equipment (e.g., a healthcare worker accompanying a patient during medical evacuation in a small airplane). Most infections come from contact with severely ill patients late in the course of illness.

Postexposure prophylaxis with oral ribavirin has been recommended for Lassa fever and other arenavirus infections and Crimean-Congo HF, although no systematically collected data on its efficacy are available. Because of the high first-pass metabolism of oral ribavirin, relatively high doses are needed to provide serum levels in the range of the minimum inhibitory concentration of most hemorrhagic fever viruses (Table 194.5). Persons taking prophylaxis who develop manifestations of VHF should also be immediately laboratory tested and converted to intravenous ribavirin unless the syndrome can be readily excluded. Convalescent plasma is also routinely given as postexposure prophylaxis for Argentine hemorrhagic fever. Numerous experimental approaches have shown efficacy as postexposure prophylaxis in VHF animal models but are not yet approved for use in humans.

Vaccines

The 17D live attenuated yellow fever vaccine has an excellent protection and safety profile, despite recent recognition of rare serious adverse events

Table 194.5. Ribavirin therapy for viral hemorrhagic fever

Indication	Route	Dose[a]	Interval
Treatment	IV[b]	30 mg/kg (maximum 2 g)[c]	Loading dose, followed by:
	IV[b]	15 mg/kg (maximum 1 g)[c]	Every 6 h for 4 days, followed by:
	IV[b]	7.5 mg/kg (maximum 500 mg)[c]	Every 8 h for 6 days
Prophylaxis	PO	35 mg/kg (maximum 2.5 g)[c]	Loading dose, followed by:
	PO	15 mg/kg (maximum 1 g)[c]	Every 8 h for 10 days

Abbreviations: IV = intravenous; PO = oral administration.

[a] Pharmacokinetic and sensitivity testing for ribavirin has not been extensively performed for each VHF. The intravenous dose used is derived from that found efficacious in Lassa fever. Oral ribavirin has also been reported to be efficacious in many VHFs, especially for Crimean-Congo HF, but few controlled data are available. IV administration is strongly suggested whenever possible.

[b] The drug should be diluted in 150 mL of 0.9% saline and infused slowly.

[c] Reduce the dose in persons know to have significant renal insufficiency (creatinine clearance of less than 50 mL/min).

in elderly persons. Confirmed previous vaccination should essentially rule out yellow fever. Candid 1, a highly efficacious live attenuated vaccine for Argentine hemorrhagic fever (only licensed in Argentina) may also be effective in Bolivian hemorrhagic fever but does not protect against other arenaviruses. Vaccines for HFRS, Rift Valley fever, and Kyasanur Forest disease exist but most are not widely tested, approved, or available. A number of experimental vaccines are efficacious in animal models of VHF. Clinical trials of various Ebola vaccines are underway.

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PART XXIV

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195. Intestinal roundworms

Kathryn N. Suh and Jay S. Keystone

Nematodes (roundworms) are the most common parasites infecting humans worldwide. Of almost half a million species of roundworms, approximately 60 are known to be pathogenic to humans. Among the most prevalent human infections are those due to the intestinal (lumen-dwelling) nematodes. *Ascaris lumbricoides* and *Trichuris trichiura* each infect over 1 billion people worldwide; hookworms (*Ancylostoma duodenale* and *Necator americanus*) infect almost the same number. Other important nematodes of humans include *Strongyloides stercoralis* and *Enterobius vermicularis*. Coinfection, in particular with *A. lumbricoides* and *T. trichiura*, is common.

Ascaris lumbricoides, hookworm, and *T. trichiura*, collectively referred to as geohelminths (or soil-transmitted helminths), share the requirement for eggs or larvae to mature in soil in order to be infective to humans. Due to this obligate soil stage of maturation, these parasites cannot be transmitted from person to person. In contrast, *S. stercoralis* is able to complete its entire life cycle within the human host, and like *E. vermicularis*, both person-to-person transmission and autoinfection can occur.

The majority of geohelminthic infections are asymptomatic and associated with low worm burdens, whereas the minority (15%–35%) of infected individuals harbor the majority of the worm burden and suffer from more intense symptoms. Geohelminthic infections are important contributors to growth retardation and cognitive delay in children, but conclusively proving the benefit of large-scale anthelminthic therapy in endemic areas is challenging for a number of reasons. Geohelminths are unaffected by host immune responses, leading to chronic infection if untreated, although the natural history of such infections (excluding hookworm) is usually one of decreasing worm burden over time; even with treatment, however, reinfection is common.

The prevalence and intensity of helminthic infections, and in particular geohelminthic infections, are related to poverty, educational and agricultural standards, population density, and sanitary (public health) conditions, all of which have a far greater impact on the burden of disease than do ecologic factors.

ASCARIASIS

Ascariasis is among the earliest recorded and most prevalent helminthic infections of humans. King Richard III's body, recently discovered in the United Kingdom, contained *Ascaris* eggs. Disease is caused by *A. lumbricoides*; infection due to the closely related porcine ascarid *Ascaris suum* has been reported following accidental ingestion of ova. Ascariasis is widely distributed throughout the world, with the highest prevalence in Asia and in young children. Complications of infection are generally related to a high worm burden, and thus only a minority of infected individuals is at risk of serious morbidity. The prevalence of ascariasis is attributable in part to the prodigious output of eggs by each adult female and the ability of these eggs to survive in a diverse range of environmental conditions.

The life cycle of *Ascaris* is shown in Figure 195.1. Fertilized eggs are excreted in stool, embryonate, and become infective after a period of weeks to months in soil, depending on environmental conditions. One to two days after infective eggs are ingested, larvae are released in the small bowel, penetrate the intestinal wall, travel to the pulmonary circulation, and enter the lungs, where they ascend the trachea and are swallowed. Approximately 10 weeks after ingestion of eggs, larvae mature into adults in the small intestine, where they live for up to 18 months. Egg production occurs 3 to 4 months after initial ingestion; females can produce more than 200 000 eggs per day.

Most *Ascaris* infections are asymptomatic. Adult worms may be seen in emesis or stool and are occasionally coughed up or extruded

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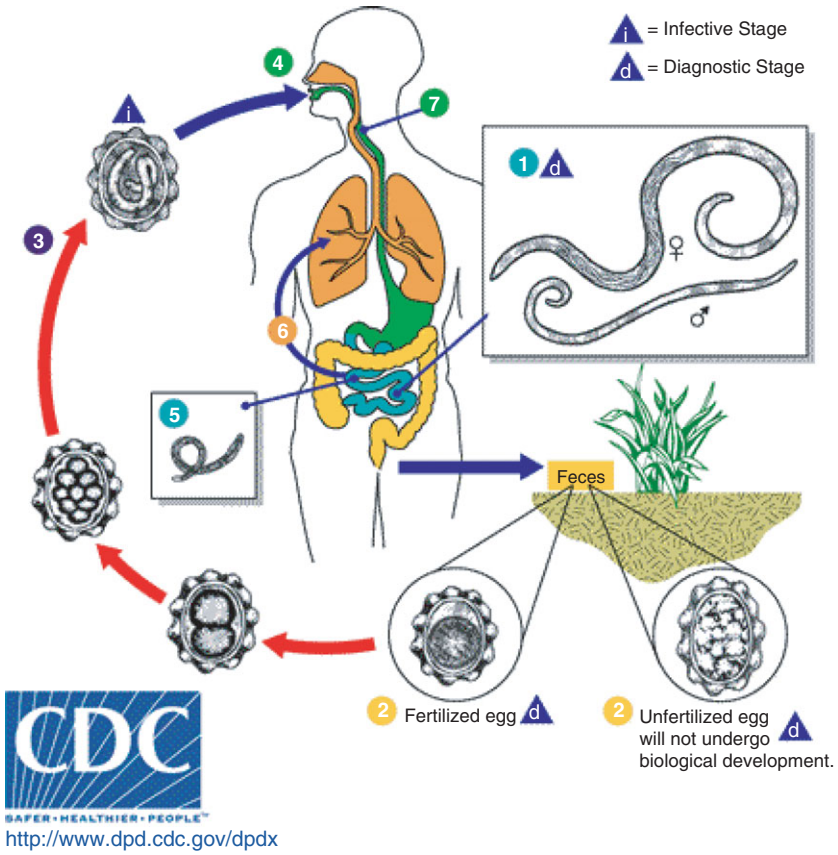

Figure 195.1 Life cycle of *Ascaris lumbricoides*. Adult worms (1) live in the lumen of the small intestine. A female may produce approximately 200,000 eggs per day, which are passed with the feces (2). Unfertilized eggs may be ingested but are not infective. Fertile eggs embryonate and become infective after 18 days to several weeks (3), depending on the environmental conditions (optimum: moist, warm, shaded soil). After infective eggs are swallowed (4), the larvae hatch (5), invade the intestinal mucosa, and are carried via the portal, then systemic circulation to the lungs (6). The larvae mature further in the lungs (10 to 14 days), penetrate the alveolar walls, ascend the bronchial tree to the throat, and are swallowed (7). Upon reaching the small intestine, they develop into adult worms (1). Between 2 and 3 months are required from ingestion of the infective eggs to oviposition by the adult female. Adult worms can live 1 to 2 years.
Source: Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, GA. http://www.dpd.cdc.gov/dpdx/HTML/Ascariasis.htm, accessed 13 September 2013.

through the nose. Loeffler's syndrome, characterized by migratory pulmonary infiltrates and peripheral eosinophilia, results from larval migration through the pulmonary parenchyma and may develop within 2 weeks of ingestion. Clinical manifestations include fever, dyspnea, wheezing, and dry cough. Gastrointestinal complications are generally due to a heavy adult worm burden (e.g., intestinal obstruction from worm masses) or to migration of a single adult worm into the bile or pancreatic duct or the appendix. Complications from worms in other organs are rare.

Ascariasis is diagnosed by the demonstration of ova, larvae, or adult worms. Eggs are readily demonstrated in stool. Barium studies occasionally demonstrate adult worms, either by outlining them with barium or by visualizing ingested barium within the gut of the worm. Eosinophilia is not a feature of adult ascariasis but is a common finding during the migration phase.

Because of the potential for worm migration, all infections, whether symptomatic or not, should be treated. When mixed helminthic infections are being treated, *Ascaris* should always be treated first, because medications may stimulate

Table 195.1 Treatment of intestinal roundworm infections

Disease	Drug	Adult and pediatric dose
Ascariasis	Albendazole	400 mg 1×
	or	
	Mebendazole	500 mg 1× or 100 mg BID × 3 d
	or	
	Pyrantel pamoate	11 mg/kg (max 1 g) daily × 3 d
	or	
	Ivermectin	150–200 μg/kg 1×
Trichuriasis	Albendazole	400 mg daily × 3 d
	or	
	Mebendazole	100 mg BID × 3 d
	or	
	Ivermectin	200 μg/kg daily × 3 d
Hookworm	Albendazole	400 mg 1×
	or	
	Mebendazole	100 mg BID × 3 d
	or	
	Pyrantel pamoate	11 mg/kg (max 1 g) daily × 3 d
Strongyloidiasis: Immunocompetent	Ivermectin	200 μg/kg daily × 2 d
	or	
	Albendazole	400 mg BID × 7 d
Strongyloidiasis: Hyperinfection	Ivermectin	200 μg/kg daily, until stools negative × 2 wk
Pinworm[a]	Albendazole	400 mg 1×
	or	
	Mebendazole	100 mg 1×
	or	
	Pyrantel pamoate	11 mg/kg (max 1 g) 1×
Trichostrongyliasis	Ivermectin	200 μg/kg 1×
	or	
	Pyrantel pamoate	11 mg/kg (max 1 g) 1×
	or	
	Albendazole	400 mg × 3 d
	or	
	Mebendazole	100 mg BID × 3 d

[a] Regardless of the agent used, therapy must be repeated 2 to 4 weeks after the first course.

worms to migrate. Mebendazole or albendazole is appropriate first-line therapy (Table 195.1). Single-dose therapy with either achieves acceptable cure rates.

TRICHURIASIS

Like ascariasis, trichuriasis is a widely distributed disease. Humans are the only hosts of *T. trichiura* (whipworm, so named for the characteristic morphology of adult worms). It is most common in tropical climates, with the highest prevalence in children. Human disease may rarely be caused by related species of porcine (*Trichuris suis*) and canine (*Trichuris vulpis*) whipworm.

Eggs passed in stool embryonate after 2 to 4 weeks of maturation in soil. There is no tissue (pulmonary) phase; eggs are deposited directly in the cecum, where larvae hatch and mature into adults over several days. Adult worms survive for up to 8 years in the cecum, where they remain attached to the intestinal mucosa. Egg production begins 2 to 3 months after initial infection, with females releasing up to 20 000 eggs per day.

Most infected individuals are asymptomatic. Moderate worm burdens may cause nonspecific gastrointestinal symptoms, including abdominal pain or distension or diarrhea. Heavy worm burdens more often affect children and may lead to profuse bloody diarrhea or rectal prolapse, the hallmark of trichuriasis in endemic areas. Iron deficiency anemia may also be present, but eosinophilia is uncommon.

The diagnosis of *T. trichiura* infection rests on demonstration of eggs or adult worms. Endoscopy may reveal colitis and the presence of visible worms hanging within the intestinal lumen. Treatment with a 3-day course of mebendazole or albendazole is recommended (Table 195.1), as single-dose therapy leads to suboptimal cure rates.

HOOKWORM INFECTION

Hookworm infection affects approximately 740 million individuals, with most cases in Asia and sub-Saharan Africa. Disease due to *Necator americanus* is most common and is found predominantly in tropical climates, whereas *Ancylostoma duodenale* infection is more geographically restricted, occurring in northern India; North Africa; the Middle East; and parts of China, Southeast Asia, and South America. Prevalence increases throughout early childhood and then plateaus in early adulthood, with worm burden remaining essentially constant (or declining modestly) throughout the life of the infected host. Other hookworm species, including *Ancylostoma ceylanicum* and *Ancylostoma caninum*, rarely cause enteritis, whereas *Ancylostoma braziliense* infection typically causes cutaneous larva migrans.

The life cycle of hookworm resembles that of *Ascaris*. Eggs are excreted in stool and hatch

in soil, and within 7 days larvae become infective. Following penetration of intact skin, larvae migrate through lymphatics to enter the bloodstream and travel to the lungs, ascend the trachea, and are swallowed. *Ancylostoma duodenale* larvae may also cause infection by the oral route. Within the small intestine, larvae mature into adults and attach themselves to the intestinal mucosa. *Ancylostoma duodenale* adults survive for up to 1 year, and *N. americanus* for up to 9 years. Egg production begins 1.5 to 2 months after infection. Females release 5 to 30 000 eggs per day, depending on the infecting species.

An intensely pruritic erythematous maculopapular eruption, "ground itch," may develop at entry points of filariform larvae. Dermatitis is more likely with repeated exposure and can be complicated by secondary infection. Loeffler's syndrome may occur 10 to 14 days after infection, and may be accompanied by an urticarial eruption. Nausea, epigastic pain, or abdominal tenderness may be present early in the course of disease and with heavy worm burdens. Infection by the oral route may lead to pharyngeal irritation, hoarseness, cough, and nausea (Wakana disease). The hallmark of hookworm infection is chronic iron deficiency anemia, which results from local blood loss at the site of attachment of the adult worms as well as from their ingestion of blood. The occurrence and severity of anemia depend on the infecting species of hookworm (*A. duodenale* causes more blood loss than *N. americanus*), the intensity of infection, the iron reserves of the host, and the availability of iron in the diet; therefore, hookworm anemia is mostly seen in developing countries, where a hemoglobin of 3 to 8 g/dL is not unusual. Complications of severe anemia, including weakness, fatigue, and high-output cardiac failure, are common. Infection and resultant anemia during pregnancy are associated with low birth weight and increased neonatal mortality.

In addition to laboratory findings of iron deficiency anemia, eosinophilia is common. Hypoalbuminemia may result from protein-losing enteropathy. The diagnosis is made by identification of hookworm ova in the stool; fecal concentration techniques are not usually required. Occasionally, rhabditiform larvae may be present in stool and must be differentiated morphologically from those of *Strongyloides*. Mebendazole and albendazole are drugs of choice for treatment (Table 195.1). Vaccine development is currently in progress.

STRONGYLOIDIASIS

Human strongyloidiasis is caused primarily by *S. stercoralis*, which is endemic to Africa, Asia, Southeast Asia, and Central and South America, where 20% or more of the population may be infected. Disease is also found in the Caribbean and to a much lesser extent in Europe, Japan, Australia, and parts of the southern United States. Infection caused by *Strongyloides fuelleborni*, found sporadically in Africa and Papua New Guinea, is relatively rare. Strongyloidiasis affects between 30 and 100 million individuals worldwide.

The life cycle of *S. stercoralis* is complex (Figure 195.2). Rhabditiform larvae released in the stool of infected hosts mature into infective (filariform) stages in soil. Infection usually results from the penetration of intact skin by filariform larvae. These travel via the circulatory system to the lungs where they penetrate the alveoli, ascend the trachea, are swallowed, and then mature into adult worms in the small intestine. Although sexual reproduction does take place within the intestine, adult females are also parthenogenetic (capable of reproduction without males). Eggs are deposited in the intestinal mucosa, hatch, and release rhabditiform larvae, which are excreted in the stool to begin another cycle. Rhabditiform larvae in the bowel may also transform directly into filariform larvae that enter the circulation and begin another cycle of infection (autoinfection) or, in the appropriate clinical setting (i.e., immunosuppression), may lead to disseminated disease (hyperinfection syndrome). Rhabditiform larvae have the capacity to develop into adults in soil where they reproduce sexually (heterogonic development) and give rise to infective filariform larvae (Figure 195.2).

Most infected persons have low worm burdens and are persistently infected for life, often with minimal or no symptoms. If symptoms are present they are generally intermittent, with long asymptomatic periods between episodes. Acute infection may be apparent with very rapid (1–2 cm/hour) migratory serpiginous skin lesions (larva currens) or urticaria at the sites of larval penetration; cutaneous larva migrans from dog or cat hookworms may produce a similar picture, but with much slower migration in skin (1–2 cm/day). Larva currens in the perianal area is pathognomonic of chronic strongyloidiasis. Urticarial rashes may occur over many years

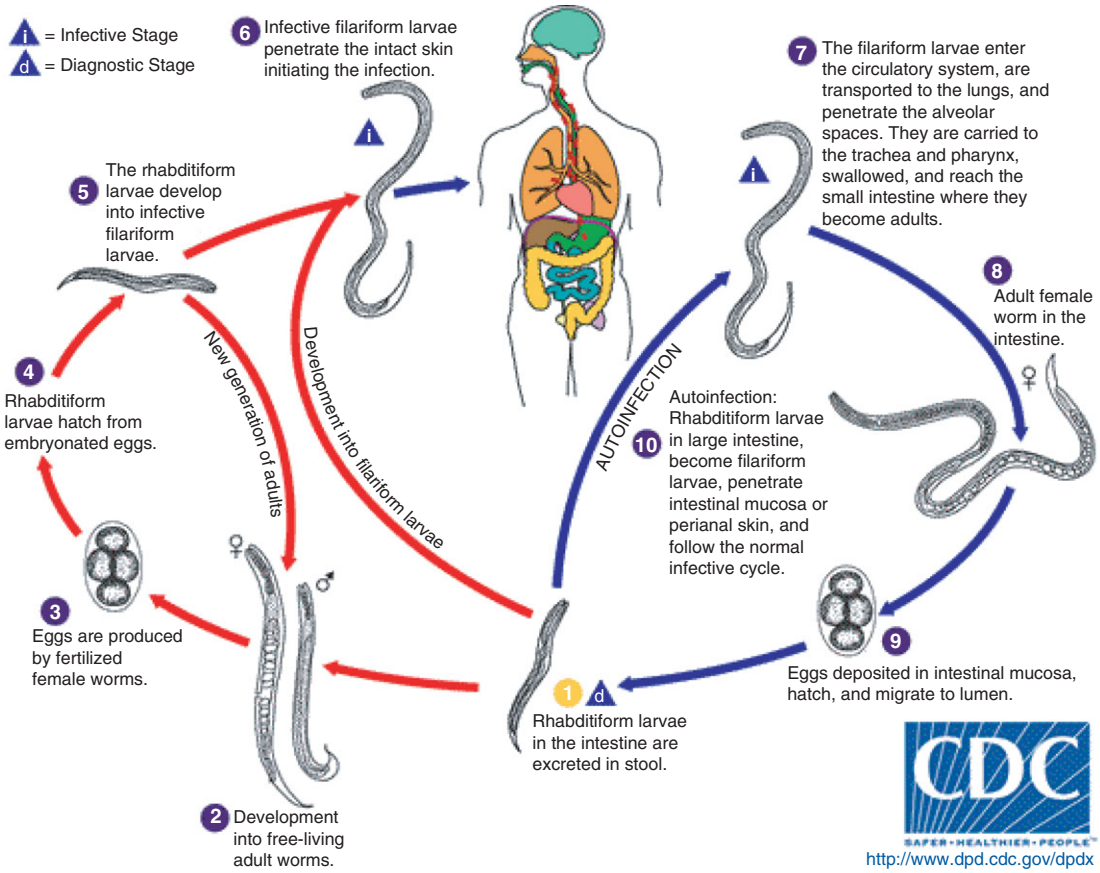

Figure 195.2 Life cycle of *Strongyloides stercoralis*. The *Strongyloides* life cycle is more complex than that of most nematodes with its alternation between free-living and parasitic cycles, and its potential for autoinfection and multiplication within the host. Two types of cycles exist:

Free-living cycle: The rhabditiform larvae passed in the stool (1) (see "Parasitic cycle" below) can either molt twice and become infective filariform larvae (direct development) (6) or molt four times and become free-living adult males and females (2) that mate and produce eggs (3) from which rhabditiform larvae hatch (4). The latter in turn can either develop (5) into a new generation of free-living adults (as represented in (2)), or into infective filariform larvae (6). The filariform larvae penetrate the human host skin to initiate the parasitic cycle (see below) (6).

Parasitic cycle: Filariform larvae in contaminated soil penetrate the human skin (6), and are transported to the lungs where they penetrate the alveolar spaces; they are carried through the bronchial tree to the pharynx, are swallowed and then reach the small intestine (7). In the small intestine they molt twice and become adult female worms (8). The females live threaded in the epithelium of the small intestine and by parthenogenesis produce eggs (9), which yield rhabditiform larvae. The rhabditiform larvae can either be passed in the stool (1) (see "Free-living cycle" above), or can cause autoinfection (10). In autoinfection, the rhabditiform larvae become infective filariform larvae, which can penetrate either the intestinal mucosa (internal autoinfection) or the skin of the perianal area (external autoinfection); in either case, the filariform larvae may follow the previously described route, being carried successively to the lungs, the bronchial tree, the pharynx, and the small intestine where they mature into adults; or they may disseminate widely in the body. To date, occurrence of autoinfection in humans with helminthic infections is recognized only in *Strongyloides stercoralis* and *Capillaria philippinensis* infections. In the case of *Strongyloides*, autoinfection may explain the possibility of persistent infections for many years in persons who have not been in an endemic area and of hyperinfections in immunodepressed individuals.

Source: Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, GA. http://www.dpd.cdc.gov/dpdx/HTML/Strongyloidiasis.htm, accessed 13 September 2013.

during chronic infection. Pulmonary manifestations of disease are unusual due to the small numbers of larvae passing through the lungs, except at the onset of a heavy infection or, more commonly, when hyperinfection syndrome is present (see below). Epigastric pain mimicking peptic ulcer disease and persistent abdominal pain, diarrhea, and anorexia are common manifestations of symptomatic chronic infection. Abdominal bloating, distension, and intestinal malabsorption can also occur.

Hyperinfection syndrome most often occurs in the presence of impaired cellular immunity, typically due to the use of systemic steroids. Other chemotherapeutic agents, hematologic malignancies (notably lymphoma), organ transplants, malnutrition, chronic alcoholism, and coinfection with human T-lymphotropic virus 1 (HTLV-1) are also predisposing factors. Interestingly, human immunodeficiency virus infection is not associated with an increased risk of disseminated disease. Insidious gastrointestinal symptoms may be present. Pulmonary disease is the most common extraintestinal manifestation of hyperinfection syndrome and is characterized by diffuse pulmonary infiltrates with dyspnea, cough, wheezing, or hemoptysis. In uncontrolled hyperinfection, filariform larvae also penetrate organs not normally involved in the life cycle, including the urinary tract, liver, and brain. Gram-negative and occasionally gram-positive bacterial infections, including bacteremia, peritonitis, meningitis, and sepsis, may result from the concurrent migration of bacteria and larvae across the bowel wall. The triad of hemorrhagic pneumonitis, enteritis, and gram-negative bacteremia in an immigrant who is immunocompromised should lead to consideration of disseminated strongyloidiasis. The mortality rate for disseminated disease is approximately 50%.

The diagnosis of chronic strongyloidiasis is difficult due to the nonspecific symptoms of the disease and the minimal, irregular larval output in stool. Demonstration of larvae in clinical specimens (e.g., stool, bronchial washings in disseminated infection) is diagnostic but insensitive. In gastrointestinal infection, a single stool specimen may fail to detect larvae in up to 70% of cases, although sensitivity approaches 100% with seven consecutive stool samples. Specialized laboratory techniques (e.g., Baermann concentration; Harada–Mori filter paper test) and duodenal aspirates are more sensitive than single stool examinations but are impractical to perform. The agar plate method, in which stool is plated on solid medium and incubated for up to 72 hours, is highly sensitive (96%) but has a slow turnaround time. Agar plate specimens containing *S. stercoralis* larvae will, after incubation, reveal linear tracks formed by bacteria that have been carried by motile larvae. Peripheral eosinophilia is present in up to 80% of patients with intestinal disease and can be a clue to diagnosis, but it is rarely a feature of disseminated infection (although pulmonary eosinophilia may be noted in the latter). *Strongyloides* serology has a reported sensitivity of 88% to 95% and specificity of 39% to 99%. Its use is limited by cross-reactivity with other helminthic infections (in particular filariasis, ascariasis, and acute schistosomiasis), and the inability of a positive result to distinguish between treated or ongoing infection, because antibodies may persist for years following effective treatment. However, antibody levels drop significantly over the first year following successful therapy, allowing serology to be used as a test of cure. Polymerase chain reaction and luciferase immunoprecipitation assays are promising new approaches to diagnosis but are currently available only in research settings.

Treatment of strongyloidiasis in asymptomatic individuals is often successful, whereas those with disseminated disease may require prolonged or repeated courses of therapy. Currently, ivermectin is considered the treatment of choice. If possible, immunosuppressant therapy should be discontinued in those with hyperinfection. Prevention of disease by screening and/or presumptive treatment of at-risk individuals is desirable. Recommended regimens are summarized in Table 195.1.

ENTEROBIASIS

In contrast to other gastrointestinal helminthic infections, *E. vermicularis* infection (pinworm, threadworm) does not respect socioeconomic boundaries. *E. vermicularis* is ubiquitous, found in both urban and rural settings worldwide. Enterobiasis is the most common helminthic infection in North America and is among the most prevalent throughout the world. Humans are the only hosts, with infection occurring most commonly in young children.

Eggs are ingested, either by the fecal–oral route or by exposure to contaminated fomites. There is no tissue phase of infection. Larvae hatch in the upper gastrointestinal tract and mature into adults. Adult worms mate in the small intestine before migrating to the appendix and cecum,

where they survive for up to 13 weeks. Gravid females migrate to the perianal area, where they release over 10 000 eggs daily, beginning 3 to 7 weeks after infection.

Symptoms are rarely serious, but may be problematic. Nocturnal pruritus ani is the most common symptom and can lead to insomnia and irritability. Local bacterial infection as a result of scratching can occur. Gastrointestinal and other attributable symptoms appear to be infrequent. Abdominal pain or diarrhea should prompt a search for *Dientamoeba fragilis*, because the coinfection rate with *E. vermicularis* may be as high as 50%; recent studies suggest that *D. fragilis* is transmitted in or on pinworm eggs. There is no evidence of an association between pinworm infection and behaviors such as tooth grinding, nail biting, or enuresis.

Eosinophilia is not a feature of enterobiasis. The diagnosis is established by identifying adult worms or eggs. The most reliable approach is the cellulose tape test using transparent adhesive tape to demonstrate eggs on perianal skin. A wooden tongue depressor draped with tape (sticky side out) is firmly pressed against the perianal skin immediately on waking in the morning, before defecation or bathing. The tape is removed, placed sticky side down on a slide, and examined under a microscope. Ninety percent of infections can be detected with three slides obtained on consecutive mornings, and seven tests detect 100% of infections. In contrast, routine stool examination for ova and parasites is positive in only 10% to 15% of infected persons. Treatment of a suspected infection "on spec" may be a more practical approach than using cellulose tape or pinworm paddles.

The treatment of enterobiasis is summarized in Table 195.1. In the absence of reinfection or autoinfection, a primary infection will clear without treatment in 30 to 45 days. Because intrafamilial transmission is common, treatment of the entire family is recommended. A second course of therapy administered 2 to 4 weeks after the first will treat possible autoinfection or reinfection because medications are relatively ineffective against developing larvae and newly ingested eggs. Specific personal hygiene measures such as good hand hygiene, daily bathing in the morning, the use of underwear and pyjamas for sleeping at night, daily change of underwear, and regular laundering of bedclothes are also important for eradication of infection. Recurring infections should be treated at least four times at 2-week intervals.

TRICHOSTRONGYLIASIS

Trichostrongylus species are parasites of herbivores such as sheep, cattle, and goats, primarily in the Middle East and Asia; humans are accidental hosts. Ova released in the feces of infected animals hatch in soil within 1 to 2 days, and pass through three free-living stages before becoming infective. Human infection typically results from ingestion of larvae in contaminated food or water, although larvae can also penetrate skin. There is no tissue phase, and adults reside embedded in the duodenal or upper jejunal mucosa. Little is known about the pathology of human trichostrongyliasis.

Most human infections are mild and asymptomatic, but diarrhea, flatulence, and epigastric pain may occur. Peripheral eosinophilia may be marked but is more commonly absent. Diagnosis depends on identification in stool of ova, which are often difficult to differentiate from hookworm ova. Treatment is outlined in Table 195.1.

ANISAKIASIS

Anisakiasis (anasakidosis; herring worm or codworm disease), caused by infection with the third-stage larvae of *Anisakis simplex* or *Pseudoterranova decipiens*, is most prevalent in Japan and less frequent in Hawaii and the coastal areas of North America and northern Europe. It is acquired by consumption of raw or inadequately cooked marine fish or squid, as found in sushi or ceviche, for example. The primary hosts of anisakids are sea mammals, including dolphins, porpoises, whales, seals, sea lions, and walruses. Eggs released in feces mature in seawater. Free-swimming second-stage larvae are ingested by small marine crustacea and develop into third-stage (infective) larvae in squid and predatory fish. Herring, salmon, mackerel, cod, and squid are important sources of infection for humans. Larvae ingested by consumption of raw or inadequately cooked fish invade the submucosa of the stomach or intestine but cannot mature into adult worms in the human host. The larvae cause local inflammation and hemorrhage that generally last about 10 days.

Anisakiasis is categorized into gastric, intestinal, or extraintestinal disease. The presentation varies depending on both geography and the infecting species. Gastric anisakiasis usually presents acutely after ingestion of infected food and presents with severe epigastric pain, nausea, and vomiting. Acute symptoms subside in a few days,

but intermittent nausea, vomiting, and vague abdominal pain may persist for weeks to months. Symptoms of intestinal anisakiasis develop 1 to 5 days after the infecting meal and are due to invasion of the distal ileum. Abdominal pain, nausea, vomiting, and mild leukocytosis occur. Extraintestinal complications include peritonitis and pleurisy caused by larval perforation of the intestinal wall. Hypersensitivity reactions, including anaphylaxis, have also been associated with anisakiasis.

With the appropriate history and presenting symptoms, the diagnosis of gastric anisakiasis can be most easily confirmed by endoscopy. An ulcerated lesion and the protruding larva may be visualized. Intestinal and extraintestinal anisakiasis are difficult to differentiate from other causes of acute abdomen, and patients often undergo laparotomy. Serologic diagnosis may be helpful but is not readily available. Peripheral eosinophilia is common. Treatment includes removal of the parasite and supportive care, although even untreated infection subsides in a few days. Anthelmintic therapy for human anisakiasis is not well established, although albendazole has been reported to be effective.

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196. Tissue nematodes

Thomas A. Moore

Tissue-dwelling helminths include a large number of nematodes, cestodes, and trematodes that cause a wide variety of clinical manifestations. Immunoglobulin E (IgE) elevations tend to accompany eosinophilia due to helminth infections, but a normal level does not eliminate parasitic disease. The diagnostic considerations can be narrowed through an understanding of the various parasites, specifically the geographic distribution, the likelihood of exposure in endemic areas, incubation periods, and knowledge of the common manifestations of infection. Serologic tests are sometimes helpful, but panels of helminth serologic tests are most likely to be unrewarding if not confusing. Treatment strategies must be tailored to the individual parasitic disease.

TRICHINELLOSIS

Trichinellosis develops when raw or inadequately cooked meat containing the encysted larvae of *Trichinella* species is eaten. The larvae are released from the cysts by digestive enzymes in the stomach of the host, migrate to the small intestine villi where they penetrate the intestinal mucosa, and undergo four successive molts in about 24 hours to develop into male and female adult worms. After ~1 week, infective newborn larvae are released and invade striated muscle via the circulation, where they encyst within individual muscle fibers.

Trichinellosis has a worldwide distribution, occurring in temperate and tropical climates. It is considered an emerging zoonosis with increased rates of infection, attributed to changing human dietary habits and breakdown in some developing countries of veterinary management practices. In the United States, trichinellosis has historically been associated with eating *Trichinella*-infected pork from domesticated sources. Improved observance of standards and regulations in the US commercial pork industry has resulted in a steady reduction of *Trichinella* prevalence among swine. The number of reported cases related to eating nonpork products has remained constant, however, and exceeds the number of reported cases related to eating pork.

Among US travelers, most cases of trichinellosis have been associated with consumption of wild pigs, especially the bush pig and warthog. Meat from other sources can result in trichinellosis as well, and outbreaks of the disease have been associated with consumption of meat from bears, walruses, and horses. Most reported travel-related infections have been associated with visits to Mexico, Southeast Asia, and sub-Saharan Africa.

In the 5-year period from 2002 through 2007, 66 cases of trichinellosis were reported to the Centers for Disease Control and prevention (CDC). Of the 54 cases available for analysis, 27 cases (50%) were exclusively associated with eating wild game: bear (22), cougar (1), wild boar (2), deer (1), and walrus or seal (1). In comparison, only 8 cases (15%) were associated with eating commercial pork products, including 2 cases traced to a foreign source. The source for 17 cases (31%) was not known.

The severity of symptoms depends on the number of ingested larvae. Because most infections result from ingestion of a small number of larvae, most infected persons are asymptomatic. The adult worm in the small intestine may cause gastrointestinal symptoms within a week of infection. Symptoms include abdominal discomfort, vomiting, and diarrhea, which may evolve into fulminant enteritis in unusually heavy infections. However, most clinical manifestations are related to systemic invasion by larvae, and they usually begin in the second week after infection, peak over a week's time, then slowly subside. These symptoms include fever and myositis with pain, swelling, and weakness. Myositis usually begins in the extraocular muscles and progresses to involve the masseters, neck muscles, and limb flexors. Other symptoms include headache,

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cough, and dysphagia. Occasionally subconjunctival or subungual splinter hemorrhages develop. A petechial or macular rash is sometimes seen. In fulminant infection myocarditis, pneumonia, and encephalitis may be fatal.

Fever and eosinophilia associated with periorbital edema and myositis are the cardinal features of trichinellosis. Eosinophilia begins about 10 days after infection and may be quite high. The erythrocyte sedimentation rate is usually normal. Elevated creatine phosphokinase and lactate dehydrogenase levels reflect extensive muscle involvement.

Serologic testing is available from the CDC, but antibodies are not detectable until at least 3 weeks after infection. Although muscle biopsy may confirm the diagnosis, it is usually unnecessary.

Therapy

The goal of treatment in early infection is to limit muscle invasion by larvae; when this has already occurred, the goal is to reduce muscle damage, which is responsible for the major clinical manifestations. Specific treatment with mebendazole, 400 mg twice daily for 10 days, or albendazole, 400 mg twice daily for 10 days, has been shown to be effective for intestinal and muscle stages. Thiabendazole is no longer used because of its side effects. The mainstays of symptomatic treatment remain bed rest and salicylates. Glucocorticoids (prednisone, 60 mg/day for 7 days with a subsequent taper over 7 days) are effective for severe symptoms not relieved by salicylates. Persons who are known to have recently eaten trichinous meat should be given a 7-day course of albendazole, 400 mg orally twice daily, or thiabendazole, 25 mg/kg/day (max, 3 g/day), in order to eliminate the intestinal infection.

FILARIASIS

Of the eight filarial species capable of infecting humans, the four that cause the most disease worldwide are *Brugia malayi*, *Wuchereria bancrofti*, *Onchocerca volvulus*, and *Loa loa*. Because only a small proportion of insect bites is infective, the disease generally occurs only after long exposure in an endemic area. The clinical manifestations of filariasis depend in part on the immune response of the host. The response to the parasite in endemic populations is dampened, and a large parasite burden is common. In contrast, individuals who have grown up outside of endemic regions and become infected manifest prominent signs and symptoms and usually have a low parasite burden.

Lymphatic filariasis

Lymphatic filariasis is caused by infection with one of the lymph-dwelling filariae, *W. bancrofti, B. malayi*, or *Brugia timori.* An infected mosquito deposits larvae in subcutaneous tissue. Over time, the larvae mature into adult worms. These threadlike adults reside in afferent lymphatic channels or sinuses of lymph nodes. All lymph-dwelling filariae contain *Wolbachia*, an intracellular bacterial endosymbiont that is essential for their growth, development, fertility, and survival.

W. bancrofti, found in tropical and subtropical regions throughout the world, is the most widely distributed human filaria. In most of the world the parasite is nocturnally periodic, with the microfilariae scarce in peripheral blood during the day but increased at night. In the Pacific Islands, however, the microfilariae are subperiodic; microfilaremia is seen throughout the day, reaching maximal levels in the afternoon. Brugian filariasis occurs throughout Asia and the Far East, including India and the Philippines. This form of filariasis is nocturnally periodic, except in forested areas, where it is subperiodic.

Among endemic populations, the common manifestations of lymphatic filariasis include asymptomatic microfilaremia, filarial fevers, and lymphatic obstruction. Most infected individuals are clinically well and have an asymptomatic condition associated with microfilaremia. More than half of these patients have hematuria, proteinuria, or both. Filarial fevers are acute episodes of fever and chills accompanied by lymphangitis and lymphadenitis with transient lymphedema. The episodes abate after a week to 10 days but can recur. Importantly, the lymphangitis develops in a descending fashion, opposite the direction seen in cellulitis. Regional lymphadenopathy is often present and thrombophlebitis may develop. Both upper and lower extremities may be involved but genital involvement, which may manifest as epididymitis, funiculitis, and scrotal pain and tenderness, is found exclusively with *W. bancrofti*.

Damage to the lymphatics, with resultant obstruction, manifests early as pitting edema. The edema eventually causes characteristic features of elephantiasis, with thickening of subcutaneous tissues, hyperkeratosis, and fissuring of skin. Lymphedema renders patients susceptible to recurrent bacterial and fungal infections.

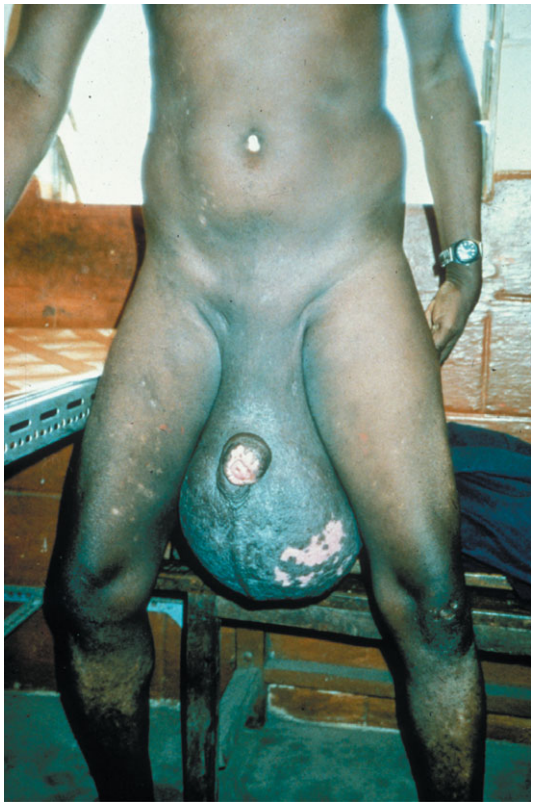

Figure 196.1 Massive scrotal swelling in lymphatic filariasis.

Hydrocele formation is the most common manifestation of lymphatic filariasis and scrotal lymphedema may develop (Figure 196.1). If retroperitoneal lymphatics are obstructed, chyluria develops.

Persons new to endemic areas who acquire lymphatic filariasis usually develop acute lymphatic inflammation with lymphangitis, lymphadenitis, and, in the case of *W. bancrofti*, genital pain, but they may also develop allergic phenomena such as hives, urticaria, and eosinophilia.

Lymphatic filariasis is suspected from epidemiologic history, physical findings, and laboratory tests. However, a definitive diagnosis can be made only by detecting the parasite. Adult worms in lymphatics are generally inaccessible and excisional biopsies are unhelpful; however, ultrasonographic examination of the scrotum or breast in females using a high-frequency (7.5–10 MHz) transducer with Doppler may demonstrate motile adult worms within dilated lymphatics (the so-called "filarial dance sign"). Additional supportive data can be obtained with the use of lymphoscintigraphy, which (in early infections) will demonstrate a paradoxically brisk lymphatic flow on the affected side.

Microfilariae can be detected in blood and occasionally in other body fluids. Detection of microfilariae in the blood is most efficiently performed by filtering 1 mL or more of blood through a polycarbonate filter with 3-μm pores or examining the sediment from a Knott's prep (1 mL of blood with 10 mL of 2% formalin). The timing of blood collection is critical and should be based on the periodicity of the microfilariae in the endemic region in question. Filtration of blood for nocturnally periodic microfilariae should be performed between 10 p.m. and 4 a.m. A 10- to 14-day period is required for microfilarial periodicity to adjust to local time zones.

Assays that detect circulating antigens of *W. bancrofti* (but not *Brugia* spp.) are commercially available and permit the diagnosis of filariasis in patients without microfilaremia. Polymerase chain reaction (PCR)-based assays that detect DNA of *W. bancrofti* and *B. malayi* have been developed but are not commercially available.

Data supporting filarial infection include eosinophilia, elevated serum IgE levels, and antifilarial antibodies in the serum. Serologic studies have greater diagnostic value in persons new to endemic areas. A negative or low antibody level effectively rules out active infection in this population. However, interpretation of serologic findings may be problematic because of cross-reactivity between filarial antigens and antigens of other helminths, such as *Strongyloides stercoralis*. In addition, residents of endemic areas may develop antibodies to filarial antigens through the bites of infected mosquitoes without developing patent infection.

THERAPY

The mainstay of treatment remains diethylcarbamazine (DEC) 6 to 8 mg/kg/day in single or divided doses for 12 days. DEC, an orphan drug, can be obtained from the CDC drug service (telephone 404–639–3670). Although extended treatment is usually necessary to kill the adults, a single dose rapidly kills microfilariae. The severity of adverse reactions correlates with the pretreatment level of microfilaremia, but the etiology is unclear and may represent either an acute hypersensitivity reaction to massive antigen release or an inflammatory reaction induced by the release of *Wolbachia*. Usually the reactions, which include fevers, headache, lethargy, arthralgias, and myalgias, can be easily managed with antipyretics and analgesics. Initiating treatment

with a small dose of DEC (e.g., a single 50 mg tablet) and premedicating the patient with corticosteroids, 0.5 to 1 mg/kg/day, minimizes side effects.

Albendazole (400 mg PO BID × 21 days) is also effective against adult worms. Doxycycline (100 mg PO BID × 4–8 weeks) targets the intracellular *Wolbachia* and also demonstrates effective macrofilaricidal activity. Additional treatment regimens shown to be effective include DEC and albendazole for 7 days or DEC and doxycycline for 21 days.

A note of caution: the geographic distribution of loiasis overlaps with lymphatic filariasis and coinfection occurs. Since treatment of loiasis with both DEC and ivermectin can result in severe adverse effects (see below), it is imperative to exclude the possibility of coinfection with loiasis prior to treating patients with lymphatic filariasis.

Because adult worms may survive the initial treatment, symptoms can recur within a few months after therapy, and retreatment is recommended for such patients. Some individuals have suggested treating such patients with DEC at the standard dose of 6 to 8 mg/kg/day for 1 week each month for 6 to 12 months. Combination therapy with DEC and either albendazole or ivermectin (sometimes preceded by doxycycline) has demonstrated efficacy for mass chemotherapy of filariasis.

The optimal treatment of acute lymphatic inflammation is unknown, and these attacks usually resolve in 5 to 7 days without therapy. Treatment of chronic lymphatic obstruction is problematic. If the infection is recognized early, some signs of lymphatic obstruction can be reversed. In severely damaged lymphatics, however, supportive measures are used, including elevation of the infected limb, elastic stockings, and foot care with antifungal ointments and antibacterial antiseptics. Prophylactic antibiotics may prevent recurrent bacteremia and cellulitis. Hydroceles can be managed surgically, and surgical decompression with a nodovenous shunt may provide relief for severely affected limbs. No treatment has proved satisfactory for chyluria. DEC is useful for prophylaxis, but the optimal dose and frequency have not been established.

Tropical pulmonary eosinophilia

Tropical pulmonary eosinophilia (TPE) is a distinct syndrome caused by immunologic hyperresponsiveness to *W. bancrofti* or *B. malayi*. The syndrome affects men four times as commonly as women, often in the third decade of life. Most cases have been reported from Pakistan, India, Sri Lanka, Southeast Asia, and Brazil.

The symptoms and signs of TPE are attributed to trapping of microfilariae in pulmonary vasculature, with resultant eosinophilic alveolitis; patients develop paroxysmal cough and wheezing that is nocturnal and due to the nocturnal periodicity of the microfilariae, anorexia, and low-grade fever. Extreme eosinophilia (>3000/mm^3), high polyclonal IgE levels, elevations of antifilarial antibodies, and a therapeutic response to DEC establish the diagnosis.

THERAPY

DEC is recommended at 4 to 6 mg/kg/day for 14 days. Symptoms usually resolve within 1 week. Most patients are already being treated with corticosteroids, which can be tapered as patients recover. Up to 25% of treated patients relapse, requiring retreatment.

Loiasis

Also known as *African eyeworm*, loiasis results from infection with *Loa loa* acquired in the rain forests of West and Central Africa. After the bite of an infected tabanid (horse) fly, the parasites are inoculated into the subcutaneous tissue, where they mature and mate. The adults reside in subcutaneous tissue and migrate widely over the body. The microfilariae released into the blood by the adult female exhibit diurnal periodicity. These parasites do not contain *Wolbachia*.

Clinical manifestations differ between natives to endemic areas and newcomers. In the indigenous population, microfilaremia is generally asymptomatic, remaining subclinical until the adult migrates through the subconjunctival tissues of the eye or causes Calabar swellings, which are angioedematous lesions in the extremities (Figure 196.2). The swelling develops after the adult has migrated through the tissue, so biopsy is fruitless. Nephropathy, encephalopathy, and cardiomyopathy are rare. In nonresidents, allergic or hypersensitivity responses predominate and microfilaremia is rare, but Calabar swellings occur more frequently and are more debilitating. Peripheral blood eosinophilia, parasite-specific immunoglobulin G (IgG), and vigorous lymphocyte proliferation to parasite antigens are typical.

Definitive diagnosis requires either identification of microfilariae in peripheral blood or isolation of the adult worm. The microfilariae can be

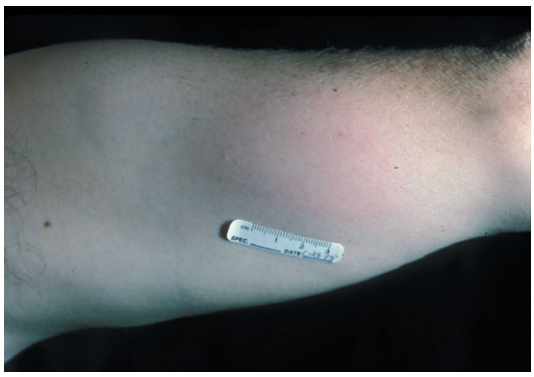

Figure 196.2 Calabar swelling of loiasis.

identified with the technique described for lymphatic filariasis. However, because the microfilariae of *Loa loa* exhibit diurnal periodicity, blood must be filtered between noon and 4 p.m. after the patient has been in the local time zone for 10 to 14 days. The adult worm is difficult to find unless it crawls across the eye. The worm is not found in Calabar swellings, and biopsy of these lesions is not indicated. In amicrofilaremic patients the diagnosis must be based on a characteristic history and clinical presentation, blood eosinophilia, and elevated levels of antifilarial antibodies.

THERAPY

The drug of choice to treat loiasis is DEC, which is effective against both the adult worm and microfilariae. It is dosed as 8 to 10 mg/kg/day (divided into three doses) for 21 days. A single course of therapy is curative in the majority of patients, although multiple courses may be required, and clinical relapses may occur up to 8 years following apparently successful treatment. It is not unusual for treated patients to develop localized inflammatory reactions such as subcutaneous papules or vermiform hives. These reactions, which are distinct from Calabar swellings, are a response to dying adult worms. The adult worms can be surgically extracted from these lesions, but removal is usually unnecessary.

Greater caution is warranted in patients who have microfilaremia. Treatment of such individuals with standard dosages of DEC has resulted in severe neurologic complications and even death caused by microfilariae in the central nervous system (CNS). In order to reduce the risk of developing treatment-induced encephalopathy, some experts have tried to reduce the microfilarial burden by performing apheresis of the blood before initiating treatment with DEC. In addition, gradual institution and escalation of DEC doses has been successful. DEC is gradually instituted, giving 0.5 mg/kg for the first dose then doubling every 8 hours until the full dose of 8 to 10 mg/kg/day (divided into three doses) is achieved. Prednisone (1 mg/kg/day) should be used during the first 3 to 6 days of treatment, and the first dose of prednisone should be given at least 6 hours before the first dose of DEC.

Since onchocerciasis occurs in the same geographic areas as loiasis and treatment of onchocerciasis with DEC can result in severe adverse effects, the clinician must rule out coinfection with onchocerciasis.

Other side effects of treatment are pruritus, fever, anorexia, lightheadedness, and hypertension. These symptoms usually resolve after the first few doses. A single course of DEC cures roughly half of those treated, and additional courses are frequently necessary to achieve cure. The decision to repeat treatment must be made on clinical grounds, since no objective laboratory data can predict treatment failures. Albendazole is an attractive treatment option for patients with high levels of microfilaremia: 200 mg twice daily for 3 weeks results in a gradual decline in microfilaremia over several months.

Once an individual has developed loiasis, prophylaxis should be considered if the patient returns to an endemic area. Once-weekly treatment with DEC is effective prophylaxis, but DEC is difficult to obtain in tropical countries since it is now manufactured only in the United States. Instead, albendazole 400 mg/day once weekly is an acceptable alternative.

Onchocerciasis

Infection with *O. volvulus* is the second leading infectious cause of blindness worldwide. Onchocerciasis occurs mainly in sub-Saharan Africa (where about 98% of the infected individuals live), and is found in savannah and rain forest. It is also found in Yemen and is scattered throughout Central and South America (Brazil, Colombia, Ecuador, Guatemala, Mexico, and Venezuela). Areas of transmission are focal because the *Simulium* blackfly vector flies only within a few kilometers of the streams where it breeds.

After the bite of an infected blackfly, larvae penetrate the skin and migrate into the subcutaneous tissue, where they mature into adults. About 7 to 36 months after infection, the gravid

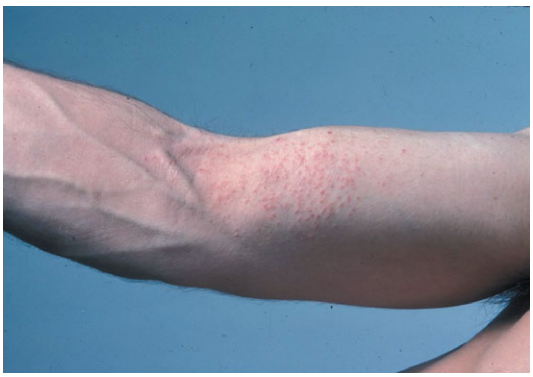

Figure 196.3 Papular eruption in onchocerciasis.

female releases microfilariae, which migrate throughout the skin and concentrate in the dermis. There they can be ingested by female blackflies during their feeding to complete the life cycle. Most symptoms of onchocerciasis result from microfilariae migrating through host tissues, primarily the skin, lymph nodes, and eyes. As with the other filariases, clinical presentations differ between individuals from endemic and nonendemic areas. However, pruritus is the most frequent manifestation of onchocerciasis in all individuals. An itchy, erythematous, papular rash prominent early in the infection is also seen (Figure 196.3). With chronic infection there is epidermal atrophy, loss of elasticity with exaggerated wrinkling, and loose, redundant skin. The pigmentary changes have led to the term "leopard skin." Lymph node involvement, usually found in persons from endemic areas, presents as inguinal and femoral lymphadenopathy that may lead to enlargement of lymph nodes which hang down (so-called "hanging groin").

The most serious result of infection is blindness. It usually affects only individuals from endemic areas with moderate to heavy infections. Ocular complications occur more frequently with savannah strains, and the endosymbiont *Wolbachia* – found in some strains – appears to play an important role. Lesions may be found anywhere in the eye, and the most common early finding is conjunctivitis with photophobia. In the cornea, microfilariae in the anterior chamber cause punctate keratitis with "snowflake" opacities. In Africa, sclerosing keratitis, which may develop later, is the most common cause of blindness. Anterior uveitis and iridocyclitis occur in about 5% of infected Africans. In the Americas, secondary glaucoma may result from damage to the anterior uveal tract. Chorioretinal lesions, constriction of the visual fields, and frank optic atrophy may also develop.

Laboratory findings differ between persons from endemic and nonendemic areas. Eosinophilia and elevated polyclonal IgE are prominent findings in infected individuals. Eosinophilia and IgE levels are greater in natives of endemic areas, a finding that is contrary to the findings in the other filariases.

Like the other filariases, definitive diagnosis rests on the detection of an adult worm in an excised nodule or, more commonly, microfilariae in a skin snip. Skin snips are easily and bloodlessly obtained by sampling the most superficial skin layers using a corneoscleral punch. However, a 25-gauge needle may also be used to carefully tent up the skin while a scalpel is used to excise the most superficial layers of skin. The sample is incubated in saline or tissue culture medium on a glass slide or in a flat-bottomed microtiter plate at 37°C (98.6°F) for at least 2 hours.

THERAPY

Until recently, ivermectin remained the drug of choice for onchocerciasis and played a key role in onchocerciasis control programs. However, strains of *O. volvulus* relatively resistant to ivermectin were reported in 2004. Doxycycline exhibits significant macrofilaricidal activity by eliminating the bacterial endosymbiont *Wolbachia*, resulting in complete cessation of embyrogenesis for at least 18 months. A current recommended regimen consists of doxycycline, 100 to 200 mg/day for 6 weeks, with ivermectin 150 μg/kg given both during the last week of doxycycline therapy and again 3 to 4 weeks later.

For pregnant women and other persons for whom doxycycline is contraindicated, ivermectin is effective, given as a single dose of 150 μg/kg on an empty stomach. Because ivermectin alone does not kill adult worms, retreatment is usually required every 6 to 12 months for the life of the parasite (up to 14 years). More frequent administration (i.e., every 3–4 months) improves pruritus in symptomatic patients.

Reactions to ivermectin treatment are usually mild, occur within 3 days following treatment, and include transient pruritus, dizziness, headache, arthralgias, rash, or edema. More serious reactions are rare and have only been reported in patients who were coinfected with *Loa loa*.

Nodulectomy has been advocated as a way to decrease the parasitic load; however, two-thirds of nodules are inaccessible, being located deep in

the body. Priority is given to removing nodules on the head, which are associated with ocular complications.

Other filarial infections

Humans can harbor infections with other filariae, most notably *Mansonella* species: *Mansonella streptocerca*, *Mansonella perstans*, and *Mansonella ozzardi*. Most of these organisms are discovered incidentally, but occasionally, infected persons develop clinical manifestations of illness.

M. streptocerca, found in central Africa, is transmitted by biting midges. The major clinical manifestations resemble onchocerciasis, with pruritus, papular rashes, pigmentation changes, and inguinal adenopathy. Diagnosis is made by finding the characteristic unsheathed microfilariae in skin snips. As with onchocerciasis, treatment is with a single dose of ivermectin (150 μg/kg).

M. perstans, also transmitted by biting midges, is found in both central Africa and South America. The clinical manifestations resemble loiasis, with pruritus and transient angioedema, fever, headache, and arthralgias. Occasionally pericarditis and hepatitis occur. The diagnosis is established by the demonstration in the blood of the microfilariae; however, the worms do not exhibit periodicity. As with other filariases, eosinophilia and antifilarial antibodies are often seen. *Wolbachia* have been found in *M. perstans*; therefore, doxycycline 200 mg/day for 6 weeks is the drug of choice for this infection.

M. ozzardi is found only in Central and South America and the Caribbean. No clear picture of infection with this organism has been established, but symptoms and signs of disease attributed to this infection include headache, fever, arthralgias, hepatomegaly, adenopathy, pruritus, and eosinophilia. Diagnosis relies on finding the microfilariae in the peripheral blood, which circulate without periodicity. A single dose of ivermectin (6 mg) is effective.

Humans are accidental hosts for a variety of filariae that primarily infect small mammals. The parasite never completely develops, and the worms are usually found incidentally. The canine heartworm *Dirofilaria immitis* occurs mainly in the southeastern United States. The bite of an infected mosquito deposits the parasite, which develops in the subcutaneous tissues, then migrates to the pulmonary vasculature, where it is trapped and dies. It usually presents as a solitary pulmonary nodule that cannot be easily differentiated from other nonparasitic causes of pulmonary nodules. Eosinophilia is seen in fewer than 15% of infected persons and is only seen in the early stages of the lesion. Other *Dirofilaria* can cause discrete subcutaneous nodules. *Brugia* of small mammals can cause isolated lymph node enlargement in humans, but eosinophilia and antifilarial antibodies are uncommon. These zoonotic infections are diagnosed and cured by excisional biopsy.

DRACUNCULIASIS

Dracunculiasis is an uncommon infection in the tropics, usually in arid regions where populations bathe or wade in water used for drinking, such as step wells. The infection develops after consumption of water contaminated with water fleas infested with *Dracunculus medinensis* larvae. The larvae are released in the stomach, pass into the small intestine, and penetrate the mucosa, ultimately reaching the retroperitoneum, where they mature and mate. The infection remains largely asymptomatic until about a year later, when the female worm migrates to the subcutaneous tissues, usually in the legs. A tender papule forms and is occasionally associated with urticaria, dyspnea, nausea, and vomiting. The lesion develops into a vesicle that ruptures and ulcerates, exposing a portion of the gravid worm. On contact with water, large numbers of larvae are released and then ingested by crustaceans to complete the life cycle.

Therapy

Treatment of dracunculiasis has remained unchanged for thousands of years and consists of extraction of the emerging worm by securing the end to a small stick and gradually winding it a few centimeters daily until it is removed. Metronidazole (750 mg/day in three divided doses for 10 days) and thiabendazole (35 mg/kg twice daily for 3 days) have been used, although neither exerts any direct antiparasitic activity. Topical applications of hydrocortisone and tetracycline ointments have the same effect.

UNUSUAL TISSUE HELMINTH INFECTIONS

Visceral and ocular larva migrans

Visceral larva migrans (VLM) is a syndrome caused by nematodes that are normally parasitic to nonhuman hosts; thus, the larvae do not develop into adult worms and elicit eosinophilic inflammation as they migrate through human tissue. Most human infections are due to

Toxocara canis from dogs; less commonly, the syndrome can occur due to *Toxocara cati* from cats, and rarely *Ascaris suum* from pigs. VLM is seen mainly among preschool children, but most infections remain subclinical.

Humans acquire toxocariasis mainly by eating soil contaminated with the infective eggs shed in the stool of the host animal. VLM is usually asymptomatic, but those who seek medical attention present with fever, malaise, anorexia, weight loss, cough, wheezing, and rashes. Eosinophilia, the hallmark feature of VLM, may be striking. Hepatomegaly is typical, but splenomegaly is seen in only a minority. Neurologic involvement is uncommon, and death, which is even rarer, is due to severe brain, lung, or heart involvement. Serum antibodies to *Toxocara* larvae are a useful adjunct in establishing the diagnosis, but elevated titers are also found in patients without VLM.

Ocular larva migrans (OLM) is occasionally associated with clinically recognized VLM but is usually unaccompanied by systemic symptoms or signs. The typical patient is an older child that presents with unilateral visual deficits, ocular pain, leukocoria, or strabismus. In the early stages, the lesion is raised above the level of the retina and closely mimics retinoblastoma. After the acute phase has subsided, the lesion remains a well-defined circumscribed area of retinal degeneration. Serum antibodies to *Toxocara* larvae may be present, but because many patients with OLM have low or negative titers, they are unhelpful unless compared with titers in vitreous and aqueous humor, which are generally higher in affected patients.

Patients with serologic evidence of toxocariasis who have mild or no symptoms fall into the category of "covert" toxocariasis. Children with hepatomegaly, cough, sleep disturbance, abdominal pain, and headache are more likely to have elevated toxocaral antibody titers. Eosinophilia, when present, is often mild. Recurrent abdominal pain is often the sole presenting complaint. Adults can be affected as well, demonstrating nonspecific symptoms of weakness, pruritus, rash, difficulty breathing, and abdominal pain.

As with other tissue nematodes, the diagnosis of toxocariasis is made initially on clinical grounds, with confirmatory testing playing a secondary role.

THERAPY

The majority of patients with toxocariasis do not require treatment. Although generalized treatment recommendations are limited by a paucity of controlled clinical data, treatment is generally reserved for patients with severe disease. In patients with CNS, heart, or lung involvement, glucocorticoids should be considered to reduce inflammation. Although no conclusive studies have shown efficacy, albendazole 400 mg twice daily for 5 days is the currently recommended therapy for acute VLM. Alternatively, a 21-day course of mebendazole (20–25 mg/kg/day) has also been shown to be effective.

Albendazole has been found to be effective in OLM, but higher doses (adults, 800 mg BID; children 400 mg BID) have been used in these clinical studies. Treatment should extend 4 weeks, with concomitant glucocorticoids (0.5–1.0 mg/kg/day) for 2 to 4 weeks.

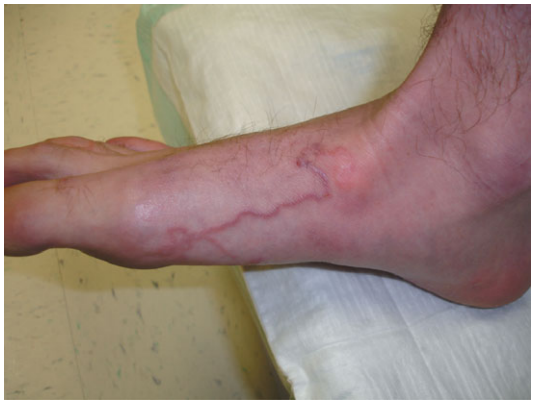

Figure 196.4. Cutaneous larva migrans.

Cutaneous larva migrans ("creeping eruption")

Cutaneous larva migrans (CLM), also known as "creeping eruption," is a zoonosis caused by animal hookworms, most often those of the dog (*Ancylostoma caninum*) or cat (*Ancylostoma braziliense*). As with human hookworms, the infection starts when the worm enters the skin from contaminated soil that is protected from desiccation and temperature extremes, as on beaches and under houses. As in toxocariasis, the worm cannot complete the infective cycle, so it continues to burrow through the subcutaneous tissues, resulting in the characteristic serpiginous, erythematous, elevated, and pruritic skin lesion (Figure 196.4). The worms may create tracks several centimeters in length per day. The infection is often seen in travelers who have walked barefoot on beaches frequented by roaming cats and dogs. Systemic symptoms and eosinophilia are rare.

THERAPY

Without treatment the lesions resolve spontaneously over 4 weeks, although patients are often miserable with pruritus. Treatment with a single dose of ivermectin (150 to 200 μg/kg on an empty stomach) or a 3-day course of albendazole (400 mg daily) has been shown to resolve the infection within 1 week, although retreatment is sometimes necessary.

Eosinophilic meningitis due to helminths

Eosinophilic meningitis due to infection with helminths is most often caused by the rat lungworm *Angiostrongylus cantonensis*, followed by the nematode *Gnathostoma spinigerum* and the raccoon ascarid *Baylisascaris procyonis*. However, the condition has been reported to be a consequence of infection with other helminths, specifically *Schistosoma japonicum*, *Paragonimus* species, and *Taenia solium* cysticerci. Eosinophilic meningitis occurs widely throughout Southeast Asia and the Pacific, including Hawaii, but is focally distributed in many other tropical areas worldwide.

Humans acquire angiostrongyliasis incidentally by eating raw infected mollusks, vegetables contaminated with mollusk slime, or marine fauna that have eaten the infected mollusks themselves, such as crabs and freshwater shrimp. Although nausea, vomiting, and abdominal discomfort may occur soon after eating the larvae, most patients have no symptoms until after an incubation period that ranges from 2 to 30 days (average about 2 weeks). At that time, patients develop an intermittent excruciating headache that may either be insidious or abrupt. Peripheral blood eosinophilia is prominent and lasts for about 3 months. Typical cerebrospinal fluid (CSF) findings consist of an elevated initial pressure, turbid fluid showing a pleocytosis with at least 10% eosinophilia, and elevated protein content but normal glucose. Diagnosis is based on the clinical findings, as recovery of the larvae from CSF or ocular fluids is rare. Treatment is mostly supportive. The headache responds poorly to analgesics and sedatives, but removal of CSF affords symptomatic relief and may be repeated as necessary. Corticosteroids have been tried in severe cases with some benefit. Because clinical deterioration and death can result from the inflammatory reaction to dying worms, anthelmintic therapy is likely contraindicated.

Infection with the raccoon ascarid *B. procyonis* causes a severe form of VLM usually associated with brain involvement and/or characteristic eye findings termed *diffuse unilateral subacute neuroretinitis* (DUSN). The developing worm can sometimes be found in the retina and killed by laser treatment. Albendazole treatment may be tried in persons with systemic disease, or if the larval worm cannot be found.

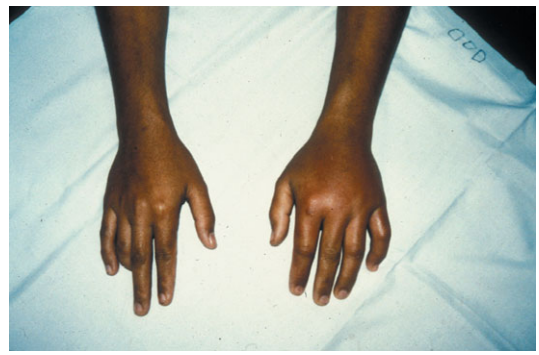

Figure 196.5. Angioedema of left hand in gnathostomiasis.

Gnathostoma, an intestinal parasite of dogs and cats, causes human infections in Southeast Asia, although foci of gnathostomiasis have been reported in Central and South America, southern and eastern Africa, India, and Australia. Humans acquire the parasite by eating undercooked freshwater fish that harbor the encysted larvae. In Asia, cases result from inadequately stored food from local restaurants. Gnathostomiasis is always associated with leukocytosis and hypereosinophilia. Intermittent subcutaneous swelling associated with nonpitting edema and pruritus is the most common manifestation (Figure 196.5), mimicking the Calabar swelling of loiasis. However, the most feared complication of gnathostomiasis is eosinophilic myeloencephalitis, which can be fatal; it begins as radicular pain followed by paralysis of the legs and urinary retention. Sudden onset of severe headache followed by coma and death may occur, usually without antecedent cutaneous swelling. The diagnosis of gnathostomiasis is usually established clinically. The only serologic test available is performed in Bangkok, Thailand, and samples can be sent via the CDC. Both albendazole (400 mg twice daily for 21–28 days) and ivermectin (200 mg/kg/day for 2 days) are effective. Occasionally, the worm will erupt from the skin shortly after treatment is initiated. Removal of the worm is both diagnostic and curative. Adjunctive treatment should include corticosteroids and adequate analgesia when indicated.

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197. Schistosomes and other trematodes

James H. Maguire

The trematode flatworms that infect human beings include the schistosomes, which live in venules of the gastrointestinal or genitourinary tract, and other flukes that inhabit the bile ducts, intestines, or bronchi. The geographic distribution of each species of trematode parallels the distribution of the specific freshwater snail that serves as its intermediate host (Table 197.1). Schistosomes infect approximately 235 million persons worldwide; infections caused by the other flukes are more limited in distribution and number. Trematode infections last for years; most are subclinical, and in general only the small proportion of persons who have heavy worm burdens develops severe disease.

Table 197.1 Geographic distribution of important trematodes[a,b]

Schistostomes	
Schistosoma mansoni	South America, Caribbean, Middle East, Africa
Schistosoma japonicum	China, Philippines, Indonesia, Thailand
Schistosoma mekongi	Cambodia, Laos
Schistosoma intercalatum, *Schistosoma guineensis*	West and Central Africa
Schistosoma haematobium	Africa, Middle East
Biliary and liver flukes	
Clonorchis sinensis	China, Taiwan, Korea, Japan, Vietnam
Opisthorchis viverrini	Thailand, Laos, Cambodia
Opisthorchis felineus	Eastern Europe, former Soviet Union
Fasciola hepatica	Europe, North Africa, Asia, western Pacific, Latin America
Lung flukes	
Paragonimus westermani and other species	Far East, South Asia, Philippines, Central and South America, West Africa, Mississippi River Basin (USA)
Intestinal flukes	
Fasciolopsis buski	Far East
Heterophyes heterophyes	Far East, Egypt, Middle East
Metagonimus yokogawai	Far East
Nanophyetus salmincola	Pacific Northwest

[a] Parasites may be limited to certain countries in the regions listed and certain foci within these countries.

[b] Many less common trematodes that infect human beings are not listed here.

SCHISTOSOMIASIS

Clinical presentation

A history of contact with possibly infested freshwater in an endemic area should prompt an evaluation for schistosomiasis, even in the absence of symptoms (Figure 197.1). Clinical manifestations that suggest the diagnosis vary according to the stage of infection. Some persons complain of intense pruritus or rash shortly after the infective cercariae penetrate the skin. Previously uninfected visitors to endemic areas may develop acute schistosomiasis, or Katayama fever, 2 to 12 weeks after exposure, as the immune system responds to maturing worms and eggs. Symptoms range from mild malaise to a serum sickness-like syndrome that lasts for weeks and may be life-threatening. Common features include fever, headache, abdominal pain, myalgia, dry cough, diarrhea, hepatosplenomegaly, lymphadenopathy, urticaria, and marked eosinophilia.

Chronic infections with schistosomes usually are asymptomatic; slight or moderate eosinophilia occurs frequently. Long-term residents of endemic areas may harbor heavy infections for long periods and thus are more likely than transient visitors to have symptoms. Disease results from egg deposition in tissues and the ensuing inflammatory and fibrotic response (Figure 197.2). In infections due to *Schistosoma mansoni*, *Schistosoma japonicum*, *Schistosoma mekongi*, *Schistosoma intercalatum*, and *Schistosoma guineensis*, involvement of the bowel leads to mucosal inflammation and microulcerations, diarrhea, bleeding, polyps, and strictures. Embolization of eggs to the liver results in hepatosplenomegaly, periportal fibrosis, portal hypertension, and esophageal varices. Hematuria and dysuria are early symptoms of chronic infection by *Schistosoma haematobium;* later, fibrosis and calcification

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Figure 197.1 Shallow pond infested with *Biomphalaria*, the snail host of *Schistosoma mansoni* in Brazil.

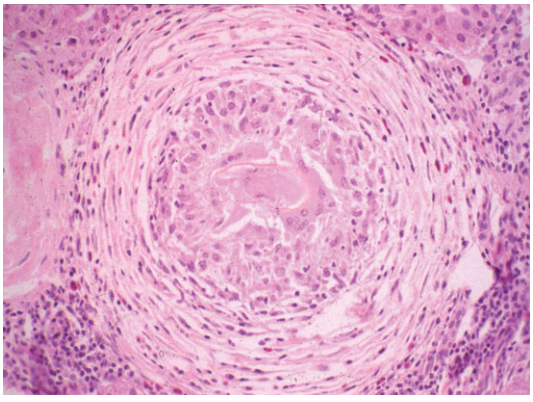

Figure 197.2 Granuloma around egg of *Schistosoma mansoni* that embolized to the liver and was trapped in a small branch of the portal vein.

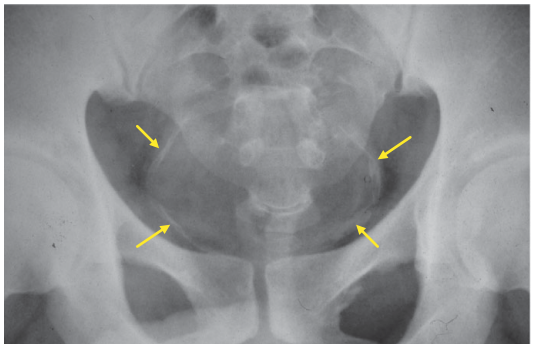

Figure 197.3 Plain radiograph of the pelvis showing calcification of the wall of the bladder and lower ureters (*arrows*).

of the bladder and lower ureters results in hydroureter and hydronephrosis (Figure 197.3), and squamous cell carcinoma of the bladder may develop. Ectopic deposition of eggs in the skin, genitalia, and other organs occurs during both the acute and chronic stages of infection. Transverse myelitis, seizures, and other serious sequelae result from egg deposition in the central nervous system. In endemic areas, chronic infections of even moderate intensity have been associated with anemia, poor nutritional status, and cognitive impairment.

Diagnosis

The most direct method of diagnosis is microscopic examination of stool or urine for schistosome eggs (Figure 197.4). Because egg output is low in light infections, concentration techniques and examination of several specimens obtained on different days should be routine. Eggs should be counted to estimate the intensity of infection and to monitor the response to therapy. Counts above 400 eggs per gram of feces or 10 mL of urine are considered heavy and are associated with higher rates of complications. Microscopic examination of snips of rectal mucosa obtained

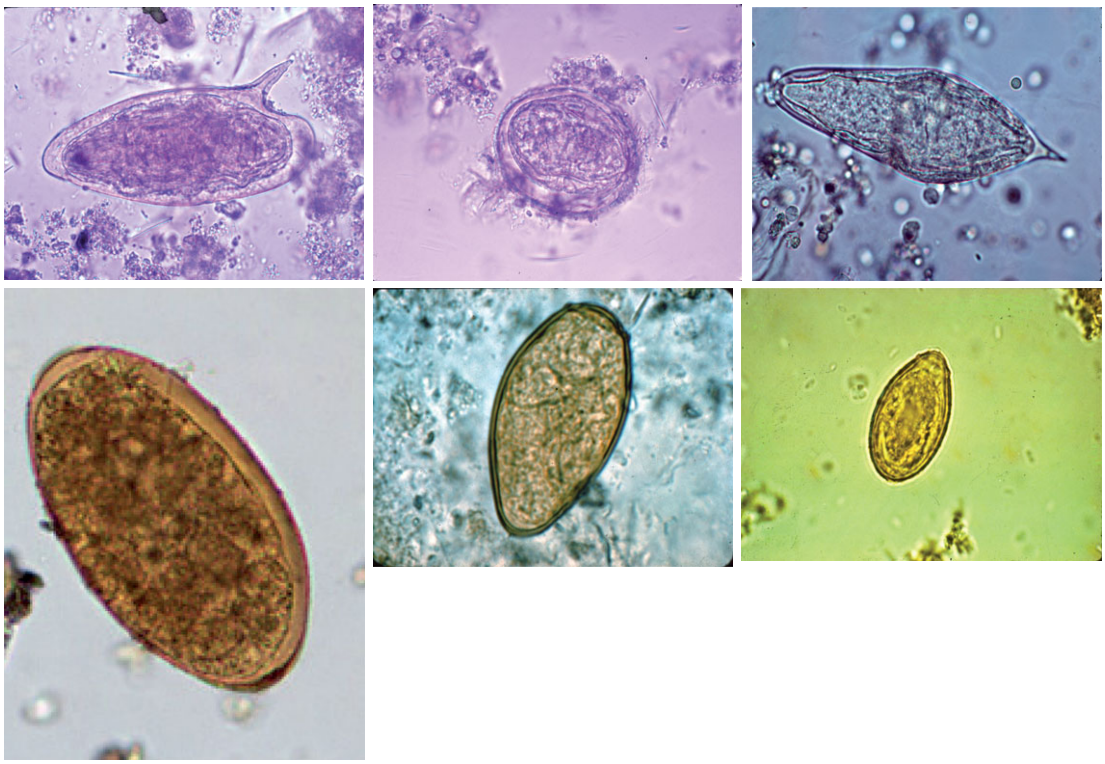

Figure 197.4 Trematode eggs. **Top row, left to right**: *Schistosoma mansoni, Schistosoma japonicum, Schistosoma haematobium*. **Bottom row, left to right**: *Fasciola hepatica, Paragonimus westermani, Clonorchis sinensis*.

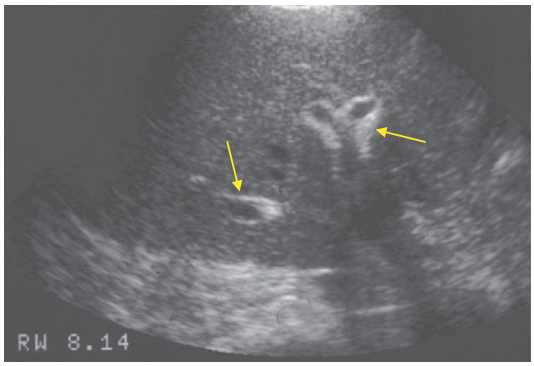

Figure 197.5 Ultrasound of the liver showing periportal fibrosis. Two portal tracts (one of the tracks is bifurcated) are surrounded with an area of increased echo (*arrows*).

at proctoscopy may reveal eggs when stool examination is negative.

Serologic tests for antibodies to schistosomes are available at commercial laboratories in the United States and at the Centers for Disease Control and Prevention (CDC) in Atlanta. The CDC uses a sensitive and specific Falcon assay screening test/enzyme-linked immunosorbent assay (FAST-ELISA) for screening and a highly specific immunoblot for confirmation and species determination. These tests cannot distinguish active from past infections but are useful for the diagnosis of acute schistosomiasis before eggs are shed in the stool. Serologic tests should be used to screen previously unexposed travelers and expatriates; a positive serologic test is presumptive evidence of infection even if subsequent microscopy is negative.

Persons with confirmed infections due to the intestinal schistosomes should be evaluated with measurement of liver function tests and tests for chronic hepatitis B and C to rule out concomitant hepatocellular disease. Heavy infection or evidence of liver disease should prompt an ultrasound to document periportal fibrosis and signs of portal hypertension (Figure 197.5). Esophageal varices are visualized by barium swallow or endoscopy. Urinalysis, urine culture, and serum creatinine determination are indicated for persons with *S. haematobium* infection. Ultrasonography or other imaging studies detect complications such as hydronephrosis, polyps, stones, and carcinoma of the bladder.

Table 197.2 Treatment of trematode infections

Parasite	Drug of choice	Dosage
Schistosoma mansoni, *S. haematobium*, *S. intercalatum*, S. *guineensis*[a]	Praziquantel	40 mg/kg/d in 2 doses ×1 d
Schistosoma japonicum, *S. mekongi*	Praziquantel	60 mg/kg/d in 2 or 3 doses ×1 d
Clonorchis sinensis, *Opisthorchis* spp.	Praziquantel	75 mg/kg/d in 3 doses ×1 d
Fasciola hepatica, *F. gigantica*	Triclabendazole	10 mg/kg ×1 or 10 mg/kg × 2 doses 6 h apart
Paragonimus spp.	Praziquantel	75 mg/kg/d in 3 doses ×2 d
Fasciolopsis buski, *Heterophyes heterophyes*, *Metagonimus yokogawai*	Praziquantel	75 mg/kg/d in 3 doses ×1 d
Nanophyetus salmincola	Praziquantel	60 mg/kg/d in 3 doses ×1 d

[a] To increase the likelihood of a complete cure, praziquantel 60 mg/kg/day in 2 or 3 split doses can be given to persons with schistosomiasis who have left an endemic area. Many experts suggest that persons who acquired *S. mansoni* infection in Africa should also receive 60 mg/kg/day in 2 or 3 split doses.

Therapy

All persons with schistosomiasis should receive treatment. Eradication of infection is desirable because even a single pair of worms may deposit eggs in the central nervous system. In endemic areas where reinfection is inevitable, the goal is to reduce worm burdens to levels that are unlikely to produce disease. Successful treatment not only prevents complications but also may cause regression of polyps and fibrotic lesions. Fortunately, the treatment of choice, praziquantel, is safe and highly effective after one or a few oral doses (Table 197.2).

Praziquantel causes an influx of calcium ions across the tegument of the adult worm, leading to a tetanic contraction and vacuolization of the tegument that makes the parasite susceptible to immune destruction. Cure rates range from 65% to 95%, and in persons not cured, egg excretion is reduced by >90%. A few reports suggest that resistance to praziquantel may be developing. Adverse effects, which are usually mild and last less than 24 hours, may be caused by reactions to dying worms rather than drug toxicity. Patients occasionally report malaise, headache, dizziness, or abdominal discomfort. Nausea, vomiting, diarrhea, bloody stools, fever, and urticaria are uncommon. The World Health Organization has judged praziquantel safe for pregnant or lactating women. Persons with known or suspected cysticercosis should remain under observation during therapy because of the risk of seizures or other neurologic consequences of dying cysticerci. Praziquantel is metabolized in the liver, and the dosage need not be reduced because of renal insufficiency.

Severely ill persons with acute schistosomiasis should receive corticosteroids as well as praziquantel, although there is controversy about timing of anthelmintic therapy. Some experts recommend delaying praziquantel treatment because maturing schistosomes are less susceptible to praziquantel than are adult worms, corticosteroids lower serum levels of praziquantel, and acute illness may be exacerbated by reactions to killing of parasites. Because of the risk of ectopic infection, we favor administration of praziquantel shortly after administration of steroids. All patients should receive a second course of treatment 4 to 6 weeks after the first. Artemisinin derivatives have activity against immature parasites, but although they can be effective in preventing infection, their utility in the management of acute schistosomiasis is uncertain.

Because antischistosomal drugs may temporarily inhibit egg laying by adult worms, stool and urine should be examined 3 and 6 months after completion of therapy. Eosinophilia, hematuria, and other symptoms that persist beyond this time should prompt repeat parasitologic studies and evaluation for causes other than schistosomiasis. Serologic tests may remain positive for years after successful treatment and are of limited utility for the assessment of cure.

OTHER TREMATODE INFECTIONS

More than 70 species of trematodes other than schistosomes infect 65 million or more persons worldwide. Most are parasites of wild and domestic animals. Human beings become infected by ingestion of metacercariae encysted in freshwater fish, crustacea, and plants, the second intermediate hosts.

Clonorchiasis and opisthorchiasis

The oriental liver flukes *Clonorchis sinensis*, *Opisthorchis viverrini*, and *Opisthorchis felineus* inhabit the biliary tree of persons who ingest

infected carp and other freshwater fish without proper cooking. Most patients are asymptomatic, but eosinophilia is common. An acute illness resembling Katayama fever occasionally occurs 2 to 3 weeks after initial exposure. Persons with heavy infections for many years develop symptoms due to irritation and inflammation of biliary epithelium. Patients complain of right upper quadrant discomfort, anorexia, and weight loss. On physical examination the liver is palpable and firm. Cholangitis, pancreatitis, and cholangiocarcinoma are infrequent complications.

Diagnosis is made by finding eggs in the stool (Figure 197.4) or identifying adult worms during endoscopic retrograde cholangiopancreatography (ERCP) or surgery for complications. In symptomatic cases, ultrasonography or computed tomography (CT) demonstrates dilation and stricture of bile ducts, thickening of the gallbladder wall, and stones. A single course of praziquantel eradicates infection in more than 85% of cases (Table 197.2). An alternative is albendazole for 7 days.

Fascioliasis

Infection with the sheep liver fluke *Fasciola hepatica* and the closely related *Fasciola gigantica* results from ingestion of uncooked watercress or other aquatic vegetation from sheep- and cattle-raising parts of the world. After excysting in the duodenum, immature worms pass through the bowel wall and peritoneal cavity, invade the liver, and burrow through the parenchyma to the bile ducts. This migration provokes an acute syndrome of fever, nausea, tender hepatomegaly, eosinophilia, and urticaria lasting weeks to months. Aberrant migration causes nodules in the skin, painful inflammation of the intestinal wall, pleural effusion, or lesions in the lungs, brain, or elsewhere. Chronic fascioliasis is usually subclinical, but some persons have symptoms due to inflammation and obstruction of bile ducts.

Diagnosis is confirmed by demonstrating eggs in samples of stool, bile, or duodenal aspirates (Figure 197.4) or by recovering worms at surgery. Serologic tests are useful during acute infection because symptoms develop 1 to 2 months before eggs appear in the stool. Ultrasonography and ERCP may demonstrate adult worms and biliary pathology, and CT or magnetic resonance (MR) shows migratory hypodense lesions in the liver corresponding to necrosis along the path of larval migration.

Treatment of fascioliasis is with one or two doses of the veterinary drug triclabendazole which is available from Victoria Pharmacy in Zurich, Switzerland (Table 197.2). Given with food, treatment is successful in approximately 80% of cases, and a repeat course cures most of the remaining cases. The alternative, nitazoxanide, is less effective, and fascioliasis responds poorly to praziquantel.

Paragonimiasis

Infection with *Paragonimus westermani*, the oriental lung fluke, and, less commonly, other species of *Paragonimus*, follows ingestion of raw or poorly cooked freshwater crabs or crayfish. An acute phase with fever, abdominal and chest pain, cough, and eosinophilia corresponds to migration of immature parasites through the bowel wall, diaphragm, and pleura en route to the lungs. The inflammatory reaction to adults encapsulated in the lungs and the shedding of eggs into the bronchial tree are responsible for chronic symptoms. Patients complain of cough, rusty or golden sputum, hemoptysis, vague chest pains, and dyspnea on exertion. Radiographs of the chest show poorly defined infiltrates, cysts, nodules, cavities, calcified lesions, and pleural effusions that on aspiration are seen to contain eosinophils. The findings may suggest tuberculosis. Bronchiectasis, bacterial pneumonia, or empyema complicates heavy infections. Extrapulmonary migration of flukes causes migratory subcutaneous nodules, involvement of abdominal viscera, or focal lesions of the central nervous system. Cerebral paragonimiasis is characterized by headache, seizures, focal neurologic deficits, cerebrospinal fluid eosinophilia, and cystic lesions on radiographs and scans.

Paragonimiasis is diagnosed by identifying expectorated eggs in the sputum, swallowed eggs in the feces, or worms and eggs in biopsy specimens (Figure 197.4). Several examinations of stool and sputum may be necessary. Serologic tests, such as the immunoblot offered by the CDC, are useful for diagnosis of early, light, and extrapulmonary infections.

The treatment of choice for paragonimiasis is praziquantel or alternatively, triclabendazole (Table 197.2). Because the inflammatory reaction to dying worms may precipitate seizures or other neurologic complications, corticosteroids should be used simultaneously with praziquantel for cerebral paragonimiasis.

Intestinal fluke infections

Adult intestinal flukes live attached to the mucosa of the duodenum and jejunum, where they cause local inflammation and ulceration. Of the dozens of species that infect human beings, *Fasciolopsis buski*, the giant intestinal fluke, is the best known. Infection is acquired by eating uncooked aquatic plants, such as water caltrop, water chestnut, and watercress. Heavily infected persons develop hunger pains that suggest peptic ulcer, diarrhea with mucus, and in extreme cases, malabsorption, ascites, anasarca, and intestinal obstruction. Eosinophilia is common.

Other important intestinal flukes include *Heterophyes heterophyes* and *Metagonimus yokogawai*, both of which are acquired by ingestion of raw or undercooked freshwater fish. Symptoms caused by these parasites resemble those produced by *Fasciolopsis*, but embolization of eggs that enter the circulation may cause severe myocarditis or cerebral hemorrhage. *Nanophyetus salmincola* is transmitted in the Northwest United States by ingestion of raw or undercooked salmon or trout. Manifestations include abdominal pain, watery diarrhea, and eosinophilia.

The diagnosis of all intestinal fluke infections is made by demonstrating eggs in the feces. Because the number of eggs excreted may be low, concentration techniques and repeated examinations are recommended. Praziquantel is the drug of choice (Table 197.2). Alternatives include triclabendazole and, for *Fasciolopsis* and *Heterophyes* infections, niclosamide.

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198. Tapeworms (cestodes)

Zbigniew S. Pawlowski

Cestodes cause intestinal (e.g., taeniasis, hymenolepiasis) and/or tissue parasitoses (e.g., cysticercosis, echinococcosis). Most of intestinal tapeworm infections are meat-borne zoonoses, whereas tissue infections with larval cestodes are fecal-borne, acquired mainly through ingestion of the tapeworm eggs from human, dog, or fox feces.

TAENIA SAGINATA AND *TAENIA ASIATICA* TAENIASIS

Taenia saginata, the beef tapeworm, sometimes >5 m long, may live up to 30 years in the small intestine of humans, who are its only natural host. Humans are infected by ingestion of the cysticercus, a bladder worm <1 cm in diameter, present in raw or undercooked beef.

Taenia saginata infections can spread easily because of a high fecundity of the tapeworm (>500 000 eggs produced daily for years), wide and long-term contamination of the environment with eggs, bovine cysticercosis that may escape routine meat inspection when of a low intensity, and, finally, common consumption of raw beef. More than 10% of nomads are infected in East Africa; in Europe the annual incidence in urban populations is <0.1%; in the United States and Canada, *T. saginata* taeniasis is uncommon and observed mainly among migrants from Latin America.

Taenia saginata infection occurs mainly in well-nourished middle-aged individuals who are raw beef eaters. Complaints include vague abdominal pains, nausea, weight loss or gain, and some perianal discomfort caused by gravid proglottids (about six per day) crawling actively out of the anus. Sometimes, the patient passes a longer part of tapeworm strobila; in that case the expulsion of proglottids may stop for some weeks. The diagnosis is set up by questioning and macroscopic examination of expulsed tapeworm proglottids. *Taenia* eggs are found more often on anal swabs than in feces. Tests detecting parasite antigen in feces are highly sensitive and specific and may detect the infections even when proglottids or eggs are not expelled.

Treatment of *T. saginata* taeniasis with praziquantel or niclosamide is safe and effective in 95% and 80% of cases, respectively. Praziquantel is given orally in a single dose of 5 to 10 mg/kg an hour after a light breakfast. Niclosamide is preferred for children younger than 4 years and for pregnant women. Niclosamide (use only the original products, recently manufactured) should be chewed thoroughly on an empty stomach in a single dose of 2 g for adults, 1 g for children who weigh 10 to 35 kg, and 0.5 g for smaller children. For both drugs adverse effects, such as abdominal discomfort, headache, and dizziness, are rare and transient. Tapeworm is usually expelled in fragments within a few hours; the scolex, indicating elimination of the entire worm, is often difficult to find. Therefore, successful therapy can be confirmed only when no proglottids reappear within 4 months after treatment.

Taenia asiatica, described recently in several Asian countries, is a sister species of *T. saginata*, similar morphologically but a distinct species when examined by molecular techniques. Its life cycle is different; small cysticerci develop in liver and viscera of pigs and a range of wild animals. Humans become infected by eating raw viscera, especially liver, of the infected animals. The diagnosis and treatment are similar to *T. saginata. Taenia asiatica* and *T. saginata* do not produce cysticercosis in humans.

TAENIA SOLIUM TAENIASIS AND CYSTICERCOSIS

Taenia solium (pork tapeworm) infection is common in Latin American countries, Central and South Africa, India, Indonesia, and China. Intestinal infection is acquired by eating undercooked pork containing cysticerci. Cysticercosis,

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a cystic larval form developing in the tissues, is acquired by ingesting *T. solium* eggs present in contaminated food or water or on hands spoiled with feces (autoinfections or family infections are not uncommon). Human cysticercosis may be common in endemic countries; sporadic cases of cysticercosis are diagnosed in humans in the United States and in Europe, having been acquired abroad or from immigrants infected with *T. solium* tapeworm.

The pork tapeworm is smaller than *T. saginata*, and its proglottids are usually expelled with feces, starting 2 months after ingestion of infected pork. Clinical symptoms and signs of taeniasis are not characteristic and are similar to *T. saginata* infection. The diagnosis is made by examination of the expelled proglottids or detecting the specific coproantigens. Finding *Taenia* eggs in feces can only confirm the diagnosis of taeniasis (*T. solium* eggs are morphologically indistinguishable from those of *T. saginata*). Proglottids and feces should be handled with care because *T. solium* eggs are infective for humans.

Treatment of *T. solium* taeniasis is mandatory as soon as possible, in both confirmed and suspected cases, due to a danger of spreading eggs causing cysticercosis in humans or pigs. Treatment of intestinal infection is the same as for *T. saginata* taeniasis; rarely, praziquantel may provoke symptoms in concomitant asymptomatic cysticercosis. Evaluation of treatment is by frequent fecal examination for *Taenia* eggs or coproantigens during the second and third months after anthelmintic therapy.

In cysticercosis, *T. solium* cysticerci may be localized in muscle and subcutaneous tissues (Figure 198.1A) without much symptomatology; the clinically important are mainly the cases of

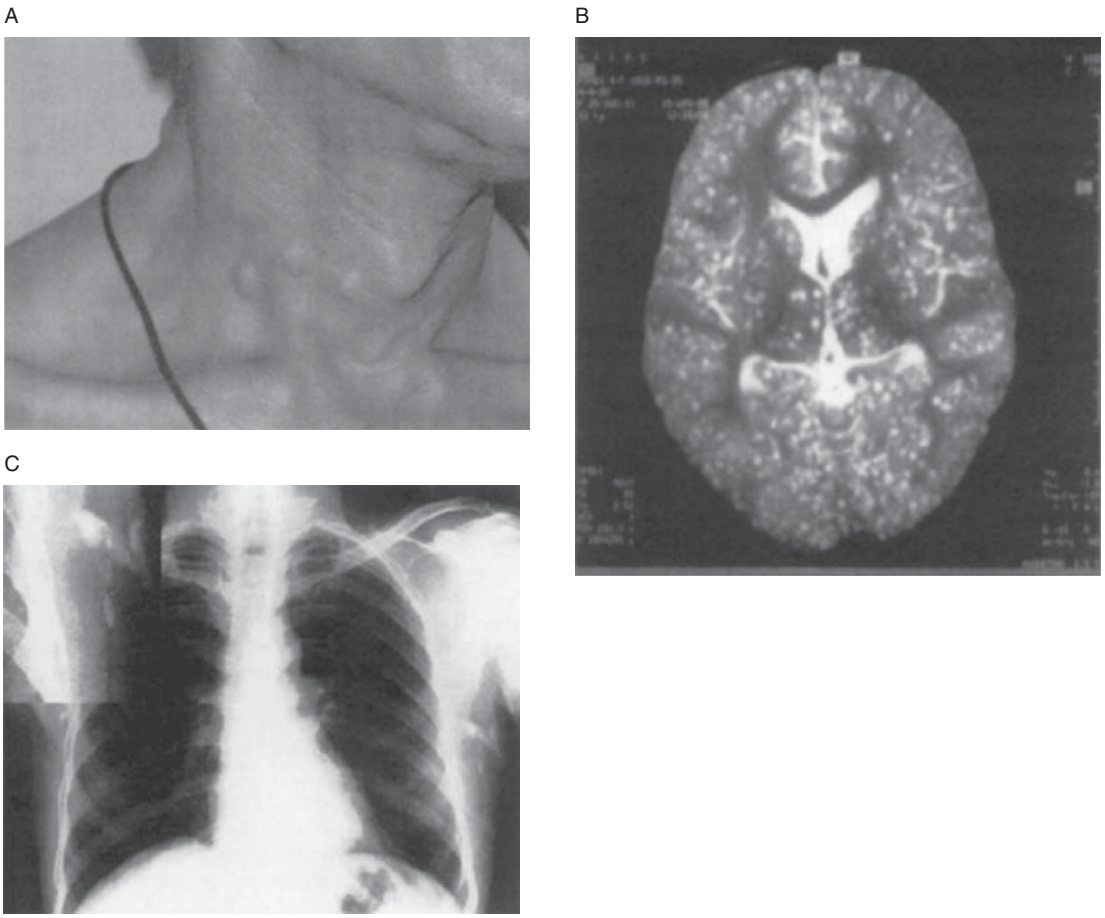

Figure 198.1 Cysticerci in subcutaneous location **(A)**, on brain computed tomography (CT) showing innumerable cysticerci (starry-night appearance) **(B)**, and calcifications in soft tissues **(C)**. (Courtesy of Dr. S. K. Gaekwed.) Bradley's *Neurology in Clinical Practice*, 4th edn. Butterworth-Heinemann; 2004.

neurocysticercosis, ocular cysticercosis, and heart cysticercosis. Neurocysticercosis is suspected when epileptiform seizures (70% to 90% of cases), intracranial hypertension, or psychiatric disturbances occur, especially in adolescents or adults in endemic areas or having contact with a *T. solium* carrier (household infection is common). The most malignant forms of cysticercosis are at ventricular and basal cisternal parasite localizations. If subcutaneous nodules are present (which is uncommon, except in India), the final diagnosis can be made by biopsy demonstrating a scolex or typical structures of cysticercus wall. Most often, cysticerci are diagnosed by finding cysticercus-like structure(s) in the brain, spine, eye, or heart by computed axial tomography (CAT) or magnetic resonance imaging (MRI) scans (Figure 198.1B). In some cases the inflammatory reaction or edema and ventricular dilatation are present. In ocular cysticercosis the diagnosis can be made by ophthalmoscopy. Less often cysticercosis is suspected on the basis of ultrasound scanning and/or x-ray examination, particularly if calcifications are present (Figure 198.1C). Positive serologic tests, especially enzyme immunoassay (EIA) and enzyme-linked immunoelectrontransfer blot (EITB) assays, support the clinical diagnosis but cannot differentiate between active and past infections.

Neurocysticercosis is often asymptomatic; in such cases, indications for treatment must be considered carefully. Symptomatic cases can be active or inactive (calcified). Therapy can be via specific anthelmintic treatment, surgery, corticosteroids, or symptomatic treatment. The choice of treatment has to be individually tailored. Anthelmintic therapy with praziquantel or albendazole is indicated in active cysticercosis with several parenchymal cysts or with clinical signs of vasculitis, encephalitis, and arachnoiditis. Traditionally, praziquantel is given orally in a daily dose of 50 mg/kg for 14 days, but a shorter regimen with a higher dose has been proposed. Albendazole is given orally in a daily dose of 15 mg/kg for 8 days. For parenchymal brain cysticerci, the efficacy is about 60% for praziquantel and 85% for albendazole. Damage to cysticerci, caused by both drugs, may result in a local inflammatory reaction and edema, which necessitates a concomitant additional corticosteroid or antihistamine drug therapy.

Surgical extirpation is indicated for single parenchymal, intraventricular, spinal, and ocular cysticerci and with focal symptoms (e.g., cranial nerve dysfunction). A ventricular shunt is indicated in hydrocephalus. Corticosteroids and immunosuppressants may control vasculitis and encephalitis. Antiepileptic drugs are used mainly in inactive cysticercosis with granulomatous or calcified lesions. The global disability and mortality from neurocysticercosis are still considerable but its control measures are introduced only locally.

HYMENOLEPIS NANA INFECTIONS

Hymenolepis nana, the dwarf tapeworm, 15 to 40 mm long, lives only up to 3 months in human small intestine. Some of the tapeworm eggs are expelled with feces and constitute a source of autoinfection or infection for other people. The other eggs hatch in the human intestine and develop within a month into cysticercoids in intestinal villi and later into the next generation of adult tapeworms in the same host.

Such a cycle facilitates spread of infection in close communities (day-care centers, schools, psychiatric institutions) as well as permits intensive infections of thousands of tapeworms, especially in malnourished or immunodeficient individuals. Usually a specific immunity develops and regulates the intensity and duration of infection, which occurs mainly in children and often clears spontaneously in adolescence. Hymenolepiasis is very common in regions with a hot, dry climate; it is rare in countries with appropriate sanitation.

Intensive infections may cause diarrhea, abdominal pains, and general symptoms such as weight loss, pallor, and weakness. Diagnosis is made by finding characteristic *H. nana* eggs in feces. Treatment with a single dose of praziquantel, 15 to 25 mg/kg, is highly effective; in intensive infections treatment must be repeated after 3 weeks. Niclosamide is much less effective and requires repeated courses of 7 days with the daily dose of 2 g for adult patients. Successful treatment has to be confirmed by negative fecal examination every 2 weeks for 2 months after therapy.

OTHER INTESTINAL CESTODES

Diphyllobothriasis, caused by *Diphyllobothrium latum*, *Diphyllobothrium dendriticum*, and *Diphyllobothrium pacificum*, still occurs around unpolluted large lakes in moderate climates (the Great Lakes in the United States and Canada and lakes in Finland and Switzerland) and along the Pacific Coast in South America. An uncommon clinical

complication of diphyllobothriasis is vitamin B_{12} deficiency. Diagnosis is made by finding characteristic eggs during fecal examination. Treatment is a single dose of praziquantel, 15 to 25 mg/kg. Evaluation of successful therapy is by repeated fecal examination some months after.

Hymenolepis diminuta (rat tapeworm) and *Dipylidium caninum* (dog tapeworm) infections occur accidentally in humans and are usually nonintensive and asymptomatic. They are diagnosed by fecal examination and can be easily treated by a single dose of praziquantel, 15 mg/kg.

Spirometra spp., a tapeworm parasitizing a broad spectrum of amphibian hosts, reptiles, birds, and mammals, occur sporadically but worldwide. It causes sparganosis, larval worm infection, mainly in the subcutaneous tissue or in an orbit.

CYSTIC ECHINOCOCCOSIS (HYDATID DISEASE)

Echinococcus granulosus is a tiny tapeworm living in the small intestine of some carnivores, mainly dogs. *Echinococcus granulosus* eggs, which are excreted in dog feces and contaminate an environment, are the source of cystic echinococcosis in various animals, mainly sheep or pigs, and sporadically in humans. Echinococcosis is still common in sheep-breeding regions in South America, Mediterranean countries, Middle East, Central Asia, and China. Small enzoonotic foci are found in Alaska, California, southern Utah, northern Arizona, and New Mexico. In Europe, sporadic cases of cystic echinococcosis are frequently caused by an *E. granulosus* strain, originating from pigs.

Echinococcus cysts develop mainly in the liver (about 65%) or lungs (25%), but they can invade any tissue, including the brain, kidney, spleen, heart, and bone. Clinical manifestations are diverse, depending on location, size, and number of the cysts as well as the complications resulting from cyst rupture and communication with biliary or bronchial systems or with adjacent body cavities. Bacterial infection of the cysts and secondary peritoneal echinococcosis are not uncommon. Clinical diagnosis is confirmed mainly by imaging techniques (sonography, CT, MRI, positron emission tomography [PET], and/or x-ray examination. Classification of cystic echinococcosis in sonography is based on cyst morphology, considering also fertility and the content of the cyst; one can differentiate a cystic lesion (CL) stage, similarly to nonparasitic cysts, and C1 to C5 stages from young active cysts to old inactive cysts. Diagnosis can be confirmed by the serologic tests (sensitive enzyme-linked immunosorbent assay [ELISA], followed by more specific immunodiffusion or immunoblot tests). In some cases the clinical picture, imaging, and serology are not conclusive, and the final diagnosis is made by finding parasite hooks, protoscolices, or cyst wall fragments in sputum or in biopsy, surgical, or necropsy samples. In some specialized centers, cyst puncture with a fine needle guided by sonography and performed under the cover of albendazole is becoming widely used. Most commonly the differential diagnosis considers liver simple nonparasitic cysts.

The echinococcus cysts may be sterile or fertile (with protoscolices), simple or multiple, small or large (up to 20 cm in diameter), asymptomatic or symptomatic, active or inactive, complicated or noncomplicated. The choices of management are surgery, chemotherapy, PAIR (puncture, aspiration, injection of a cysticidal substance, and reaspiration), or observation without any intervention. Major indications for surgery are large, active, superficially located, and easy-to-rupture liver cysts and most of the brain, spinal, heart, and bone cysts. Surgery can be radical (removal of the whole intact cyst) or conservative (cystectomy and removal of the parasite but not the host pericyst). Surgery brings a risk of complications, such as anaphylactic shock or secondary echinococcosis and death (0.5% to 4%).

Chemotherapy is used more widely, mainly but not exclusively in inoperable cases. An important indication for chemotherapy before surgery or a puncture is prevention of secondary echinococcosis due to unintentional spillage of a cyst's contents. The drugs used are mebendazole, 40 to 50 mg/kg daily for at least 3 months, or albendazole, 10 to 15 mg/kg daily for at least 1 month. Sometimes repeated courses of treatment are necessary. Chemotherapy with both drugs brings a risk of embryotoxicity in early pregnancy. Careful clinical monitoring can prevent hepatotoxicity, neutropenia, and thrombocytopenia but not alopecia, which may occur.

PAIR is used in endemic regions with poor healthcare facilities. Unfortunately, no protoscolicide is both effective and safe; widely used now are 75% to 95% ethanol, 20% hypertonic sodium chloride solution, and 0.5% cetrimide. Formalin solution should no longer be used, as it can provoke sclerotic cholangitis.

ALVEOLAR AND POLYCYSTIC ECHINOCOCCOSIS

Echinococcus multilocularis tapeworms develop in the intestine of some carnivores, mainly foxes, but also dogs; the intermediate hosts are rodents such as voles, lemurs, and mice. Large natural enzoonotic foci of alveolar echinococcosis are in the Northern Hemisphere, especially the region of the Alps (France, Switzerland, Germany, Austria), Siberia, northern Japan, and Alaska. Humans are infected accidentally by *E. multilocularis* eggs present in fecally polluted natural environments (water, soil, berries) or on fox's skin or dog's hair.

Incidence of human alveolar echinococcosis varies between 0.02 and 0.18 per 100 000 inhabitants. However, a spread of *E. multilocularis* is observed in Europe westward (France), eastwards (Poland and Lithuania), northwards (Norway and Sweden), and southwards (northern Italy). In addition to its natural foci it spreads, together with foxes, in some urbanized areas.

Echinococcus multilocularis lesions, composed of clusters of tiny vesicles, usually begin in the liver, grow slowly over the years in a tumorlike pattern, and may metastasize to lungs and brain. Modern (PNM) classification of alveolar echinococcosis lesions in liver is based on the size of parasitic mass, involvement of the neighboring tissues, and distant metastases. The early clinical manifestations are usually vague; the advanced disease is invariably symptomatic due to liver lesions or lung or brain metastases. Diagnosis is based on imaging techniques and molecular and immunologic tests; the latter (e.g., Em2G11) are highly specific. The differential diagnosis is mainly with neoplasma conditions. Treatment is by radical surgical resection of liver lesions followed by at least 2 years of chemotherapy. Recurrent or nonresectable lesions require lifelong chemotherapy with mebendazole or albendazole, which are parasitostatic rather than parasitocidal. Nitrazoxanide and amphotericin B are now suggested as potential alternative additional or combined drugs. The treatment has to be performed in specialized centers because of various and frequently severe complications, which may need another surgery or in rare cases a liver transplantation.

Polycystic echinococcosis occurs in humans in Central and South America and is caused by *Echinococcus vogeli* and *Echinococcus oligartrus*, the parasites of wild mammals. The numerous small cystic lesions can be found in the liver, lungs, abdominal cavity, stomach, heart, and orbit. The clinical course is similar to alveolar echinococcosis. Polycystic echinococcosis frequently requires surgery and responds well to albendazole.

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199. *Toxoplasma*

Roderick Go and Benjamin J. Luft

Toxoplasmosis, caused by the obligate intracellular parasite *Toxoplasma gondii,* is responsible for significant morbidity and mortality throughout the world. Although it has long been recognized as a serious congenital disease, it is only with the advent of acquired immunodeficiency syndrome (AIDS) and the increased use of immunosuppressive therapy that toxoplasmosis has reached epidemic proportions.

Humans are incidental hosts in the life cycle of *T. gondii*. Acute infection occurs via ingestion of meats or water contaminated with tissue cysts or tachyzoites or by handling cats, the definitive host. Once the human host develops an adequate immune response, tissue cysts are formed and a chronic or latent infection ensues. Antibodies against *T. gondii* will be present in serum for life. When a chronically infected person becomes immunocompromised, particularly with defects in cell-mediated immunity, devastating reactivation of the latent infection may occur.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

In the immunocompetent host, primary infection is often asymptomatic. Acute infection can mimic the symptoms of mononucleosis with a common manifestation of cervical or occipital lymphadenopathy. The lymph nodes usually are nontender, are nonsuppurative, and persist for less than 4 to 6 weeks. Infrequently, toxoplasmosis can lead to myocarditis, hepatitis, polymyositis, pneumonitis, and encephalitis.

Toxoplasmosis in the immunocompromised patient is most commonly manifested by toxoplasmic encephalitis (TE), usually alone but sometimes as part of a multiorgan infection. Isolated organ involvement without central nervous system (CNS) disease is uncommon. In the AIDS patient, TE usually develops when the CD4 lymphocyte count falls below $100/mm^3$, although the risk of developing overt infection begins when CD4 counts fall below $200/mm^3$. The clinical manifestations of TE are protean, including signs and symptoms of focal or generalized neurologic dysfunction or more commonly both, depending on the number, size, and location of the lesions. Cerebral edema, vasculitis, and hemorrhage, which can accompany active infection, also contribute to the disease process. Toxoplasmic encephalitis most commonly presents with a subacute onset of focal neurologic deficits with or without evidence of generalized cerebral dysfunction. Less often, seizures are the initial manifestation. Occasionally, signs and symptoms of generalized cerebral dysfunction dominate the presentation, and patients develop focal deficits as the infection progresses. The clinical presentation varies from an insidious process evolving over several weeks to a more acute or even fulminant course. Headaches may be focal or generalized and unremitting.

Serologic tests for diagnosis of toxoplasmosis in AIDS patients are useful only to identify human immunodeficiency virus (HIV)-infected individuals at risk for development of TE and as support for the diagnosis in AIDS patients with focal brain lesions. The Sabin–Feldman dye test is the accepted standard for measurement of immunoglobulin G (IgG) antibodies, which have been shown to be higher in AIDS patients with TE than in those without TE. The immunofluorescence assay (IFA), which is more commonly used, measures the same IgG antibodies as the dye test. Almost all AIDS patients with TE have detectable IgG. The absence of these antibodies strongly suggests another cause of the neurologic signs and symptoms.

The standard of care allows for the treatment of TE to be initiated on presumptive diagnosis when a typical neuroradiographic abnormality is noted on computed tomography (CT) or magnetic resonance imaging (MRI). MRI is more sensitive than CT in the demonstration of focal CNS lesions. The clinical diagnosis is a result of clinical and radiographic response to specific therapy

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because patients may have similar symptoms resulting from lesions of other causes, such as CNS lymphoma, progressive multifocal leukoencephalopathy, brain abscess, and focal lesions caused by other organisms, including *Cryptococcus neoformans, Aspergillus* spp., *Mycobacterium tuberculosis,* and *Nocardia* spp. The practice of presumptive therapy for patients who have not been receiving effective prophylaxis for *Toxoplasma* with a characteristic finding on CT or MRI and positive serology for *Toxoplasma* is widely accepted. With the use of these criteria, the predictive value has been estimated at 80%. However, for patients such as intravenous drug abusers in whom other CNS processes are more prevalent, the predictive value of a positive serology for *Toxoplasma* is reduced, and the widespread use of prophylaxis may further reduce it. Toxoplasmic encephalitis is predominantly intra-axial, so significant meningeal involvement is uncommon. Examination of cerebrospinal fluid (CSF) is used to exclude other diseases. Detection of *T. gondii* DNA by polymerase chain reaction (PCR) in CSF has demonstrated high specificity but variable sensitivity in establishing the diagnosis of TE in AIDS patients with focal lesions.

The lungs are the second most common site of infection in AIDS patients and in recipients of bone marrow transplants. The clinical manifestations of toxoplasma pneumonia are nonspecific, similar to those seen with *Pneumocystis jirovecii* (*carinii*) pneumonia (PCP). Most patients have fever, a nonproductive cough, dyspnea, and occasionally hemoptysis. However, the onset of disease tends to be faster than with PCP. The chest roentgenogram typically reveals bilateral interstitial infiltrates, although multiple nodular infiltrates, single nodules, isolated cavitary disease, lobar infiltrates, pleural effusions, and hilar adenopathy may occur. Pneumothorax complicating toxoplasmic pneumonia has been reported, as well as acute respiratory distress syndrome (ARDS). The diagnosis relies on a high index of suspicion and the demonstration of *T. gondii* from bronchoalveolar lavage (BAL) fluid or biopsy specimens, given the nonspecific nature of both clinical and radiologic manifestations in most cases.

Ocular toxoplasmosis is the most common retinal infection in the United States and is the second most common retinal infection in patients with AIDS after cytomegalovirus (CMV) retinitis. Patients usually present with decreased visual acuity and, less often, eye pain. Ocular toxoplasmosis may be the sole manifestation of infection or may accompany TE or disseminated disease. At times, in the immunocompromised host, ocular toxoplasmosis is a harbinger of TE. A CT scan of the head should be obtained to assess presence of concomitant TE. Fundoscopic findings are consistent with a necrotizing chorioretinitis. The lesions, which may be single or multiple and bilateral and are usually nonhemorrhagic, are yellow-white areas of retinal necrosis with ill-defined fluffy borders. They occur at the posterior pole and may be associated with a moderate to severe inflammatory response in the vitreous and anterior chamber. These characteristics help in the differential diagnosis with CMV retinitis. Fluorescein angiography may also be helpful. Dye leakage tends to occur along the edge of the lesions in toxoplasmosis and to be more prominent in the center of lesions in CMV retinitis. Ocular toxoplasmosis should be suspected in the AIDS patient who is seropositive for *T. gondii* and has changes in visual acuity with accompanying fundoscopic changes. A prompt response to specific therapy should also be expected. Definitive diagnosis has been made by demonstrating the organism in retinal biopsy specimens or isolation of *T. gondii* from vitreal fluid or PCR.

THERAPY

Immunocompetent host

Most infections in immunocompetent hosts are asymptomatic and do not require therapy. Lymphadenopathy, the most common manifestation, is self-limited and usually resolves within 1 to 3 weeks. Treatment should be considered only if systemic symptoms are severe or long lasting or in the rare event of visceral involvement (encephalitis, myocarditis, pneumonitis). Acute infection as a result of laboratory accidents or transfusions may be severe and should be treated. The treatment regimen of choice consists of a combination of pyrimethamine (Daraprim) and sulfadiazine given for 2 to 4 weeks with folinic acid (leucovorin) (Table 199.1). In the event of pyrimethamine-induced hematologic toxicity, the dosage of folinic acid can be increased to 20 to 50 mg/day. For patients allergic to sulfa, clindamycin in combination with pyrimethamine and folinic acid has been used successfully (see Table 199.1).

For ocular toxoplasmosis, the drugs of choice are pyrimethamine and sulfadiazine or trisulfapyrimidine with folinic acid in the same dosages

Table 199.1 Drugs for treatment of toxoplasmic encephalitis and extraneural toxoplasmosis

Antimicrobial	Mode of action	Metabolism	Adverse effects	Recommended dosage (immunocompromised)	Recommended dosage (immunocompetent)
Pyrimethamine (Daraprim) oral	Inhibits folic acid synthesis	Readily absorbed by gut; hepatic metabolism, lipid soluble	Cytopenias, rash, GI intolerance	Acute: loading dose 200 mg then 50–75 mg daily; with oral folinic acid (leucovorin) 10–20 mg/d Maintenance: 25–50 mg/day with oral folinic acid 10–25 mg/d	Loading dose 200 mg daily for 2 d, then 50–75 mg daily for 2–4 wk; with oral folinic acid 10–20 mg/d
plus					
Sulfadiazine[a] oral	Inhibits folic acid synthesis; acts synergistically and sequentially with pyrimethamine	Readily absorbed by the gut; penetrates blood–brain barrier; some hepatic metabolism	GI intolerance, rash (Stevens–Johnson syndrome), cytopenias, nephrolithiasis, crystalluria, interstitial nephritis, encephalopathy	Acute: 1–1.5 g q6h Maintenance: 500–1000 mg/day QID	1–1.5 g q6h, 2–4 wk
or					
Clindamycin[a] oral and IV	Unknown; possibly inhibition of plastid and/or mitochondrial protein synthesis	Readily absorbed by gut; excellent tissue penetration	GI intolerance, rash, pseudomembranous colitis	Acute: 600 mg q6h (up to IV 1200 mg q6h) Maintenance: 300–450 mg PO q6–8h	300 mg q6h, 4 wk, repeat as needed

Abbreviation: GI = gastrointestinal.

[a] Used in combination with pyrimethamine.

Adapted from Mofenson *et al. MMWR Recomm Rep.* 2004;53(RR–14):1.

as described earlier. Therapy is given for 4 weeks and repeated as needed. Treatment is required to prevent relapse with the risk of progressive vision loss and other complications such as glaucoma. Adjunctive therapy with systemic corticosteroids (prednisone, 80 to 120 mg/day, or an equivalent) is indicated if the macula, optic nerve, or papillomacular bundle is involved.

Immunocompromised host

For TE, the combination of pyrimethamine, 200 mg loading dose in two divided doses followed by 50 to 75 mg/day orally, plus sulfadiazine, 4 to 6 g/day orally in four doses, remains the mainstay of treatment (see Table 199.1). Oral folinic acid is added to preclude the hematologic toxicities associated with antifolate agents. Acute therapy is recommended for at least 6 weeks. Longer treatment durations may be needed if there is extensive clinical and radiographic disease or the response is incomplete at 6 weeks. Patients who cannot tolerate sulfas can be given clindamycin in combination with pyrimethamine as described. Prophylactic use of anticonvulsants is not recommended. Corticosteroids should not be used routinely but are indicated if there is evidence of increased intracranial pressure. In one study, 70% of AIDS patients treated for TE had a quantifiable clinical improvement by day 7 of therapy. Conversely, patients not responding to empiric therapy had evidence of progressive disease within the first 10 days. Ninety percent of patients had improvement on neuroradiographic studies within 6 weeks of starting therapy.

In immunocompromised hosts, maintenance therapy (secondary prophylaxis) should be initiated. The regimen is usually the same as that used for primary treatment but at half dose. Maintenance therapy should be continued for the life of the patient or until the underlying immunosuppression has resolved. In patients with AIDS, secondary prophylaxis can be discontinued if they have sustained CD4 counts greater than 200 cells/mm^3 for longer than 6 months.

The same chemotherapeutic regimens are used for extraneural toxoplasmosis; however, there are limited data available on the optimal length and outcome of treatment. As a rule, ocular

Table 199.2 Alternative treatments of toxoplasmosis in immunocompromised patients

Antimicrobial	Mode of action	Metabolism	Adverse effects	Recommended dosages
Atovaquone (Mepron)[a] oral	Uncoupling electron biosynthesis; inhibition of de novo pyrimidine biosynthesis	Suspension has better bioavailability than old tablet formulation; improved absorption if taken with food, particularly fatty foods	Rash, elevated liver function tests	Acute: suspension 1500 mg q12h Maintenance: suspension 750 mg q6–12h
Azithromycin (Zithromax)[a] oral	Unknown; possibly inhibition of plastid and/or mitochondrial protein synthesis	Readily absorbed by gut; high intracellular levels	GI intolerance	Acute: 900–1200 mg/d Maintenance: same
Trimethoprim–sulfamethoxazole (TMP–SMX)[b] (Bactrim, Septra) oral or IV	Inhibits folic acid synthesis	Renal metabolism	Rash, Stevens–Johnson syndrome, bone marrow suppression, hepatotoxicity, increased serum creatinine	Acute: 5 mg/kg TMP and 25 mg/kg SMX IV or oral BID

Abbreviations: GI = gastrointestinal.

[a] Used in combination with pyrimethamine or sulfadiazine.

[b] Used in combination with pyrimethamine.

toxoplasmosis responds favorably to therapy, and treatment of pulmonary infection has been reported to be successful in 50% to 77% of patients.

Intravenous trimethoprim–sulfamethoxazole (TMP–SMX, Bactrim, Septra), at 5 mg/kg/day trimethoprim component, has been used when oral therapy is contraindicated. Although TMP–SMX is available for oral use, response rates have been lower than standard regimens. Recently, trials have shown higher initial response rates when the dose was increased (trimethoprim, 6.6 to 10 mg/kg body weight per day).

The drugs described thus far are active only against the tachyzoite form of *T. gondii*. Surviving tissue cysts can reinitiate TE and other manifestations of reactivated latent disease if treatment is discontinued. Therefore it is necessary to give long-term suppressive therapy. Pyrimethamine, 25 to 50 mg/day, and sulfadiazine, 2 to 4 g/day orally in four doses, with 10 mg/day of oral folinic acid is recommended because of the low relapse rate associated with this combination. Clindamycin is used in cases of sulfa allergy. Atovaquone monotherapy at 750 mg two to four times a day may be considered in patients who are unable to tolerate pyrimethamine; however, this regimen has a 1-year relapse rate of 26%.

Primary chemoprophylaxis is a very attractive therapeutic option for patients known to be at risk for toxoplasmosis (i.e., those with CD4 counts less than 100 cells/mm^3 and seropositive for anti-*T. gondii* antibodies). Retrospective data suggest that TMP–SMX, one double-strength tablet per day orally, is efficacious. Neither dapsone nor pyrimethamine, when used as a single agent, is consistently effective. However, the combination of pyrimethamine, 50 mg/week, plus dapsone, 50 mg/day, plus folinic acid has been a useful alternative. In patients with a sulfa allergy, desensitization is also an option. Primary prophylaxis can be safely discontinued when the patient has sustained immune reconstitution with a CD4 count greater than 200 cells/mm^3 for 3 months.

Other drug regimens that have proven useful as initial and maintenance therapy (Table 199.2) include atovaquone (Mepron). An AIDS Clinical Trials Group (ACTG) trial evaluating the efficacy of atovaquone-containing regimens (either in combination with pyrimethamine or sulfadiazine) showed encouraging results, with 77% response to therapy. As salvage therapy, atovaquone alone induced initial clinical response in 50% of study patients. The response to therapy with atovaquone has been directly correlated with serum drug levels achieved. The macrolide antibiotics azithromycin (Zithromax) and clarithromycin (Biaxin) in combination with pyrimethamine have limited utility as alternative agents.

Pregnancy

Women who acquire toxoplasmosis (primary infection) during pregnancy expose their fetuses to risk of infection. Infection of the fetus may result in stillbirth, spontaneous abortion, or birth of a symptomatic or an asymptomatic infant. Rarely, transmission has been reported in cases

Table 199.3 Drugs used in treatment of toxoplasmosis in pregnant women

In pregnant women infected during gestation	Medication	Dosage	Duration of therapy
First 18 wk of gestation or until term if fetus found not to be infected by amniocentesis at 18 wk	Spiramycin[a]	1 g every 8 h without food	Until fetal infection is documented or until it is excluded at 18 wk of gestation
If fetal infection confirmed, after wk 18 of gestation and in all women infected after wk 18	Pyrimethamine[b] plus	Loading dose: 50 mg each 12 h for 2 d; then beginning on day 3, 50 mg/d	Until term
	Sulfadiazine plus	Loading dose: 75 mg/kg; then beginning 50 mg/kg each 12 h (maximum 4 g/d) 10–20 mg daily	Until term
	Leucovorin (folinic acid)		During and for 1 wk after pyrimethamine therapy

[a] Spiramycin is not commercially available. Available only on request from the US Food and Drug Administration (telephone number: 301–443–5680), and then with approval by physician's request to Sanofi–Aventis (908–231–3365).

[b] Adjusted for megaloblastic anemia, granulocytopenia, or thrombocytopenia.

From Remington JS, McLeod R, Thulliez P, Desmonts G. Toxoplasmosis. In: Remington JS, Klein JO, Wilson CB, Baker CJ, eds. *Infectious Diseases of the Fetus and Newborn Infant*, 6th edn. Philadelphia, PA: Elsevier; 2006.

where the mother contracts acute toxoplasmosis 6 to 8 weeks before conception. Fetal infection is less common when the mother is treated during pregnancy. Early diagnosis, through serology, amniotic sampling for PCR, and fetal ultrasonography, is important in further management (antibiotics or therapeutic abortion).

Pyrimethamine plus a sulfonamide or spiramycin, a macrolide antibiotic available in western Europe, Mexico, and Canada and through the Food and Drug Administration of the United States, appears to decrease the incidence of congenital toxoplasmic infection when given to women who acquire *T. gondii* during pregnancy (Table 199.3). Pyrimethamine is teratogenic and should not be used until after the first trimester. There is no optimal medical therapy in the United States for treatment of women who become infected during the first trimester. However, sulfadiazine or trisulfapyrimidines should be used during the first trimester because sulfonamides alone have been shown to be effective in acute toxoplasmosis in animal models. If spiramycin can be obtained, pregnant women acutely infected in the first trimester may be treated until term with 30 to 50 mg/kg/day in three doses until fetal infection is confirmed or excluded. Treatment with spiramycin alone decreases the incidence of transmission but not the severity of established congenital infection. As spiramycin does not readily cross the placenta, treatment should be switched to pyrimethamine, sulfadiazine, and folinic acid in pregnant women with confirmed or a high possibility of fetal infection after the 18th week of gestation. If maternal or fetal infection is suspected or confirmed after the first trimester, pyrimethamine and sulfadiazine plus folinic acid should be used for treatment.

Pregnant women or women who are trying to become pregnant should be advised about risk factors for primary infection with toxoplasmosis. Education has been shown to be effective in decreasing the seroconversion rate during pregnancy. Women with cats should have someone else changing the litter box daily. They should avoid consuming undercooked meats, raw eggs, unpasteurized milk, or unfiltered water. All uncooked fruits and vegetables should be washed. Gloves should be used if they are working with soil, if they are preparing raw meat, or if they must change the cat litter box themselves. Proper hand hygiene should be practiced after working with soil, after handling the cat or the litter box, or after touching raw or undercooked meat.

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200. Malaria

Jessica K. Fairley and Henry M. Wu

Malaria remains a life-threatening parasitic infection endemic throughout much of the world. It is estimated that in 2010 there were 216 million infections and 655 000 deaths due to malaria, with the majority of deaths among African children. In nonendemic countries, it is one of the most common causes of fever in returned travelers and recent immigrants, and several thousand people with malaria arrive in nonendemic countries yearly.

Malaria is a mosquito-borne protozoal infection caused by one of four human *Plasmodium* species (*Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, and *Plasmodium malariae*), or with the monkey parasite, *Plasmodium knowlesi*, which has been increasingly described in parts of Southeast Asia. Malaria endemic countries are shown in Figure 200.1. Given the risk of rapid progression to severe disease in nonimmune individuals, a high index of suspicion is critical when evaluating patients with febrile illness following travel to malarious areas, especially those endemic for *P. falciparum*. Proper treatment of malaria requires knowledge of the infecting species and where it was acquired, since drug resistance patterns vary geographically. Widespread chloroquine-resistant *P. falciparum* (CRPF) malaria and emergence of resistance to other drugs have complicated treatment and prophylaxis.

CLINICAL ASPECTS

Fever in a patient who has recently traveled to an area endemic for malaria should be considered a medical emergency. The minimum incubation period is generally considered to be 7 days after inoculation, and of greatest concern is the patient who has traveled to a *P. falciparum* endemic area within 2 months of presentation, since an incubation period of 2 to 4 weeks is typical for falciparum malaria. Presentation several months to 1 year after departing an endemic region is also possible, particularly when infected with *P. vivax* or *P. ovale*, since infection with these species can result in a dormant liver stage. Patients with falciparum malaria can also present months after exposure, as the use of prophylaxis or presence of semi-immunity can modify or delay the onset. For these reasons, febrile patients who have traveled to a malarious region in the preceding year should be ruled out for malaria, regardless of prophylaxis history.

Malaria transmission occurs when a malaria-infected female *Anopheles* mosquito inoculates sporozoites into a human host. Initially, infected persons are asymptomatic as the sporozoites enter the bloodstream and travel to the liver where maturation occurs in hepatocytes. Malaria symptoms begin when merozoite forms are released into the bloodstream, and the erythrocytic stage begins. In this stage, merozoites infect erythrocytes and replicate within them, resulting in rupture and further merozoite release. Symptom severity typically depends on the percentage of erythrocytes infected and the presence or absence of partial immunity due to previous infection.

Initial symptoms are nonspecific and include fever, chills, malaise, anorexia, headaches, and myalgias. Cough, abdominal pain, and diarrhea may also be present. The illness may resemble numerous other febrile syndromes including enteric fever, dengue fever, influenza, meningitis, and septicemia, so a high index of suspicion for malaria is critical, even when an alternate diagnosis appears more likely. Although regular periodicity of fever is classically described, this is unlikely early in the disease course and may not be seen at all, particularly with falciparum malaria.

Severe falciparum malaria is a multiorgan system disease. Infected erythrocytes adhere to vascular endothelium cells, resulting in sequestration, circulatory obstruction, and inflammation in the affected organ. Complications include

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A

B

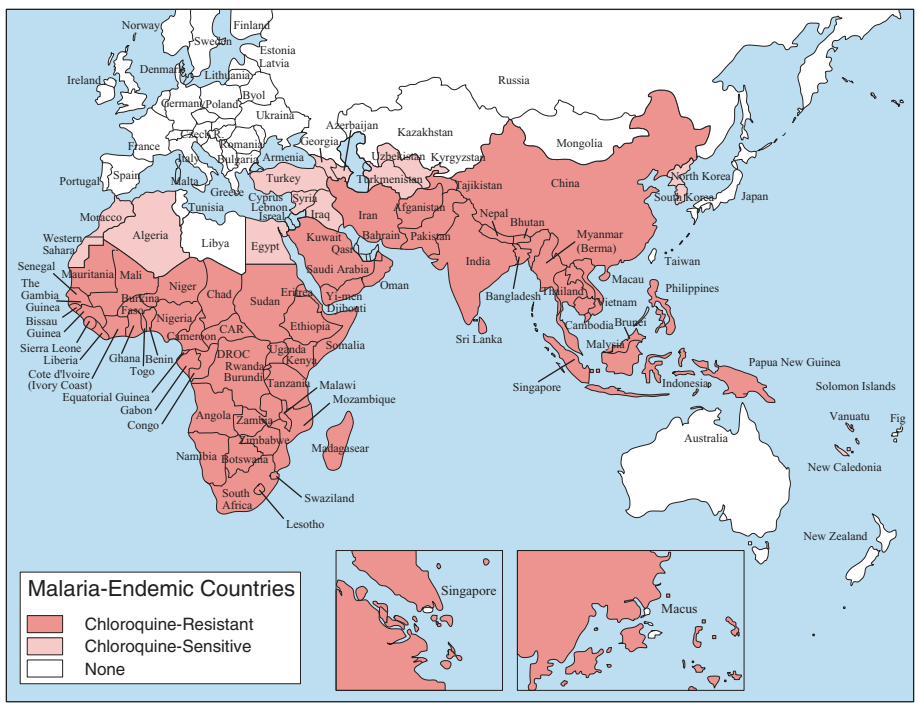

Figure 200.1 (A and B) Malaria-endemic countries of the Western and Eastern Hemispheres. (Courtesy of the Centers for Disease Control and Prevention, 2014.)

severe anemia, jaundice, thrombocytopenia, hypoglycemia, pulmonary edema, acute respiratory distress syndrome (ARDS), renal failure, and disseminated intravascular coagulation (DIC). Seizures, impaired consciousness, and coma may result from hypoglycemia or suggest the presence of cerebral malaria. Even with treatment, the case-fatality rate of severe malaria is 15% to 20%. Lactic acidosis suggests a worse prognosis. Nonimmune pregnant woman are at higher risk for severe disease, as well as preterm birth and fetal loss. Among travel-associated cases in nonendemic countries, patients over 65 years old have the worst outcomes. Though *P. vivax* typically causes uncomplicated malaria, severe *P. vivax* malaria can occur. However, since severe disease is most associated with falciparum malaria and mixed infection with multiple species is possible, severe disease in a patient diagnosed with non-falciparum malaria should raise the possibility of coexisting falciparum malaria.

P. vivax and *P. ovale* infections can also result in a dormant hypnozoite liver stage which requires special consideration for treatment and prophylaxis. Patients carrying hypnozoites are asymptomatic until the infection reactivates, resulting in a relapsed infection.

DIAGNOSIS

Prompt and accurate diagnosis is critical in malaria management. The diagnostic gold standard is examination of Giemsa-stained thick and thin blood smears. Thick smears are highly sensitive and can detect parasites in patients with low parasitemia levels that might be missed in thin smears. However, thin smears are best for speciation, quantification of parasites (i.e., percent of erythrocytes parasitized), and assessment of treatment response. If the initial blood smears are negative, they should be repeated at 12- to 24-hour intervals for a total of three sets before considering the disease ruled out. When expertise to prepare or examine thick smears is not immediately available, thin blood smears alone are better than none at all, since a negative thin smear suggests a high parasitemia infection is unlikely. Wright's stain, which is typically used in clinical laboratories for peripheral blood smears, is not optimal for blood parasites; however, it can be helpful when Giemsa staining is unavailable.

A number of rapid diagnostic tests (RDTs) are available for malaria diagnosis when blood smears are not readily available. These tests rely on the detection of *Plasmodium* spp. antigens, including histidine-rich protein 2 (HRP2) and parasite lactate dehydrogenase. These tests can be highly sensitive and specific for falciparum malaria. However, test performance can vary widely among different kits and false results can occur if instructions on use and storage are not strictly followed. Nonetheless, RDTs can be important in situations where microscopy is not feasible or timely.

THERAPY

The increasing prevalence of drug-resistant plasmodia has complicated malaria treatment. In addition to widespread CRPF, mefloquine-resistant *P. falciparum* is endemic in several Southeast Asian countries, and strains of *P. vivax* resistant to drugs including chloroquine and primaquine have emerged. In contrast, drug resistance has not been described in *P. ovale* or *P. malariae*. When species identification is uncertain in a patient with malaria, clinicians should treat for the worst-case scenario, i.e., infection caused by CRPF. Malaria acquired while taking prophylaxis should not be treated with the same medication used for prophylaxis. Recommended drug regimens for treatment in the United States are listed in Table 200.1. Since effective malaria therapy requires consideration of the infecting species and local resistance patterns, clinicians are strongly advised to review current recommendations and to seek diagnostic assistance when needed. Suspected or confirmed malaria should always be treated with the assistance of an infectious diseases or tropical medicine specialist when available. Updated country guides and detailed US treatment recommendations are available from the Centers for Disease Control and Prevention (CDC), either online (www.cdc.gov/malaria/index.html) or by phone through the CDC Malaria Hotline (1–770–488–7788 or 1–855–856–4713 toll free, weekdays 9AM–5PM; or 1–770–488–7100 for emergency consultation after hours).

Plasmodium malariae, *Plasmodium knowlesi* and uncomplicated chloroquine-sensitive *P. falciparum* malaria

Chloroquine-sensitive *P. falciparum* malaria is confined to Central America north of the Panama Canal, Haiti, the Dominican Republic, and parts of the Middle East. Chloroquine or

Table 200.1 Treatment of malaria (United States guidelines). Readers are strongly recommended to see www.cdc.gov/malaria/diagnosis_treatment/index.html for further details, updated recommendations, and recommendations for pregnant women

Clinical severity/species	Resistance	Recommended treatments for adults[1]	Recommended pediatric treatments[1]
Uncomplicated *P. falciparum* or species not identified **NOTE: If an unidentified species is subsequently determined to be *P. vivax* or *P. ovale*, addition of primaquine therapy is indicated to prevent relapse, see below**	Chloroquine-resistant or unknown	**Atovaquone-proguanil:** **Adult tablet = 250 mg atovaquone/100 mg proguanil** 4 adult tablets daily × 3 d	**Atovaquone-proguanil:** **Pediatric tablet = 62.5 mg atovaquone/25 mg proguanil** **Adult tablet = 250 mg atovaquone/100 mg proguanil** 5–8 kg: 2 ped tabs daily × 3 d 9–10 kg: 3 ped tabs daily × 3 d 11–20 kg: 1 adult tab daily × 3 d 21–30 kg: 2 adult tabs daily × 3 d 31–40 kg: 3 adult tabs daily × 3 d >40 kg: 4 adult tabs daily × 3 d
		Artemether–lumefantrine: One tablet = 20 mg artemether/120 mg lumafantrine Three-day treatment with total of 6 oral doses based on weight. Initial dose is followed by second dose 8 h later, then 1 dose BID for the following 2 days. 5–<15 kg:1 tab/dose 15–<25 kg: 2 tab/dose 25–<35 kg: 3 tabs/dose ≥35 kg: 4 tabs/dose	
		Quinine sulfate: 542 mg base (=650 mg salt) PO TID × 3 or 7 days[2] **PLUS one of the following:** **Doxycycline:** 100 mg PO BID × 7 d **OR** **Tetracycline:** 250 mg PO QID × 7 d **OR** **Clindamycin:** 20 mg base/kg/day PO divided tid × 7 d **Mefloquine**[4]: 684 mg base (=750 mg salt) PO as initial dose, followed by 456 mg base (=500 mg salt) PO given 6–12 h after initial dose	**Quinine sulfate:** 8.3 mg base/kg (=10 mg salt/kg) PO TID × 3 or 7 days[2] **PLUS one of the following:** **Doxycycline**[3]: 2.2 mg/kg PO BID × 7 d **OR** **Tetracycline**[3]: 25 mg/kg/day PO divided QID × 7 d **OR** **Clindamycin:** 20 mg base/kg/day PO divided tid × 7 d **Mefloquine**[4]: 13.7 mg base/kg (=15 mg salt/kg) PO as initial dose, followed by 9.1 mg base/kg (=10 mg salt/kg) PO given 6–12 h after initial dose
Uncomplicated *P. falciparum* or species not identified acquired in area with no chloroquine resistance ***P. malariae* (all regions)** ***P. knowlesi* (all regions)** **NOTE: If an unidentified species is subsequently determined to be *P. vivax* or *P. ovale*, addition of primaquine therapy is indicated to prevent relapse, see below**	Chloroquine-sensitive	**Chloroquine phosphate:** 600 mg base (=1000 mg salt) PO immediately, followed by 300 mg base (=500 mg salt) in 6, 24, and 48 h **Hydroxychloroquine:** 620 mg base (=800 mg salt) PO immediately, followed by 310 mg base (=400 mg salt) in 6, 24, and 48 h	**Chloroquine phosphate:** 10 mg base/kg (=16.7 mg salt/kg) PO immediately, followed by 5 mg base/kg (=8.3 mg salt/kg) PO at 6, 24, and 48 h **Hydroxychloroquine:** 10 mg base/kg (=12.9 mg salt/kg) PO immediately, followed by 5 mg base/kg (=6.5 mg salt/kg) at 6, 24, and 48 h
Uncomplicated *P. vivax or P. ovale*[6]	Chloroquine-sensitive[6]	**Chloroquine phosphate or hydroxychloroquine (doses as above)** **PLUS** **Primaquine phosphate**[5]: 30 mg base (=52.6 mg salt) PO qd × 14 d	**Chloroquine phosphate or hydroxychloroquine (doses as above)** **PLUS** **Primaquine phosphate**[5]: 0.5 mg base/kg (=0.8 mg salt/kg) PO qd × 14 d
Severe malaria (usually *P. falciparum*)	All resistance profiles	**Quinidine gluconate:** 6.25 mg base/kg (=10 mg salt/kg) loading dose IV over 1–2 h, then 0.0125 mg base/kg/min (=0.02 mg salt/kg/min) by continuous infusion Alternate regimen: 15 mg base/kg (=24 mg salt/kg) loading dose IV infused over 4 h, followed by 7.5 mg base/kg (=12 mg salt/kg) IV infused over 4 h every 8 h (starting 8 h after loading dose)	**Quinidine gluconate:** Same dosing as adults **PLUS** **One of the following for 7 days:** **Doxycycline**[3]: As above or may be given IV if patient cannot take oral medication If <45 kg: 2.2 mg/kg IV q12h If ≥45 kg: use adult dose

Clinical severity/species	Resistance	Recommended treatments for adults[1]	Recommended pediatric treatments[1]
		After at least 24 h IV treatment, if parasite density <1% and patient can tolerate oral medications, treat with PO quinine as above to complete 3 or 7 days[2] total course of quinidine/quinine **PLUS** **One of the following for 7 days:** **Doxycycline:** As above or may be given as 100 mg IV q12h if patient cannot take PO medication. Switch to PO regimen when able to take oral medications **Tetracycline:** As above **Clindamycin:** As above or may give as 10 mg base/kg loading dose IV followed by 5 mg base/kg IV q8h if patient cannot take oral medication. Switch to PO regimen when able to take oral medications **Investigational new drug:** Artesunate followed by atovaquone-proguanil, doxycycline, or mefloquine. Contact CDC Malaria Hotline (see text) for information	Switch to PO regimen when able to take oral medications **Tetracycline**[3]: As above **Clindamycin:** As above or may give as 10 mg base/kg loading dose IV followed by 5 mg base/kg IV q8h if patient cannot take oral medication. Switch to PO regimen when able to take oral medications **Investigational new drug:** Artesunate followed by atovaquone-proguanil, clindamycin, or mefloquine. Contact CDC Malaria Hotline (see text) for information

[1] Malaria acquired while taking prophylaxis should not be treated with the same medication used for prophylaxis.

[2] Infection acquired in Southeast Asia should be treated for 7 days with quinine/quinidine, and infections acquired in Africa and South America should be treated with 3 days of quinine/quinidine.

[3] Doxycycline and tetracycline are not indicated for children <8 years old.

[4] Treatment with mefloquine is not recommended for infections acquired in Southeast Asia due to *P. falciparum* resistance in this region. Due to high rates of neuropsychiatric side effects at treatment doses, mefloquine is only recommended when other options (i.e., atovaquone/progruanil, artemether–lumefantrine, quinine-based regimens) cannot be used.

[5] G6PD deficiency and pregnancy must be ruled out prior to primaquine use to eradicate hypnozoites in *P. vivax* and *P. ovale* infections. Expert consultation recommended in patients with G6PD deficiency or pregnant patients.

[6] *P. vivax* acquired in Papua New Guinea or Indonesia should be considered as potentially chloroquine-resistant and treated with alternative regimens. See www.cdc.gov/malaria/diagnosis_treatment/index.html for recommendations.

Adapted from: Centers for Disease Control and Prevention, 2013.

hydroxychloroquine should be used to treat *P. falciparum* from these areas, as well as *P. malariae* and *P. knowlesi* infections from any part of the world.

Uncomplicated chloroquine-resistant *P. falciparum* malaria

With the exception of the regions mentioned above, CRPF is widespread. Artemisinin-based combination therapies (ACTs) are rapidly becoming the treatment of choice for CRPF. Artemisinin and its derivatives are well tolerated and lead to a rapid reduction in parasitemia and fever. Since monotherapy is associated with a high rate of recrudescence, the addition of a second agent is necessary. ACTs currently recommended by the World Health Organization (WHO) include artemether–lumefantrine, artesunate–amodiaquine, artesunate plus mefloquine, artesunate plus sulfadoxine–pyrimethamine, and dihydroartemisinin–piperaquine. Recently, artemether–lumefantrine has been approved in the United States for the oral treatment of uncomplicated falciparum malaria. Atovaquone–proguanil is another recommended and well-tolerated oral regimen for uncomplicated falciparum malaria. These regimens are effective against multidrug-resistant falciparum malaria acquired in Southeast Asia.

When artemether–lumefantrine and atovaquone–proguanil are not available or are contraindicated, oral quinine sulfate in combination with tetracycline, doxycycline, or clindamycin is an effective regimen, though longer and less well tolerated. Clindamycin is usually reserved for pregnant women and for young children (those

less than 8 years old) in whom tetracycline derivatives are generally avoided. Patients taking quinine typically experience cinchonism, the reversible symptom complex that includes tinnitus, dizziness, headache, nausea, visual disturbances, and hearing loss. These side effects usually do not necessitate drug change. If oral medication is not tolerated, parenteral treatment is necessary (see parenteral regimens below for severe malaria).

Mefloquine is also effective therapy for uncomplicated CRPF malaria, but it is not recommended for patients who might have multidrug-resistant infections acquired in Southeast Asia, particularly along the Thai–Myanmar (Burma) or Thai–Cambodian borders. Furthermore, concern for significant side effects generally restrict its use and make it an alternative regimen for uncomplicated malaria. Severe neuropsychiatric adverse reactions (psychosis, convulsions) are more likely to occur when the drug is used at treatment doses compared to prophylaxis dosing. Due to the QTc prolonging effects of mefloquine, an alternative regimen should be used in patients with a history of arrhythmia.

The use of pyrimethamine–sulfadoxine (Fansidar) is no longer recommended due to widespread resistance to this regimen. Though halofantrine is widely used in malaria endemic areas, the CDC recommends against its use due to the risk of potentially fatal cardiac adverse events.

Plasmodium vivax malaria

The erythrocytic stage of *P. vivax* malaria is effectively treated with chloroquine or hydroxychloroquine. Eradication of hepatic hypnozoites requires treatment with primaquine. Primaquine is a potent oxidizing agent; therefore, glucose-6-phosphate dehydrogenase (G6PD) deficiency must be ruled out before primaquine therapy is initiated to avoid severe hemolysis.

Chloroquine-resistant *P. vivax* malaria was first described on the island of New Guinea in 1989 with subsequent spread across Indonesia. Since then, there are sporadic reports of declining chloroquine efficacy elsewhere in Southeast Asia, Africa, and the Amazon Basin of South America. Malaria caused by chloroquine-resistant *P. vivax* should be suspected when the illness recurs within 28 days after a patient has received standard therapy with chloroquine and primaquine. Due to the risk of chloroquine resistance, *P. vivax* malaria originating from Indonesia or Papua New Guinea should be treated with alternative regimens (Table 200.1). Notably, a recent Cochrane review concluded that some ACTs are as effective as chloroquine in treating the blood stage *P. vivax* infection, suggesting a potential strategy for simplifying empiric treatment for all forms of uncomplicated malaria where *P. falciparum* and *P. vivax* coexist.

Though somewhat controversial, primaquine-resistant *P. vivax* malaria has been reported from the island of New Guinea, other parts of Southeast Asia, Somalia, and Colombia. When a relapse of *P. vivax* occurs more than 28 days after treatment with chloroquine and primaquine, primaquine resistance should be considered.

Plasmodium ovale malaria

Malaria caused by *P. ovale*, found mostly in Africa, is managed in the same way as chloroquine-sensitive *P. vivax*. No drug-resistant strains of *P. ovale* have been documented.

Severe *P. falciparum* malaria

Even with appropriate treatment, the mortality rate of severe falciparum malaria ranges from 15% to 20%. Management comprises four main areas: clinical assessment, specific antimalarial treatment, adjunctive therapy, and supportive care. Severe falciparum malaria is typically defined by the presence of parasitemia of $\geq$5% or signs of major organ failure. Signs of major organ failure may include impaired consciousness/coma, severe anemia, renal failure, ARDS, hypotension, DIC, spontaneous bleeding, acidosis, hemoglobinuria, jaundice, and repeated seizures.

Patients with severe malaria require parenteral therapy with quinidine (or parenteral quinine, if available). Continuous electrocardiographic monitoring is essential due to the high rates of cardiac arrhythmias with treatment. Intravenous artesunate has also been found to be a safe and effective treatment, and it is a WHO preferred treatment for severe falciparum malaria. In the United States, artesunate is not Food and Drug Administration (FDA)-approved; however, in cases where IV quinidine is either contraindicated or unavailable, artesunate is available from the CDC through an investigational new drug (IND) protocol. Clinicians needing artesunate should contact the CDC Malaria Hotline (see above for contact information). Both quinidine and

artesunate regimens require the addition of a second drug as outlined in Table 200.1.

Supportive care is critical for the effective management of severe malaria. Blood glucose must be monitored closely, as hypoglycemia is a common complication, especially in pregnant women and children, and can contribute to impaired consciousness and seizure activity. Furthermore, both quinine and quinidine cause insulin to be released from the pancreas. Fluid balance should be corrected judiciously with the aim of avoiding fluid overload that increases the risk of ARDS. Exchange transfusion has historically been used as an adjunctive treatment for severe malaria, but a 2013 CDC analysis did not show a survival benefit and it is no longer recommended. Other important supportive measures include mechanical ventilation for ARDS and hemodialysis for renal failure. Ruling out coexisting infections such as meningitis and septicemia is important, and empiric antimicrobials might be indicated.

PREVENTION

Malaria prevention in travelers involves both prophylaxis and protective measures against mosquito bites. The primary goal of prophylaxis is to prevent *P. falciparum* infection in nonimmune travelers because almost all fatal cases are associated with illness caused by this species. Careful review of itineraries is important when advising travelers to assess whether they will enter malaria endemic areas and the presence of any drug resistance. Risk can vary widely within a country. For example, when travel to Thailand is limited to the malaria-free cities of Bangkok and Phuket, prophylaxis is not needed, whereas travel to many rural areas in Thailand warrants prophylaxis against multidrug-resistant *P. falciparum*. Travel timing should also be considered, as some regimens require starting 1 to 2 weeks prior to departure, and the number of tablets prescribed will be determined by the duration of travel. Other considerations include medical contraindications to specific regimens, drug–drug interactions between prophylaxis drugs and the traveler's usual medications, and client preference. Client preference is often based on side-effect profile, convenience of the regimen, and cost. A general algorithm for determining an appropriate prophylactic regimen is shown in Figure 200.2. Since malaria distribution and resistance patterns can change, clinicians are strongly advised to review current country-specific recommendations, such as those provided by the CDC (www.cdc.gov/malaria/travelers) when advising travelers.

The various malaria prophylactic agents have different schedules, though all require starting prior to arrival in the malarious area and continuation after departure for a specified period (Table 200.2). Weekly chloroquine remains an excellent option for travel to the limited endemic areas without CRPF, though atovaquone-proguanil, doxycycline, and mefloquine are also options. For most areas with CRPF, prophylaxis with atovaquone–proguanil, doxycycline, and mefloquine are recommended. An exception exists for travel to areas in Southeast Asia with multidrug-resistant strains where atovaquone–proguanil and doxycycline are the only options.

Mefloquine prophylaxis has a weekly schedule and should be started 2 weeks prior to entering malaria-risk areas. It is generally well tolerated by most travelers, though it can cause sleep disturbance, dizziness, and abnormal dreams. Mefloquine has been associated with rare but severe neurologic or neuropsychiatric side effects, including permanent vestibular toxicity, seizures, psychosis, anxiety, and depression. Its use is contraindicated in travelers with a history of active or recent major psychiatric or seizure disorder, and travelers prescribed mefloquine should be informed of potential adverse effects. Because the majority of adverse reactions to mefloquine occur with the first three doses, if possible it is prudent to commence the drug 4 weeks prior to departure to ascertain drug tolerance. Atovaquone–proguanil and doxycycline have daily schedules and can be started 1 to 2 days prior to arriving to the malaria-risk area. Both drugs are usually well tolerated, but doxycycline can cause photosensitivity and gastrointestinal side effects such as nausea and esophagitis. Travelers taking doxycycline should be advised to take it with food and sufficient fluids, and it should not be taken at bedtime. Mefloquine and doxycycline need to be continued for 4 weeks after departing from the malaria-risk area, while atovaquone–proguanil needs only to be continued for 7 days.

Prolonged exposure to malaria in areas intensely endemic for *P. vivax* or *P. ovale* (e.g., Central America, northwest Africa, South Asia, Oceania) warrants terminal prophylaxis with primaquine to eradicate hypnozoites. As previously noted, G6PD deficiency should be ruled out before prescribing this drug, and it is contraindicated during pregnancy. Primaquine also has a potential role in

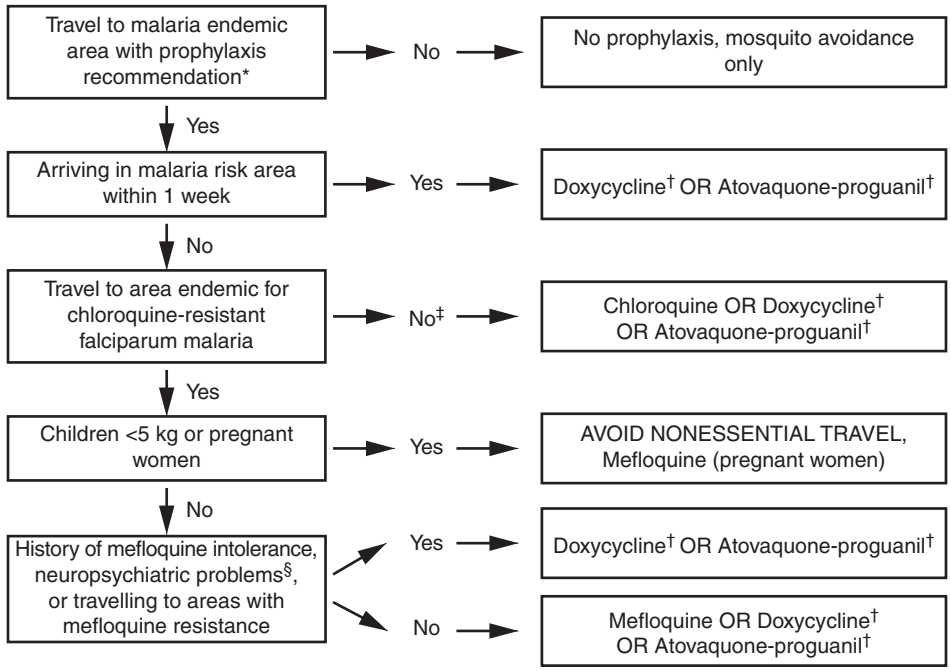

Figure 200.2 Algorithm for the prophylaxis of malaria. See Table 200.2 for dosages.
* Country-specific recommendations available at: www.cdc.gov/malaria/travelers.
† Contraindicated or not recommended in pregnancy.
‡ If traveling for short durations to an area with primary *P. vivax* malaria, primaquine primary prophylaxis is an option if glucose-6-phosphate deficiency and pregnancy are ruled out.
§ Seizures, psychosis, schizophrenia, generalized anxiety disorder, active or recent depression, other major psychiatric disorders.

primary prophylaxis for short-term travelers to areas with primarily *P. vivax* malaria.

Prophylaxis options for pregnant women are limited to mefloquine in areas with CRPF and chloroquine in areas without CRPF. Unfortunately, there are no recommended prophylactic regimens for pregnant women traveling to areas with multidrug-resistant *P. falciparum* in Southeast Asia. Long-term travelers (such as missionaries or overseas workers) and immigrants visiting their countries of origin pose additional challenges. These travelers often have itineraries and accommodations that are higher risk for malaria than those of typical short-term travelers. Long-term travelers often adhere poorly to prophylaxis and mosquito-bite avoidance recommendations. Immigrants visiting friends and relatives in their country of origin often do not seek pre-travel advice and are often unaware that any malaria semi-immunity wanes quickly. Substandard or counterfeit drugs are also a common problem in developing countries, so travelers should be strongly cautioned against obtaining prophylaxis medications locally.

Because no prophylaxis regimen is 100% effective, all travelers to malarious regions need to be meticulous about personal protection measures. Furthermore, malarious areas are often endemic for other mosquito-transmitted infections, such as dengue fever. Insect repellents containing 30% to 50% of diethyltoluamide (DEET) are very effective. The CDC, American Academy of Pediatrics, and US Environmental Protection Agency have indicated that 30% DEET is safe for infants as young as 2 months of age. Other effective compounds used in repellents include picaridin, oil of lemon eucalyptus (OLE), PMD, and IR3535. Permethrin-impregnated protective clothing (long sleeves, pants) add further protection. Travelers should always follow product instructions carefully so they are used safely and are reapplied at appropriate intervals. Since *Anopheles* mosquitoes typically bite between dusk

Table 200.2 Malaria chemoprophylaxis regimens

Drug	Adult dose	Pediatric dose	Adverse effects
Chloroquine phosphate	300 mg base (=500 mg salt) PO weekly, starting 1 wk before entering malarious area and continue for 4 wk after departing risk area	5 mg base/kg (=8.3 mg salt/kg) PO weekly, starting 1 wk before entering malarious area and continue for 4 wk after departing risk area	Bitter taste, headache, pruritus, rash, blurry vision, reversible corneal opacity, partial alopecia. Rare: retinopathy, blood dyscrasias, nail discoloration, nerve deafness, myopathy. May exacerbate psoriasis
Hydroxychloroquine	310 mg base (=400 mg salt) PO weekly, starting 1 wk before entering malarious area and continue for 4 wk after departing risk area	5 mg base/kg (=6.5 mg salt/kg), maximum 310 mg base, PO weekly, starting 1 wk before entering malarious area and continue for 4 wk after departing risk area	As for chloroquine
Atovaquone–proguanil	250 mg atovaquone and 100 mg proguanil (1 adult tablet) PO daily, starting 1–2 d before entering malarious area and continue for 7 d after departing risk area	Weight-based daily dose starting 1–2 d before entering malarious area and continue for 7 d after departing risk area. Pediatric tablet contains 62.5 atovaquone and 25 mg proguanil: 5–8 kg: ½ ped tab PO daily >8–10 kg: ¾ ped tab PO daily >10–20 kg: 1 ped tab PO daily >20–30 kg: 2 ped tab PO daily >30–40 kg: 3 ped tab PO daily >40 kg: see adult dosing	Nausea, abdominal pain, headache. May transiently increase transaminases. Rare: rash. Take with food. Do not use if creatinine clearance ≤30 mL/min. Not recommended for pregnant women, breastfeeding women, or children <5 kg
Doxycycline	100 mg PO daily, starting 1–2 d before entering malarious area and continue for 4 wk after departing risk area	≥8 years old: 2.2 mg/kg PO daily (maximum dose 100 mg/d), starting 1–2 d before entering malarious area and continue for 4 wk after departing risk area	Esophageal irritation, gastrointestinal upset, photosensitivity, candida vaginitis. Stains teeth of children aged ≤8 yr and fetuses. Contraindicated in pregnancy
Mefloquine	One 228 mg base tablet (=250 mg salt) PO weekly, starting ≥2 wk before entering malarious area and continue for 4 wk after departing risk area	Weight-based daily dose starting ≥2 wk before entering malarious area and continue for 4 wk after departing risk area: ≤9 kg: 4.6 mg base/kg (=5 mg salt/kg) PO weekly >9–19 kg: ¼ tablet PO weekly >19–30 kg: ½ tablet PO weekly >30–45 kg: ¾ tablet PO weekly >45 kg: 1 tablet PO weekly One tablet contains 228 mg base (=250 mg salt)	Dizziness, nausea, diarrhea, headache, nightmares, altered dreams, insomnia, mood changes. Rare: seizure, psychosis, permanent vestibular toxicity. Do not use if history of seizures, psychosis, schizophrenia, generalized anxiety disorder, active or recent depression, other major psychiatric disorders, or cardiac conduction abnormality present
Primaquine			
Terminal prophylaxis	30 mg base (52.6 mg salt) PO daily for 14 d	0.5 mg base/kg (0.8 mg salt/kg) PO daily for 14 d	G6PD deficiency should be ruled out prior to use to prevent hemolysis. Contraindicated in pregnancy and breastfeeding women. Should be taken with food to prevent gastrointestinal upset
Primary prophylaxis (for short-duration travel to areas with primarily *P. vivax*)	30 mg base daily, starting 1–2 d before entering malarious area and continue for 7 d after departing risk area	0.5 mg base/kg (0.8 mg salt/kg) PO daily, starting 1–2 d before entering malarious area and continue for 7 d after departing risk area	

and dawn, sleeping under permethrin-impregnated bed netting or in screened-in or air-conditioned rooms is important.

Because malaria prophylaxis recommendations often vary according to different authorities, travelers should be cautioned about potentially conflicting advice from fellow travelers and overseas healthcare providers. Also, travelers should be advised to seek medical attention immediately in the event of high fever during travel, as well as

those that occur up to a year after travel. Acutely ill travelers should seek the best medical care available and follow local treatment recommendations. However, since malaria is often overdiagnosed in developing countries, travelers should be strongly cautioned against discontinuing their prophylaxis regimen if they are diagnosed with malaria.

ACKNOWLEDGMENTS

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201. Human babesiosis

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Babesiosis is an emerging zoonotic disease caused by intraerythrocytic protozoa and transmitted by ticks. The first well-documented case of human *Babesia* infection was reported in 1957 in a splenectomized resident of Yugoslavia, who died after an acute illness marked by anemia, fever, hemoglobinuria, and renal failure. Intraerythrocytic parasites were noted and tentatively identified as *Babesia bovis*. Since then, other *Babesia* species have been found to cause disease in humans: *Babesia microti*, *Babesia duncani*, *Babesia duncani*-type, and *Babesia divergens*-like in North America; *B. divergens*, *B. microti*, and *Babesia venatorum* in Europe; and *B. microti*-like and KO-1 in Asia. The clustering of cases of human *B. microti* infection in the United States contrasts with the sporadic occurrence of the disease in Europe, Africa, and Asia. Rarely, babesiosis may be transmitted through blood transfusion or transplacentally.

EPIDEMIOLOGY

More than 90 species in the genus *Babesia* infect a wide variety of wild and domestic animals. Humans are an uncommon and terminal host for *Babesia* species, which depend on other species for their development and transmission. The most common cause for human babesiosis is *B. imicroti*, a babesia of rodents. The primary reservoir for *B. microti* in eastern North America is the white-footed mouse (*Peromyscus leucopus*). As many as two-thirds of *P. leucopus* have been found to be parasitemic in endemic areas. *Babesia* species are transmitted by hard-bodied (ixodid) ticks. The primary vector in eastern North America is *Ixodes scapularis* (also known as *Ixodes dammini*), which is the same tick that transmits *Borrelia burgdorferi*, the etiologic agent of Lyme disease, and *Anaplasma phagocytophilum*, the agent of human granulocytic anaplasmosis. Thus, simultaneous human infection with two or more of these pathogens may occur.

Each of the three active stages in the life cycle of *I. scapularis* (larva, nymph, and adult) takes a blood meal from a vertebrate host to mature to the next stage (Figure 201.1). The *Babesia* species ingested by one tick stage are transmitted to the next stage. The tick transmission cycle begins in late summer when newly hatched larvae ingest the parasite during a blood meal from an infected rodent and maintain the parasite to the nymphal stage. Nymphs transmit the *Babesia* species to rodents in late spring and summer of the following year. Larvae, nymphs, and adults can feed on humans, but the nymph is the primary vector (Figure 201.2). All active tick stages also feed on the white-tailed deer (*Odocoileus virginianus*), which is an important host for the tick but is not a reservoir for *B. microti*. An increase in the deer population over the past few decades is thought to be a major factor in the spread of *I. scapularis* and in the resulting increase in human babesia cases.

Beginning in the 1980s, human babesiosis has been described with increasing frequency at sites in the northeastern and northern midwestern United States. Recent studies suggest that the endemic range continues to expand. In certain sites during years of high transmission, babesiosis may constitute a significant public health burden. For example, in one study of a highly endemic area in Rhode Island, approximately 9% of the population had serologic evidence of previous *B. microti* infection compared with 11% of previous Lyme disease. Most human cases of babesiosis occur in the summer and in areas where the vector tick, rodents, and deer are in close proximity to humans. Rarely, babesiosis is acquired through transfusion of blood products, including whole blood, packed red cells, cryopreserved red cells, and platelets. Transplacental/perinatal transmission of babesiosis has also been described.

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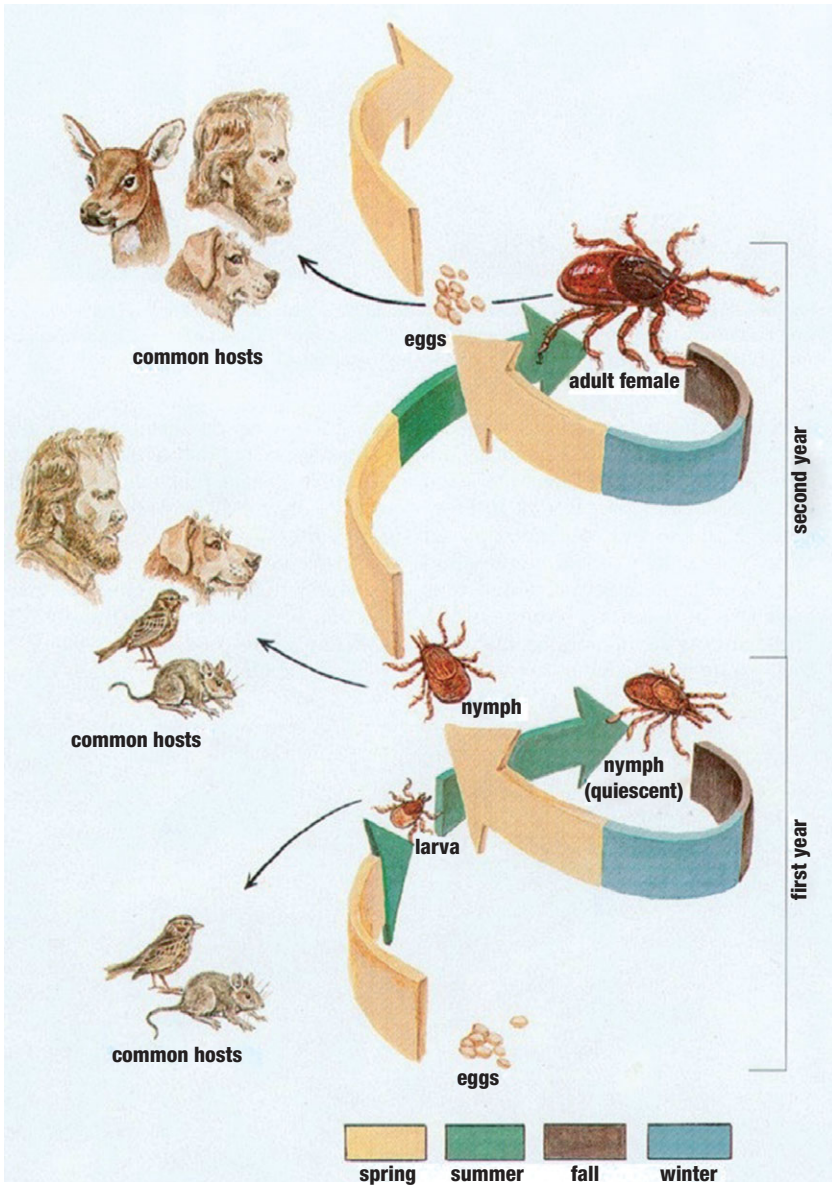

Figure 201.1 Life cycle of *Ixodes scapularis*. (Reproduced with permission from D. W. Miller.)

PATHOGENESIS

Our understanding of the pathogenesis of human babesiosis is incomplete and is primarily based on studies done in animals. Cytoadherence of infected erythrocytes to vascular epithelium may diminish access of host immune factors to babesia. Cytoadherence may prevent transit of infected erythrocytes through the spleen where they would be destroyed, thus allowing babesia to complete their life cycle and invade other erythrocytes. Excessive cytoadherence may lead to erythrocyte sequestration and obstruction of microvasculature with subsequent tissue anoxia, as has been demonstrated in cattle infected by *B. bovis*. Similarly, production of host proinflammatory cytokines such as tumor necrosis factor (TNF) and interleukin (IL)-1 help to destroy intracellular babesia; however, excessive cytokine production associated with moderate to severe disease probably accounts for the majority of

Figure 201.2 *Ixodes scapularis* (also known as *Ixodes dammini*) ticks showing larval, nymphal, and adult stages.

clinical manifestations and complications of the disease. T cells, B cells, macrophages, neutrophils, antibody, and complement also are important in clearing parasitemia and may contribute to disease pathogenesis.

CLINICAL MANIFESTATIONS

The clinical severity of babesiosis ranges from subclinical infection to fulminating disease resulting in death. In clinically apparent cases, symptoms of babesiosis begin after an incubation period of 1 to 9 weeks from the beginning of tick feeding or 6 weeks to 6 months after transfusion. In most cases, there is a gradual onset of malaise, anorexia, and fatigue followed by intermittent temperatures as high as 40°C (104°F) and one or more of the following symptoms: chills, sweats, myalgia, arthralgia, nausea, and vomiting. Less commonly noted are emotional lability, hyperesthesia, headache, sore throat, abdominal pain, conjunctival injection, photophobia, weight loss, and nonproductive cough. The findings on physical examination generally are minimal, often consisting only of fever. Mild splenomegaly, hepatomegaly, or both are noted occasionally. Slight pharyngeal erythema, jaundice, retinopathy with splinter hemorrhages, and retinal infarcts also have been reported. Rash is seldom noted, although ecchymoses and petechiae have been described in severe disease.

Symptoms usually persist for a few weeks to several months, with prolonged recovery of up to 18 months in severe cases. Parasitemia may continue even after a person feels well and may persist for >2 years with subsequent relapse of illness. Although prolonged symptomatic disease unresponsive to antimicrobial therapy or death may occur in immunocompromised hosts, complete recovery with or without therapy is the rule.

Patients at increased risk for more severe babesial disease include those with malignancy, concomitant human immunodeficiency virus (HIV) infection, asplenia, age greater than 50 years, immunosuppressive medication regimens, or infection with *B. divergens* or *B. duncani*. Concurrent babesiosis and Lyme disease infection occurs in about 3% to 15% of patients experiencing Lyme disease in parts of southern New England and results in more severe acute Lyme disease illness. Moderate to severe babesiosis may occur in children, but infection often results in mild disease and is generally less debilitating than in adults. Several cases of neonatal babesiosis have been described, usually following transfusion with infected blood, and sometimes resulting in severe illness. Symptoms and signs include lethargy, tachypnea, pallor, poor feeding, splenomegaly, hepatomegaly, jaundice, and generalized macular rash.

COMPLICATIONS

A severe form of babesiosis has been noted in some patients, consisting of fulminant illness lasting about a week and ending in death or a prolonged convalescence. Although more common in immunocompromised hosts or those experiencing *B. divergens* or *B. duncani* infection, severe babesiosis can occur in otherwise healthy individuals who are infected with *B. microti*. In a retrospective study of 136 patients with *B. microti* infection from Long Island, New York, 7 patients (5%) died. The patients with fatal illness ranged in age from 60 to 82 years, and only one was known to be immunocompromised. Signs and symptoms in severe cases include high fever, severe hemolytic anemia, hemoglobinemia and hemoglobinuria, jaundice, ecchymoses, petechiae, congestive heart failure, pulmonary edema, renal failure, adult respiratory distress syndrome, and coma. Patients with asplenia, malignancy, and/or HIV infection may experience a chronic form of babesiosis that is unresponsive to multiple courses of standard antibabesial therapy.

DIAGNOSIS

Babesiosis should be suspected in any patient with unexplained febrile illness who has recently lived or traveled in endemic regions during the months of May through September, with or without a history of tick bite. There is often no

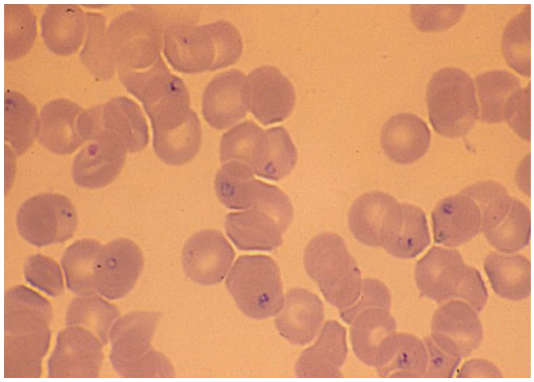

Figure 201.3 Ring forms of *Babesia microti* in human blood film (1000×).

recollection of a tick bite, because the unengorged *I. scapularis* nymph is difficult to discern with the naked eye (~2 mm in length). Babesiosis also should be suspected in any patient with unexplained febrile illness who has had a blood transfusion within the previous 6 months.

Laboratory findings reflect the invasion and subsequent lysis of erythrocytes by the parasite and the immune response to infection. They include moderate to severe hemolytic anemia, an elevated reticulocyte count, thrombocytopenia, an elevated erythrocyte sedimentation rate, elevated serum bilirubin and liver enzyme concentrations, elevated serum blood urea nitrogen and creatinine concentrations, and proteinuria. The leukocyte count is normal to slightly decreased, with a "left shift." Atypical lymphocytes also may be noted on manual differential blood smear examination.

Specific diagnosis of babesiosis is made by microscopic demonstration of the organism using Giemsa-stained thin blood smears. Giemsa-stained *Babesia* parasites appear as round, oval, or pear-shaped microorganisms with a blue cytoplasm and a red chromatin membrane (Figure 201.3). Multiple blood fields should be examined because only a few erythrocytes are infected in the early stage of the illness when most people seek medical attention. Fewer than 1% of erythrocytes may be parasitized initially and may escape detection. Maximum erythrocyte infection is approximately 10% in normal hosts but up to 85% in people who are immunocompromised. Thick blood smears may be examined, but the organisms appear as simple chromatin dots that may be mistaken for stain precipitate or iron inclusion bodies. Accordingly, only someone with extensive experience in interpreting thick smears should perform this method. The ring form is most common and is very similar to the intraerythrocytic ring forms of *Plasmodium falciparum*. Although the presence of tetrad forms ("Maltese cross") is said to be diagnostic, such elements are rarely encountered. Similarly, the absence of hemozoin (malarial pigment) is often considered to be generally diagnostic for the small blood stage parasites (piroplasms), but early ring stages of the plasmodia also lack pigment. Diagnosis is thus made by a combination of criteria and, in severe cases, includes the presence of high parasitemia, erythrocytes infected by multiple parasites, and basket-shaped merozoites that are often extracellular.

Physicians can further confirm babesial infection by use of polymerase chain reaction (PCR), serologic testing, and small animal inoculation. Both immunoglobulin G and immunoglobulin M antibodies can be detected using an immunofluorescent assay (IFA). The babesia IFA is sensitive and specific and may quickly confirm a diagnosis of babesiosis when parasites are rare or not detectable. During the acute phase of the illness, titers usually exceed 1:1024 but decline to 1:64 or less within 8 to 12 months. Thus, a babesial IFA titer of 1:1024 or greater usually signifies active or recent infection. A serologic cutoff point of 1:64 generally is considered to be diagnostic. Although cross-reactions occur to different *Babesia* species and *Plasmodium* species with the IFA test, these titers are almost always low (1:16 or less). The PCR is a sensitive and specific test for detection of babesia DNA. Proper technique must be used to prevent false-positive results. Where laboratory expertise exists, blood from the patient can be injected by the intravenous (IV) or intraperitoneal route into small laboratory animals such as hamsters or gerbils. If present in the patient, *B. microti* usually appears in the blood of the inoculated animal within 2 to 4 weeks. The diagnosis of babesiosis is suspect in symptomatic patients whose serum contains antibody to babesia, but whose blood lacks identifiable babesial parasites on smear or babesia DNA by PCR.

For *B. divergens* babesiosis, specific antibodies do not become detectable until at least 1 week after onset of illness. Because this infection is rapidly fulminating, serologic diagnosis is not practical in the diagnosis of acute infection, but serologic conversion serves as an aid in retrospective diagnosis during convalescence. The high parasitemias that are present are easily detected by blood smear in the acute phase of

Table 201.1 Treatment of babesiosis

Medication	Dose of antibabesia drug (all drugs given for 7 to 10 days or longer)		Comment
	Adults	**Children**	
Clindamycin plus	300–600 mg IV q6h or 600 mg PO q8h	7–10 mg/kg/dose IV or PO q6–8h (maximum 600 mg/dose)	This combination is the treatment of choice for severe babesiosis. Exchange transfusion or partial exchange transfusion should be considered in such patients
Quinine	650 mg PO q6–8h	8 mg/kg/dose PO q8h (maximum 650 mg/dose)	
Atovaquone plus	750 mg PO q12h	20 mg/kg/dose PO q12h (maximum 750 mg/dose)	This combination is the treatment of choice for mild to moderate babesiosis. A dose of 600–1000 mg/q24h may be used for immunocompromised adult patients
Azithromycin	500–1000 mg PO on d 1, then 250 mg PO/q24h	10 mg/kg as a single dose PO on d 1 (maximum 500 mg/dose), then 5 mg/kg PO q24h (maximum 250 mg/dose)	

infection. Infection by *B. duncani* may readily be detected by blood smear or by demonstrating specific antibody by IFA. This species may be cultivated in vitro. Unlike the IFA for *B. microti*, a higher cutoff value (>1:160) is required to impart specificity, for unknown reasons. In humans and in rodent models, tetrad forms are frequently seen in blood smears, but otherwise this agent is difficult to distinguish from *B. microti*.

Coinfection with the agents of Lyme disease (*B. burgdorferi*), human granulocytic anaplasmosis (*A. phagocytophilum*), or both may occur in patients experiencing babesiosis in geographic areas where these pathogens are endemic. Coinfection should be considered in patients who present with rash or more severe initial symptoms than are commonly observed with babesiosis alone, or who do not respond to standard therapy.

TREATMENT

Early efforts to treat patients with babesiosis were unsuccessful, including use of the antimalarial drug chloroquine. The combination of clindamycin and quinine was the first effective antimicrobial therapy and remains the treatment of choice for severe babesiosis. Clindamycin is given to adults as 300 to 600 mg IV every 6 hours or 600 mg orally every 8 hours and to children in a 7 to 10 mg/kg/dose, up to a maximum dose of 600 mg, given IV or orally every 6 to 8 hours. Quinine is given as 650 mg orally every 6 to 8 hours in adults and 8 mg/kg/dose up to a maximum dose of 650 mg, given orally every 6 hours, in children. The clindamycin and quinine combination generally is administered for 7 to 10 days. This combination frequently produces untoward reactions, such as tinnitus, QT prolongation, allergic reaction, vertigo, and gastrointestinal upset. Treatment failures have been reported in patients with splenectomy, HIV-infected patients, and those receiving concurrent corticosteroid therapy (Table 201.1).

The successful use of atovaquone and azithromycin for treatment of malaria and for treating babesiosis in a hamster model of infection suggested that this combination might also be useful against human babesiosis. In the first prospective, randomized trial of antibabesial therapy in humans, the combination of atovaquone and azithromycin was compared with that of clindamycin and quinine for treatment of adults with *B. microti* infection. The atovaquone and azithromycin combination was found to be as effective in clearing parasitemia and resolving symptoms as the clindamycin and quinine combination. Both drug combinations were given by mouth for 7 days. After 3 months, there was no evidence of piroplasms or amplifiable *B. microti* DNA in either group. Significantly fewer adverse effects were associated with the atovaquone and azithromycin combination. Three-fourths of patients receiving clindamycin and quinine experienced adverse drug reactions, and one-third were forced to decrease the dose or to discontinue the medication. Adverse effects of therapy included hearing loss, tinnitus, syncope, hypotension, and gastrointestinal symptoms (anorexia, vomiting, and diarrhea). In contrast, only 18% in the azithromycin and atovaquone group experienced symptoms consistent with adverse drug reaction, and none required a

decrease in dosage or discontinuation of medication. The conclusions of this study were (1) antibabesial therapy based on the atovaquone and azithromycin drug combination generally is superior to that based on clindamycin and quinine, mainly because the atovaquone and azithromycin regimen is well tolerated, whereas the clindamycin and quinine regimen frequently is not, and (2) physicians should consider the use of atovaquone and azithromycin in adult patients experiencing mild or moderate babesial symptoms and in others who cannot tolerate clindamycin and quinine. The currently recommended dose for atovaquone is 750 mg orally every 12 hours in adults or 20 mg/kg/dose up to a maximum dose of 750 mg, given orally every 12 hours, in children, whereas that for azithromycin is 500 to 1000 mg on day 1 and then 250 mg/day thereafter in adults or 10 mg/kg/day as a single dose (up to a maximum dose of 500 mg) given orally on day 1, and 5 mg/kg/dose (up to a maximum dose of 250 mg) given orally once per day thereafter in children. Higher doses of 600 to 1000 mg/day may be used for immunocompromised patients experiencing babesiosis.

The combination of pentamidine (240 mg IV/day) and trimethoprim–sulfamethoxazole (3 g/day) was found be moderately effective in clearing parasitemia and symptoms due to *B. divergens*. Potential adverse reactions to pentamidine that include pain at the site of injection, formation of sterile abscess, hyperglycemia or hypoglycemia, and nephrotoxicity limit the use of this combination.

Clindamycin (administered intravenously) and quinine should be given to patients experiencing babesiosis who are more severely ill with high parasitemia (>10%), significant hemolysis, or renal or pulmonary compromise. In addition, exchange transfusion should be considered in such patients. Partial exchange transfusion (packed red blood cells) or complete exchange (whole blood exchange) as well as plasmapheresis are rapid and reliable methods of decreasing parasitemia by removing parasite-infected red blood cells from the circulation. They also help remove vasoactive elements such as cytokines and thromboplastic substances that may contribute to renal failure and disseminated intravascular coagulation. Due to the risks associated with multiple blood exposures, these techniques should not be considered as routine therapy but only used for those severely ill with babesiosis, such as patients with a high parasitemia and coma, hypotension, congestive heart failure, pulmonary edema, or renal failure. In combination with clindamycin and quinine, exchange transfusion is the treatment of choice for all cases of *B. divergens* babesiosis.

Patients with babesiosis should be monitored closely during therapy. In most cases, improvement will occur within 1 or 2 days after antiprotozoal therapy is begun. Symptoms generally resolve within 1 or 2 months after clindamycin and quinine or atovaquone and azithromycin therapy is completed. In severely ill patients (especially those with asplenia or HIV), the hematocrit and percentage of erythrocytes parasitized should be monitored daily or every other day until the patient has improved and the parasitemia has decreased to less than 5%. Blood smears should be examined every 4 hours following the first dose of clindamycin and quinine, and alternative therapy should be considered if parasitemia does not appreciably decline within 24 hours. Some patients may have persistence of low-grade parasitemia for months following antibiotic therapy. Because low-grade parasitemia may be difficult to detect on thin blood smear, the more sensitive PCR for amplifying parasite DNA should also be considered. Physicians should consider retreatment of patients with antibabesial therapy if patients show evidence of parasitemia in their blood for more than 3 months after initial therapy, especially if parasitemia is increasing.

Physicians also should consider the possibility of coinfection with Lyme disease, human granulocytic anaplasmosis, or both in patients who experience especially severe or persistent symptoms despite appropriate antibabesial therapy. Such patients may benefit from the addition of doxycycline therapy because neither clindamycin and quinine nor atovaquone and azithromycin have been shown to be effective for the treatment of Lyme disease or human granulocytic anaplasmosis.

PREVENTION

Prevention of babesiosis can be accomplished by avoiding areas from May through September where ticks, deer, and mice are known to thrive. It is especially important for those at increased risk in endemic areas, such as asplenic individuals, to avoid tall grass and brush where ticks may abound. Use of clothing that covers the lower part of the body and that is sprayed or impregnated with diethyltoluamide (DEET), dimethyl phthalate, or permethrin (Permanone) is recommended for those who travel in the foliage of endemic areas. DEET has been shown to be more effective than other repellents against ticks,

but the risk of adverse effects is greater. Topically applied DEET is absorbed into the systemic circulation and as much as 10% to 15% of each dose can be found in the urine. Dermatologic effects such as bullous eruptions and urticaria have been documented. Systemic effects such as toxic encephalopathy, anaphylaxis, and grand mal seizures have been noted with higher DEET concentrations. Finally, DEET ingestion may be fatal to both children and adults. Thus, although DEET can help to prevent tick bites and is generally well tolerated when applied to the skin properly, care must be taken with repeated use of high concentration products.

A search for ticks on people and pets should be carried out and the ticks removed using tweezers to grasp the mouthparts without squeezing the body of the tick. Prophylactic antibiotics after a tick bite to prevent babesiosis are not indicated. The effects of reduction of the tick, mouse, or deer populations in endemic areas on the incidence of human babesiosis have not been evaluated. Blood donors with a history of babesiosis are excluded from donating blood to prevent transfusion-related cases. Effective vaccines have been developed to prevent *B. divergens* and *B. bovis* infections in cattle, but no vaccines are currently available for the prevention of human babesiosis.

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202. Trypanosomiases and leishmaniases

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American trypanosomiasis (Chagas disease), human African trypanosomiasis (HAT, sleeping sickness), and leishmaniasis are caused by related protozoa of the family Trypanosomatidae, order Kinetoplastida (see Table 202.1). They have a unique mitochondrial structure, the kinetoplast, are transmitted in nature by insect vectors, and exist in multiple morphologic forms in their human hosts and insect vectors. They are important causes of morbidity and mortality in endemic areas of the world: Chagas disease in South and Central America, sleeping sickness in sub-Saharan Africa, and leishmaniasis in scattered areas on every continent except Antarctica. Although uncommon in industrial countries in North America and Europe, these diseases have been the source of increased attention in recent years. Infection with *Trypanosoma cruzi*, the cause of Chagas disease, is well documented among Latin American immigrants to North America and Europe and poses a risk to them, children of infected mothers, and to recipients of contaminated blood or transplanted organs. Cutaneous leishmaniasis is seen among tourists returning from endemic areas in Latin America and the Middle East as well as in military personnel who have served in Iraq, Afghanistan, and other endemic areas. Imported cases of visceral leishmaniasis in travelers or immigrants from the Indian subcontinent, East Africa, South America or southern Europe, some in association with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), occur, but are rare. Canine visceral leishmaniasis has been reported in the United States among foxhounds and other dogs, but to date, humans have not been infected.

Despite several important recent advances, the treatment of Chagas disease, African trypanosomiasis, and leishmaniasis leaves much to be desired. Many of the drugs (Table 202.2) used for them are associated with frequent and potentially severe untoward effects, some require parenteral administration, and many must be administered over prolonged periods of time. The only drugs approved by the US Food and Drug Administration (FDA) for these diseases are liposomal amphotericin B for visceral leishmaniasis and miltefosine for visceral and cutaneous leishmaniasis. Other drugs listed in the table are investigational or used off-label. Several can be obtained from the Centers for Disease Control and Prevention (CDC) Drug Service (Atlanta, Georgia) along with detailed information about administration

Table 202.1 Diseases caused by protozoa of the family Trypanosomatidae

Disease	Causative agent	Geographic distribution	Vector	Reservoir
American trypanosomiasis (Chagas disease)	*Trypanosoma cruzi*	Americas	Triatomine (Reduviid) bugs; occasionally infected juices or foods	Multiple species of animals
African trypanosomiasis (sleeping sickness)	*Trypanosoma brucei gambiense* *Trypanosoma brucei rhodesiense*	West and Central Africa East Africa	Tsetse flies (*Glossina* species)	Humans, domestic animals (minor role) Large game animals
Leishmaniasis (visceral, cutaneous, mucosal)	*Leishmania* species	Worldwide	Sand flies (*Phlebotomus* species and *Lutzomyia* species)	Rodents, canines (dogs, foxes), or humans

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Table 202.2 Treatment of trypanosomiasis and leishmaniasis

Drug of choice	Adult dosage	Pediatric dosage
American trypanosomiasis/Chagas disease (*Trypanosoma cruzi*)		
Nifurtimox[a,b]	8–10 mg/kg/d in 3–4 doses × 90 d	1–10 yr : 15–20 mg/kg/d in 3–4 doses × 90 d
Or		11–16 yr: 12.5–15 mg/kg/d in 3–4 doses × 90 d
		≥17 yr: same as adult dose × 90 d
Benznidazole[a,b]	5–7 mg/kg/d in 2 divided doses × 60 d	<12 yr: 5–7.5 mg/kg/d in 2 doses × 60 d
		≥12 yr: 5–7 mg/kg/d in 2 doses × 60 d
East African sleeping sickness (*Trypanosoma brucei rhodesiense*)		
Hemolymphatic stage		
Suramin[a,b]	100 mg (test dose) IV, then 1 g IV on days 1,3,5,14, and 21	100 mg (test dose), then 20 mg/kg (max 1 g) on days 1,3,5,14, and 21
Late stage with central nervous system involvement		
Melarsoprol[a,b,c]	2–3–6 mg/kg/d × 3 d; after 7 d	2–3.6 mg/kg/d × 3 d; after 7 d
	3.6 mg/kg/d × 3 d; repeat again after 7 d	3.6 mg/kg/d × 3 d; repeat again after 7 d
West African sleeping sickness (*Trypanosoma brucei gambiense*)		
Hemolymphatic stage		
Pentamidine[d,e]	4 mg/kg/d IM or IV × 7–10 d	4 mg/kg/d IM or IV × 7–10 d
Alternative: Suramin[a]	100 mg (test dose) IV, then 1 g IV on days 1,3,5,14, and 21	100 mg (test dose) IV, then 20 mg/kg/d (max 1 g) on days 1,3,5,14, and 21
Late stage with central nervous system involvement		
Eflornithine[a,f]	400 mg/kg/d IV in 4 doses × 14 d	400 mg/kg/d IV in 4 doses × 14 d
Leishmaniasis (*Leishmania* species)		
Visceral[g]		
Liposomal amphotericin B[h,i]	3 mg/kg IV (d 1–5, 14, and 21)	3 mg/kg IV (d 1–5, 14, and 21)
Alternatives		
Sodium stibogluconate[a]	20 mg sb/kg/d IV or IM × 28 d[j]	20 mg sb/kg/d IV or IM × 28 d[j]
Or		
Meglumine antimonate[a]	20 mg sb/kg/d IV or IM × 28 d[j]	20 mg sb/kg/d IV or IM × 28 d[j]
Or		
Miltefosine[k]	50 mg PO TID × 28 d	≥12 yr and 30–44 kg: 50 mg PO BID × 28 d
		≥45 kg: same as adult dose × 28 d
Or		
Amphotericin B[d]	0.5–1 mg/kg IV daily or every second day for a total dose of 15–20 mg/kg	1 mg/kg IV daily or every second day for a total dose of 15–20 mg/kg
Cutaneous[l]		
Local therapy:	Cryotherapy (with liquid nitrogen)	
	Thermotherapy (use of localized current field radiofrequency heat)	
	Intralesional administration of Sb^V (not covered by CDC's protocol for Pentostam)	
	Application of paromomycin (as an ointment containing 15% paromomycin; not commercially available in the United States)[m]	
Systemic therapy:	Application of imiquimod	
Sodium stibogluconate[a]	20 mg sb/kg/d IV or IM × 20 d[h]	20 mg sb/kg/d IV or IM × 20 d[j]
Or		
Meglumine antimonate[a]	20 mg sb/kg/d IV or IM × 20 d[j]	20 mg sb/kg/d IV or IM × 20 d[j]
Or		
Liposomal amphotericin	3 mg/kg/d IV for 6–10 doses	3 mg/kg/d IV for 6–10 doses
Or		
Amphotericin B deoxycholate[d]	0.5–1.0 mg/kg daily or every other day for a total dose of approx. 20 mg/kg	0.5–1.0 mg/kg daily; or every other day for a total dose of approx. 20 mg/kg
Or		
Miltefosine[n]	50 mg PO TID × 28 d	≥12 yr and 30–44 kg: 50 mg PO BID × 28 d
		≥45 kg: same as adult dose × 28 d
Or		
Fluconazole[d,o]	8 mg/kg/d PO for 4–6 wk	8 mg/kg/d PO for 4–6 wk

Table 202.2 *(continued)*

Drug of choice	Adult dosage	Pediatric dosage
Mucosal[p]		
Sodium stibogluconate[a]	20 mg sb/kg/d IV or IM × 28 d[j]	20 mg sb/kg/d IV or IM × 28 d[j]
Or		
Meglumine antimonate[a]	20 mg sb/kg/d IV or IM × 28 d[j]	20 mg sb/kg/d IV or IM × 28 d[j]
Or		
Amphotericin B[d]	0.5–1 mg/kg IV daily or every second day for up to 8 wk	0.5–1 mg/kg IV daily or every second day for up to 8 wk for cumulative dose of 20–45 mg/kg
Or		
Liposomal amphotericin[d]	3 mg/kg daily or every other day for a dose of 35 mg/kg	3 mg/daily or every other day for a dose of 35 mg/kg
Or		
Miltefosine[q]	50 mg PO TID × 28 d	≥12 yr and 30–44 kg: 50 mg PO BID × 28 d ≥45 kg: same as adult dose × 28 d

[a] Based on the recommendations of the Centers for Disease Control and Prevention, 2013 and the Medical Letter for Drugs and Therapeutics, 2008

[b] Available under an Investigational New Drug (IND) protocol from the CDC Drug Service, Centers for Disease Control and Prevention, Atlanta, GA 30333; 404–639–3670 (evenings, weekends, or holidays: 404–639–2888).

[c] In frail patients, begin with as little as 18 mg and increase the dose progressively. Pretreatment with suramin has been advocated for debilitated patients. Corticosteroids have been used to prevent arsenical encephalopathy. Up to 20% of patients with *T. b. gambiense* fail to respond to melarsoprol.

[d] An approved drug, but considered investigational for this condition by the FDA.

[e] For treatment of *T. b. gambiense*, pentamidine and suramin have equal efficacy, but pentamidine is better tolerated.

[f] Eflornithine is highly effective in *T. b. gambiense* but not against *T. b. rhodesiense* infections. It is available in limited supply only from the World Health Organization (WHO) and the CDC.

[g] Visceral infection is most commonly caused by *Leishmania donovani* and *Leishmania infantum* (previously known as *Leishmania chagasi* in Latin America). Treatment may vary based on symptoms, host immune status, species, and resistance pattern in the area where infection was acquired.

[h] Several lipid formulations of amphotericin B have been used for treatment of visceral leishmaniasis. Largely based on clinical trials in patients infected with *L. infantum*, the FDA approved liposomal amphotericin B (AmBisome) for treatment of visceral leishmaniasis. Amphotericin B lipid complex (Abelcet) and amphotericin B cholesteryl sulfate (Amphotec) are considered investigational.

[i] The FDA-approved dosage regimen for immunocompromised patients (e.g., HIV infected) is 4 mg/kg/d (d 1–5) and 4 mg/kg/d on d 10, 17, 24, 31, and 38. The relapse rate is high; maintenance therapy may be indicated, but there is no consensus as to dosage or duration.

[j] May be repeated or continued; a longer duration or higher dose may be needed for some patients treated with liposomal amphotericin.

[k] Gastrointestinal adverse effects are common, and the drug is contraindicated in pregnancy and breastfeeding. Resistance has been reported. Miltefosine is approved for *L. donovani* infection acquired in the Indian subcontinent.

[l] Cutaneous infection is most commonly due to the Old World species *Leishmania major*, *Leishmania tropica* and *Leishmania aethiopica* and New World species *Leishmania mexicana*, *Leishmania amazonensis, Leishmania (Viannia) panamensis*, *Leishmania (Viannia) braziliensis*, and others. The choice of treatment varies based on the location and characteristics of the lesion(s), host immune status, infecting *Leishmania* species, and area of the world where infection was acquired. If lesions are small, few in number, cosmetically inconsequential, and not caused by *Leishmania* species associated with mucosal disease, they can be followed expectantly if there is evidence of self-healing or the lesions may be treated locally. An oral or parenteral systemic option is used for the rest. The final choice depends on the infecting species or geographic location of acquisition and the relative toxicity of the treatment modality.

[m] Topical paromomycin should be used only in geographic regions where cutaneous leishmaniasis species have low potential for mucosal spread.

[n] Oral miltefosine is approved for the treatment of cutaneous and mucosal leishmaniasis due to *L. (V.) panamensis*, *L. (V.) braziliensis*, and *L. (V.) guyanensis*. See note k for adverse effects.

[o] Several azoles have been used with variable effects. Early reports suggested that fluconazole 200 mg/d for 6 weeks was effective in American military personnel with *L. major*, but failures have been reported with that dose with lesions caused by other *Leishmania* species. Fluconazole at higher doses, 8 mg/kg for 4–6 weeks, has been reported to be effective in the treatment of *L. (V.) braziliensis* in an observational study in Brazil.

[p] American mucosal leishmaniasis is most often due to *L. (V.) braziliensis*, but may be seen in persons infected with *L. (V.) panamensis, L. (V.) guyanensis* and other species. The selection among treatment options is based on symptoms, host immune status, infecting *Leishmania* species, and site where the infection was acquired.

Abbreviations: CDC = Centers for Disease Control and prevention; FDA = Food and Drug Administration; IV = intravenously; IM = intramuscularly; sb = pentavalent antimony.

and side effects and administered under an Investigational New Drug (IND) protocol. The high cost of some of these medications and the lack of availability of others are important determinants in therapeutic decisions in impoverished endemic areas. Hopefully, more effective, less toxic approaches to chemotherapy and/or protective vaccines will become available in the future.

AMERICAN TRYPANOSOMIASIS (CHAGAS DISEASE)

Chagas disease, which is caused by *T. cruzi*, is transmitted by triatomine (reduviid or kissing) bugs that reside in buildings in rural areas of Latin America and occasionally in contaminated juices or foods. *Trypanosoma cruzi* infects a large number of animal species as well as humans.

There are an estimated 8 to 10 million persons infected in the world. The parasite develops in the intestine of the triatomine bug and is passed in feces when it takes a blood meal. The bite causes itching, and parasites may enter the skin through the imperceptible bite site when the person scratches. They may also be transferred to the conjunctiva where they can enter in the absence of a lesion.

The invasion that follows can elicit a local inflammatory nodule or chagoma. When parasites invade through the conjunctiva, unilateral, painless, periorbital edema (Romaña's sign) may develop. After a period of local multiplication, trypomastigotes disseminate through the bloodstream, causing acute Chagas disease with fever, other constitutional symptoms, carditis, and, rarely, meningoencephalitis. Death can result, but the acute phase is often mild or asymptomatic. Symptoms usually resolve over 4 to 8 weeks as host immune responses develop. The indeterminate phase of infection follows in which persons are entirely asymptomatic but continue to harbor the parasite. Eventually, 20% to 30% of infected individuals progress to chronic Chagas with cardiac, esophageal, or large intestinal involvement. Progressive, disseminated Chagas disease with carditis and/or brain abscesses has been reported in a limited number of persons with AIDS, following transplants or associated with other immunocompromising conditions. *Trypanosoma cruzi* is present in the bloodstream and organs of persons throughout the period of infection. Transmission can occur through transfusion of contaminated blood or transplantation of contaminated organs. This has posed ongoing problems in endemic areas in Latin America and is of increasing concern in North America and Europe related to immigration. Congenital transmission and accidental laboratory infections are well documented.

The diagnosis of acute Chagas disease is frequently made by identifying the parasite in blood or body tissues (Figure 202.1). Several serologic assays have been developed to detect antitrypanosomal antibodies in persons with indeterminate phase or chronic Chagas disease. The tests tend to be highly sensitive, but not always specific. They are routinely used in blood banks in endemic areas. A screening test for anti-*T. cruzi* immunoglobulin G antibodies approved by the FDA is used to detect infected blood and organ donors in the United States. In addition to protecting potential recipients, screening has brought to medical attention a number of infected immigrants now living in the United States and Canada.

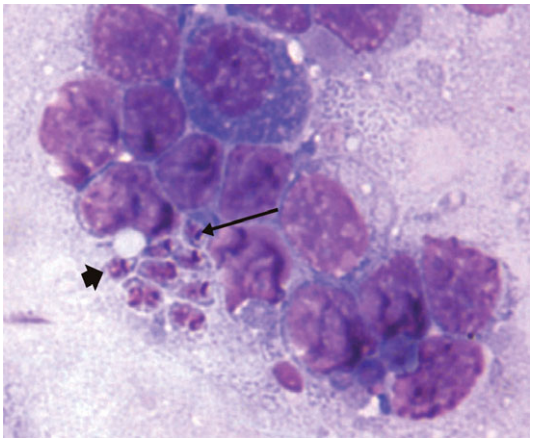


Figure 202.1 An imprint from a lymph node biopsy of a child with acute Chagas disease showing amastigotes (*arrowhead*), with large kinetoplast (*arrow*). Culture in LIT from the node and from whole blood grew *Trypanosoma cruzi*.

The drugs of choice are benznidazole or nifurtimox. Both are available under an IND protocol from the CDC Drug Service. Benznidazole has been the mainstay of therapy in Latin American countries. Nifurtimox has been used in the United States. Untoward effects are common with both drugs and may necessitate premature discontinuation of therapy.

Nifurtimox (Bayer 2502, Lampit; Bayer) is typically given for 90 days (see Table 202.2 for dosage). The drug is better tolerated in children and adolescents than in adults; higher doses per kilogram of body weight are used in younger patients. Neurologic and gastrointestinal side effects are common. They include sleep disturbances, restlessness, tremor, memory loss, paresthesias, weakness, polyneuritis, and, rarely, seizures, as well as anorexia, nausea, vomiting, abdominal pain, and weight loss. Other, rare side effects include fever, pulmonary infiltrates, and effusions.

Benznidazole (Rochagan, Roche) is usually administered for a period of 60 days. Higher doses are used in children. Side effects are frequent and include gastrointestinal disturbances, psychiatric manifestations, dose-dependent neuropathy, and cutaneous hypersensitivity reactions. On rare occasions hepatitis or neutropenia develops.

Treatment is indicated for all cases of acute or reactivated Chagas disease and for indeterminate or congenital infection up to age 18 years. Treatment is strongly recommended for adults up to

50 years old with chronic infection who do not already have advanced cardiomyopathy. For those older than 50 years with chronic *T. cruzi* infection, the decision to treat is individualized, weighing the potential benefits and risks, based on the patient's age, clinical status, and preference.

Once the cardiac, esophageal, or large intestinal manifestations of chronic Chagas disease develop, neither drug appears to alter the outcome. Supportive therapy includes cardiotropic drugs for congestive heart failure and arrhythmias, pacemaker placement for heart block, and palliative endoscopic or surgical procedures for esophageal and intestinal megadisease. Nifurtimox has been used to treat disseminated infection in persons who have undergone cardiac transplantation for chagasic cardiomyopathy in the United States.

HUMAN AFRICAN TRYPANOSOMIASIS (HAT, SLEEPING SICKNESS)

Human African trypanosomiasis is caused by *Trypanosoma brucei gambiense*, which is endemic in West and Central Africa, and *Trypanosoma brucei rhodesiense* in East Africa. Uganda is the only country where both exist. The African trypanosomes are transmitted by tsetse flies, which are found only in sub-Saharan Africa. Humans are the primary reservoir of *T. b. gambiense*, whereas *T. b. rhodesiense* is found primarily in large game animals. There are an estimated 50 000 to 70 000 new cases yearly although reporting is poor. Transplacental transmission and transmission through contaminated blood or transplanted organs can occur but are uncommon. *Trypanosoma b. gambiense* (West African trypanosomiasis) accounts for approximately 90% of all cases of HAT worldwide, but it is rarely encountered in the United States and in industrialized areas. There is on average approximately one case of HAT per year, with most being due to *T. b. rhodesiense* (East African trypanosomiasis) in the United States.

An indurated chancre may develop at the site of parasite inoculation. It is more likely to come with *T. b. rhodesiense* than *T. b. gambiense* infection. The early (hemolymphatic) stage of *T. b. gambiense* is characterized by recurrent bouts of fever, rash, headaches, edema of the face, myalgias, arthralgias, other constitutional symptoms, and lymphadenopathy. Swollen posterior cervical nodes are known as Winterbottom's sign. Trypanosomes may be seen in the blood or aspirates of lymph nodes. After a period of several weeks to months they invade the central nervous system, producing meningoencephalitis. Symptoms and findings include headaches, which may be severe, loss of concentration, personality changes, memory loss, seizures, difficulty walking, increased sleeping, and eventually obtundation, coma, wasting, and death.

In *T. b. rhodesiense* infection, systemic symptoms develop a few days to several weeks after the tsetse fly bites. A chancre may be present. Fever, headache, severe fatigue, irritability, lymphadenopathy, myalgias, and arthralgias follow. Death can occur within several weeks or months if treatment is not initiated. The courses may be indistinguishable, but *T. b. rhodesiense* infection is usually more acute and severe, and lymphadenopathy is not as prominent as it is with *T. b. gambiense* infection.

All cases of human African sleeping sickness must be treated. Given the complexity of the treatment regimens and toxicity of the drugs, consultation with experts at the CDC or elsewhere is recommended. Eflornithine, which has been called the "resurrection drug," is highly effective for hemolymphatic and central nervous system disease caused by *T. b. gambiense* and, when available, is the treatment of choice for West African sleeping sickness. Unfortunately, it is expensive and logistically difficult to administer in rural, endemic areas of Africa, and supplies are very limited. A 14-day course administered intravenously (IV) is recommended for late stage disease (Table 202.2). The combination of eflornithine and nifurtimox appears promising for central nervous system disease with *T. b. gambiense* based on recent studies. Eflornithine is not active against *T. b. rhodesiense*.

When eflornithine is not available, persons with hemolymphatic disease due to *T. b. gambiense* can be treated with either pentamidine isethionate, a 7-day course administered parenterally, or suramin. Pentamidine and suramin are of comparable efficacy for *T. b. gambiense*, but pentamidine is less toxic.

Toxicity is frequent with suramin and includes gastrointestinal disturbances such as nausea and vomiting; neurologic side effects such as photophobia, hyperesthesias, and peripheral neuropathy; and urticaria and pruritus. Administration of the drug is occasionally associated with shock, renal toxicity, optic atrophy, or blood dyscrasias. A test dose of suramin is given IV prior to the administration of treatment doses.

Pentamidine isethionate is administered daily, intramuscularly (IM) or IV. If infused too rapidly, IV pentamidine can produce hypotension and shock. Gastrointestinal disturbances, pain at the injection site when the drug is given IM, liver enzyme abnormalities, and nephrotoxicity are other side effects. Some patients develop life-threatening hypoglycemia due to pancreatic beta cell injury and insulin release; insulin-dependent diabetes may follow. Rare side effects include acute pancreatitis, hyperkalemia, anaphylaxis, and ventricular arrhythmias.

Melarsoprol (*Arsobal*, Rhone-Poulenc Rorer) is used to treat persons with central nervous system involvement with *T. b. gambiense* in sites where eflornithine is not available, and it is the only effective drug for persons with central nervous system disease due to *T. b. rhodesiense*. Melarsoprol is administered IV (see Table 202.2). Untoward effects are common with melarsoprol. In addition to encephalopathy, which occurs in as many as 18% of recipients and is fatal in 3% to 10%, treatment is frequently associated with nausea, vomiting, abdominal pain, peripheral neuropathy, hypertension, allergic reactions, and, rarely, shock. Administration of prednisolone, 1 to 2 mg/kg/day, appears to reduce the severity of arsenical encephalopathy and the risk of death by approximately half. A number of dosage regimens have been studied. Reduced doses of melarsoprol have been used in cachectic patients. Low-dose melarsoprol plus nifurtimox (see Chagas disease above) has also been used.

LEISHMANIASIS (CUTANEOUS, MUCOSAL, AND VISCERAL)

Leishmaniasis refers to the spectrum of disease caused by more than 20 *Leishmania* spp. that infect humans and other vertebrate hosts. The major clinical syndromes include cutaneous, mucosal, and visceral leishmaniasis, but a variety of other presentations, including post-kala-azar dermal leishmaniasis, diffuse cutaneous leishmaniasis, disseminated cutaneous leishmaniasis, and viscerotropic leishmaniasis, have been described. *Leishmania* spp. are transmitted by sand flies in nature. In many areas of the world, leishmaniasis is a zoonosis with dogs, other canines, or rodents serving as reservoirs, and humans becoming infected when they venture into endemic habitats. An outbreak of canine visceral leishmaniasis has been reported in the United States among foxhounds and some other dogs. Infection seems to occur by dog-to-dog or in utero transmission. There have been no human cases. In some sites such as India, humans are the only reservoir of visceral leishmaniasis. The manifestations of disease depend on interactions between the infecting *Leishmania* sp. and the genetically determined cell-mediated immune responses of its human host (Figures 202.2–202.9).

In persons with cutaneous leishmaniasis, parasites multiply in macrophages at the site of inoculation in the skin and in draining lymph nodes. The morphology of the resulting lesion is variable. Often, a nodule develops, expands, and then ulcerates over a course of weeks. Lesions may be single or multiple. Some have a "pizza-like" appearance with a raised, erythematous, outer border, a central area of red granulation tissue, and a yellowish or brown overlying crust. Others are "volcano-like" or flat and plaque-like. Lesions can persist for months to years but eventually heal leaving a burn-like scar as evidence of disease. In mucosal leishmaniasis due to *Leishmania (Viannia) braziliensis* and related species in Latin America, mucosal lesions of the nose, oral pharynx, and occasionally other sites develop months to years after the initial skin lesion has healed.

The majority of persons infected with *Leishmania donovani*, *Leishmania infantum* (formerly known as *Leishmania chagasi* in Latin America), or other *Leishmania* species associated with visceral leishmaniasis are asymptomatic, despite parasitemia in some instances, and have spontaneously resolving infections. In the subset of persons who develop progressive visceral leishmaniasis, known as kala-azar, parasites disseminate throughout the reticuloendothelial system. They are found within macrophages in the liver, spleen, bone marrow, and occasionally other organs. Patients typically present with massive splenomegaly, hepatomegaly, fever, weight loss, constitutional symptoms, and hypergammaglobulinemia. Visceral leishmaniasis has emerged in Spain, southern France, Italy, and elsewhere in southern Europe as well as Brazil as an opportunistic infection in persons with AIDS and others with compromised cell-mediated immunity. Persons with concurrent visceral leishmaniasis and AIDS may present in the classical manner, but atypical presentations are common. Splenomegaly may be absent, and gastrointestinal and pleuropulmonary involvement are often seen.

The diagnosis of cutaneous or visceral leishmaniasis is suggested by a history of exposure in

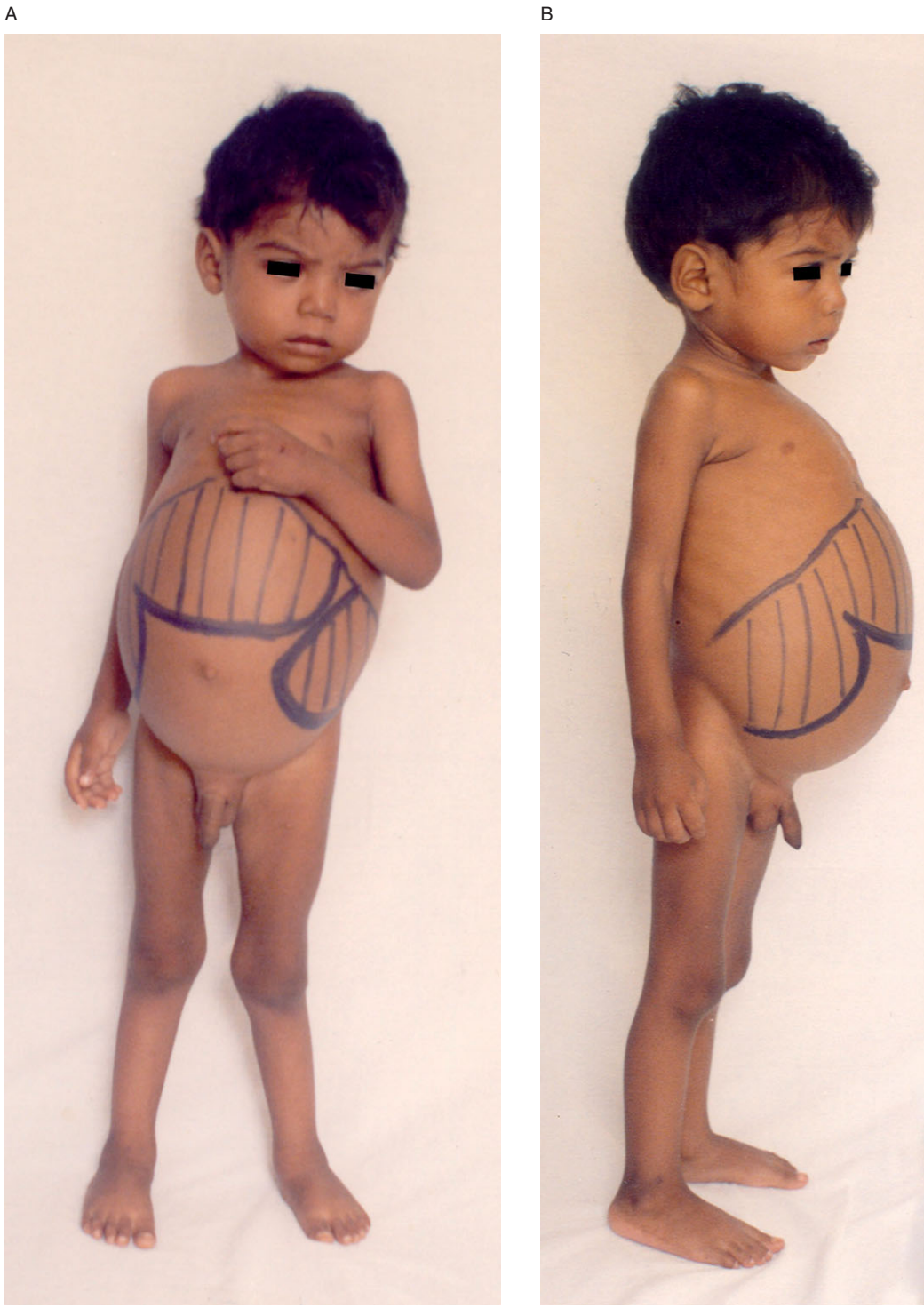


Figure 202.2 (**A and B**) Brazilian child with advanced visceral leishmaniasis and massive hepatosplenomegaly.

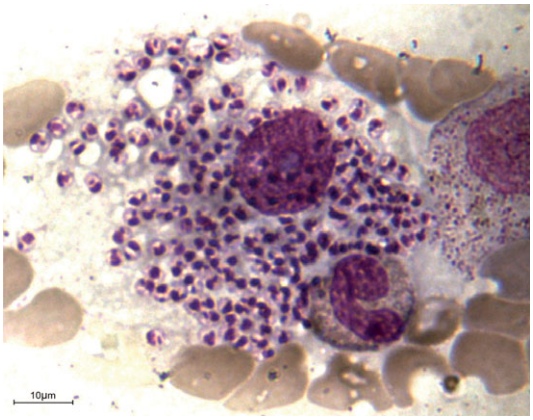
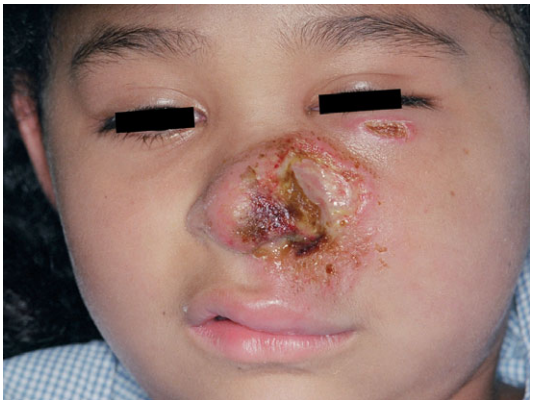


Figure 202.3 A macrophage with more than 100 amastigotes from a bone marrow aspirate of an AIDS patient with kala-azar.

an endemic region and the clinical findings. It is confirmed by identifying leishmania amastigotes, by smear, culture, or molecular tests for DNA, in blood, bone marrow, splenic aspirates, lymph node, or other tissue from patients with visceral leishmaniasis or in biopsies of skin lesions from those with cutaneous leishmaniasis. Antileishmanial antibodies are present at high titer in persons with visceral leishmaniasis but may be absent in persons with AIDS. Several assays are available; an enzyme-linked immunosorbent assay using a recombinant 39-kDa kinesin-like antigen is the most sensitive and specific for visceral leishmaniasis. Serology is not diagnostic in cutaneous leishmaniasis, as antileishmanial antibodies are variably present and at low titer. The leishmanin (Montenegro) skin test (Figure 202.10) is not

A



B

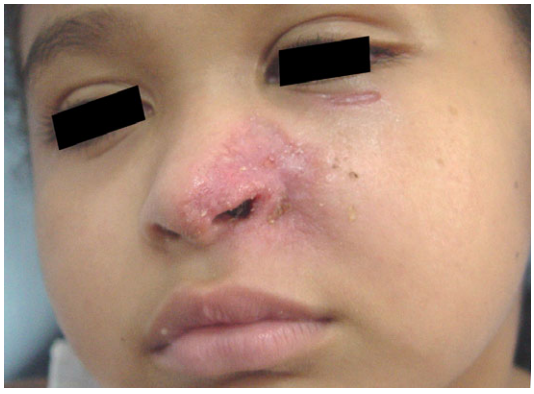


Figure 202.4 (**A and B**) A child with cutaneous leishmaniasis with involvement of the nose, due to *Leishmania* (*Viannia*) *braziliensis*. Before and after treatment.

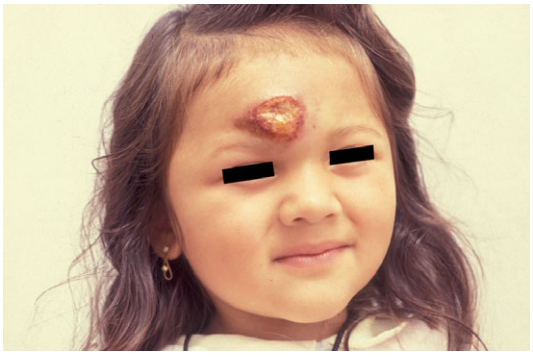


Figure 202.5 Brazilian child with cutaneous leishmaniasis due to *Leishmania* (*Viannia*) *braziliensis*.

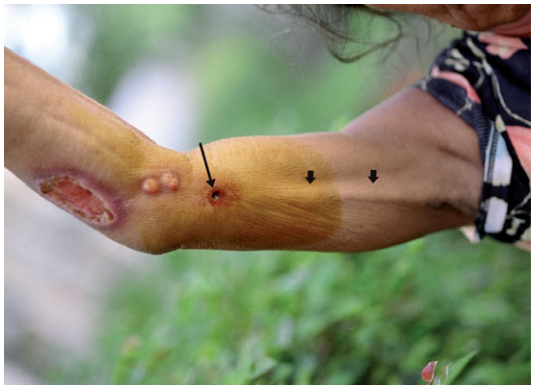


Figure 202.6 A Brazilian woman with cutaneous leishmaniasis, with lymphatic involvement (sporotricoid type) due to *Leishmania* (*Viannia*) *braziliensis*. Lymphatic (*arrowheads*) and where a punch biopsy was taken (*arrow*). Leishmania were seen in imprint and grown in NNN culture.

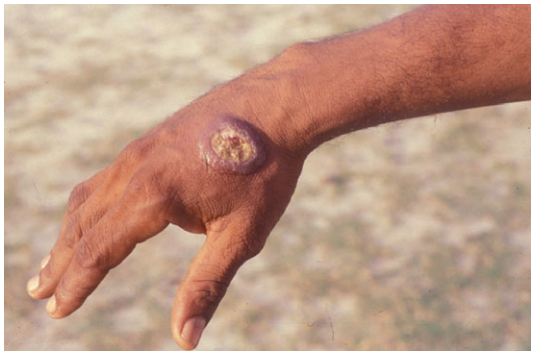


Figure 202.7 Patient with cutaneous leishmaniasis, due to *Leishmania* (*Viannia*) *braziliensis*. Hand involvement.

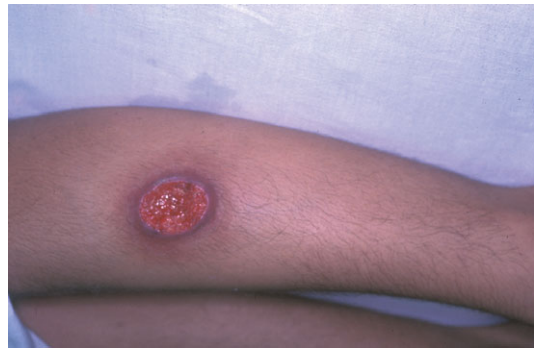
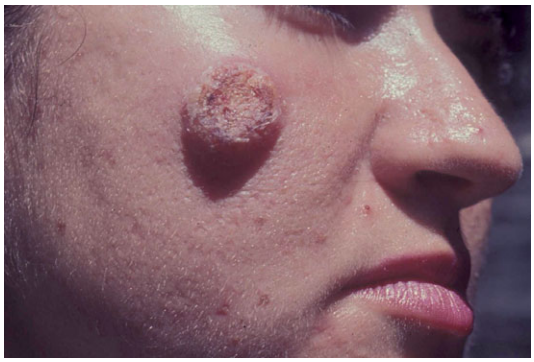


Figure 202.8 Patient with cutaneous leishmaniasis, due to *Leishmania* (*Viannia*) *braziliensis*. Leg involvement.

A



B

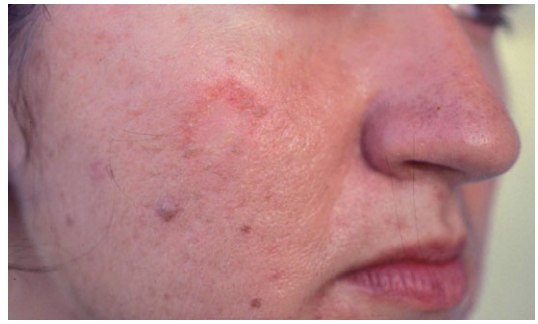


Figure 202.9 (**A and B**) Cutaneous leishmaniasis due to *Leishmania* (*Viannia*) *braziliensis* before and after treatment.

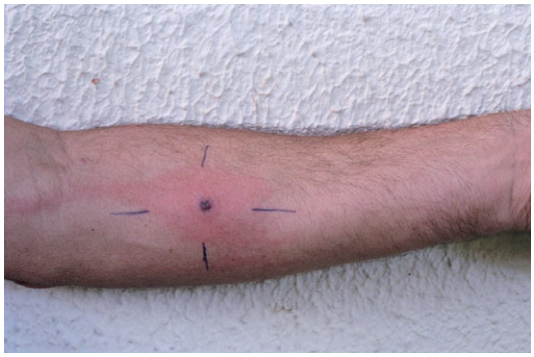


Figure 202.10 Positive Montenegro test (leishmanin skin test), 50 mm, with central necrosis, of a patient with mucosal leishmaniasis.

available in the United States. It is negative in patients with visceral leishmaniasis, but it usually becomes positive after successful treatment. The test is typically positive in persons with cutaneous and mucosal leishmaniasis.

Liposomal amphotericin B (AmBisome, Fugisawa) is licensed in the United States for visceral leishmaniasis. It is highly effective, as is amphotericin B deoxycholate, but it is less toxic. Although it is the drug of choice in industrialized countries, its cost and availability have limited its use in impoverished endemic areas.

Sodium sibogluconate (Pentostam) and meglumine antimonate (Glucantime), both pentavalent antimony compounds, have been used for decades to treat leishmaniasis. Pentostam is available through the CDC Drug Service in the United States. These drugs are dosed on the basis of their pentavalent antimony content; Pentostam contains 100 mg of pentavalent antimony/mL and Glucantime contains 85 mg/mL. They are used to treat visceral leishmaniasis in some areas of the world, but antimony resistance and treatment failures are now common in the Indian subcontinent and other areas. In South America, and other areas where pentavalent antimony failures are infrequent, either Glucantime or Pentostam is given at a dose of 20 mg of

pentavalent antimony/kg body weight/day IV or IM for 28 days.

When relapses occur, they are usually observed within the first 6 months. They can be treated with a second course of the same drug or an alternative therapeutic regimen. Relapses are particularly common and toxicity greater with pentavalent antimony in persons with AIDS. Liposomal amphotericin B is the treatment of choice. It is important to optimize antiretroviral therapy. Suppressive antileishmanial therapy has also been used in those with AIDS, but there have been no controlled trials to suggest the optimal drug or regimen. Persons with visceral leishmaniasis in the developing world are severely wasted when they present and die from secondary bacterial or viral infections. Attention should focus on addressing their nutritional needs as well as treating secondary bacterial infections with appropriate antibiotics.

The emergence of pentavalent antimony resistance in India and other areas stimulated the search for new drugs. Miltefosine, a phosphocholine analog that is administered orally, is FDA-approved for the treatment of visceral leishmaniasis due to *L. donovani* in India and adjacent areas. Gastrointestinal effects are a problem but have not prevented the completion of therapy in most study patients. The drug is embryotoxic and contraindicated in pregnancy and breastfeeding. Resistance has been reported. Studies now underway should determine its role in the treatment of visceral leishmaniasis in Latin America and elsewhere.

Cutaneous leishmaniasis typically has a self-resolving course and is rarely life threatening. If lesions are small, few in number, cosmetically inconsequential, and not caused by *Leishmania* species associated with mucosal disease, they can be followed expectantly if there is evidence of self-healing or the lesions may be treated locally. Options include thermal therapy where it is available, cryotherapy for very small lesions, or topical administration of paromomycin (15%) in an effective vehicle. Intralesional injections with Pentostam have been used for uncomplicated Old World leishmaniasis, but the drug is currently available only for systemic administration in the United States. The choice of treatment depends on the infecting *Leishmania* species; the number, location, and size of the skin lesions; and the availability of the therapeutic modality. None of these are FDA approved. Cutaneous lesions respond slowly to any form of therapy and often take weeks to epithelialize. The result is typically an atropic, burn-like scar.

When lesions are large, cosmetically significant, or caused by *L.* (*V.*) *braziliensis* or related New World species associated with mucosal leishmaniasis, systemic oral or parenteral treatment is advisable. There are several options, but only miltefosine is FDA approved, and then only for *L. braziliensis* and two other New World species.

Historically, either Pentostam or Glucantime, 20 mg of pentavalent antimony/kg/day, for 20 days was used, but it is associated with substantial toxicity. Oral fluconazole has been effective in some settings. Fluconazole, 200 mg/day for 6 weeks, resulted in a high response rate in persons with cutaneous leishmaniasis due to *Leishmania major*, but *L. major* infections often heal spontaneously in a matter of weeks to months without treatment. While fluconazole at 200 mg/day has failed in other settings, persons infected with *L. braziliensis* have been successfully treated with high-dose fluconazole (8 mg/kg daily for 4–6 weeks) in northeastern Brazil. Amphotericin B deoxycholate and liposomal amphotericin are often effective, but costly and potentially toxic alternatives. Pentamidine has activity against *Leishmania* species, but its toxicity precludes its use for cutaneous leishmaniasis.

Persons with mucosal leishmaniasis are often treated initially with Pentostam or Glucantime, 20 mg of pentavalent antimony/kg/day for 28 days, usually in combination with pentoxifylline; failures and relapses are common. Alternatives include liposomal amphotericin B, amphotericin B deoxycholate, and miltefosine. Plastic surgical repairs in persons with mucosal lesions should be delayed for 12 months to ensure clinical cure because grafts may be lost if a relapse follows surgery.

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203. Intestinal protozoa

Paul Kelly

Intestinal protozoal infection produces substantial morbidity and mortality in people of all ages, particularly in tropical and subtropical parts of the world. Amebiasis, giardiasis, cryptosporidiosis, and those infections associated with acquired immunodeficiency syndrome (AIDS) are important problems for health in many parts of the world, but some protozoa found in the human digestive system do not cause disease. Vaccines are not yet available for protection against these infections, and many are difficult to treat. The intestinal protozoa that produce important human infections are summarized in Table 203.1. There are differences between protozoa in their impact in patients with AIDS: cryptosporidiosis is an AIDS-defining infection, but neither the incidence nor the severity of amebiasis or giardiasis are affected by HIV.

Table 203.1 Intestinal protozoa

The sarcodina (amebae)	Pathogenic Nonpathogenic	*Entamoeba histolytica* *Entamoeba dispar* *Entamoeba moshkovskii* *Entamoeba chattoni* *Endolimax nana* *Iodamoeba butschlii* *Dientamoeba fragilis*
The mastigophora (flagellates)	Pathogenic Nonpathogenic	*Giardia lamblia* *Trichomonas hominis* *Chilomastix mesnili* *Embadomonas intestinalis* *Enteromonas hominis*
The ciliophora		*Balantidium coli*
The coccidia		*Cryptosporidium parvum* *Isospora belli* *Sarcocystis* species *Cyclospora cayetanensis*
The microspora		*Enterocytozoon bieneusi* *Encephalitozoon intestinalis*
Stramenopile		*Blastocystis hominis*

ENTAMOEBA HISTOLYTICA

Entamoeba histolytica causes dysentery, chronic colonic amebiasis, and hepatic amebiasis. The last topic is dealt with in Chapter 204, Extraintestinal amebic infection. Amebic dysentery is a syndrome of bloody diarrhea caused by invasion of the colonic wall by trophozoites of *E. histolytica*. It is common in many parts of the world, especially West and southern Africa, Central America, and south Asia. In the United States, 3000 to 4000 cases are reported each year. There is now consensus that the species formerly recognized as *E. histolytica* in fact comprises two species: *E. histolytica* and *Entamoeba dispar*. The first is the pathogenic protozoan long associated with human invasive disease and with hepatic amebiasis, and the latter is a morphologically identical nonpathogenic protozoan first recognized as the nonpathogenic zymodeme of *E. histolytica*. The latter does not require treatment, but it cannot be differentiated from *E. histolytica* morphologically. Diagnosis of invasive amebiasis is achieved by the identification of hematophagous trophozoites in very fresh stool smears or in colonic biopsies; the latter may also show typical flask-shaped ulcerations. Serologic testing using an immunofluorescent antibody test is now an important contribution to the diagnosis of a seriously ill patient, particularly in distinguishing colonic dilation resulting from amebiasis from that caused by ulcerative colitis. Serology does not distinguish between *E. histolytica* and *E. dispar*. Diagnosis using the polymerase chain reaction (PCR), which detects specific DNA sequences of genetic material, is increasingly available, and it does allow species identification.

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Table 203.2 Drug treatment of amebiasis

		Adult dosage	Child dosage
Tissue infection			
First choice	Metronidazole[a]	750 mg TID for 10 d	50 mg/kg/d for 10 d[b]
	Tinidazole[a]	2 g/d for 3 d	60 mg/kg/d for 3 d
Second choice	Nitazoxanide	500 mg BID for 3 d	Age 2–3 years: 100 mg BID; age 4–11 years: 200 mg BID for 3 d
	Paromomycin	30 mg/kg/d for 10 d[b]	30 mg/kg/d for 10 d[b]
Luminal carriage			
First choice	Diloxanide furoate	500 mg TID for 10 d	20 mg/kg/d for 10 d[b]
Second choice	Paromomycin	30 mg/kg/d for 10 d[b]	30 mg/kg/d for 10 d[b]

[a] Must be followed by eradication of luminal carriage.

[b] In three doses.

Treatment of invasive amebiasis is shown in Table 203.2. Treatment can be divided into two stages: (1) eradication of tissue forms with metronidazole, tinidazole, or nitazoxanide and (2) eradication of luminal carriage with diloxanide furoate. Dehydroemetine and iodoquinol, used formerly for the treatment of amebiasis, are toxic and no longer used.

Intestinal amebiasis may be complicated by acute toxic colitis, presenting in a similar manner to the dilation of acute severe ulcerative colitis. The patient will be febrile and unwell, sometimes with signs of peritoneal irritation, and a plain abdominal radiograph will indicate dilation. Intravenous fluids must be given, the patient starved, and metronidazole and a third-generation cephalosporin given intravenously. Worsening dilation of the colon or perforation will necessitate surgery, but in the event of perforation, the outcome is poor. If treatment with metronidazole is started early in patients with severe amebic colitis, medical management should nearly always suffice, but surgery should not be delayed if perforation is impending.

Chronic amebiasis may be difficult to distinguish from intestinal tuberculosis or Crohn's disease but responds to metronidazole and diloxanide as above. Surgery is sometimes necessary because stricturing may persist.

GIARDIA LAMBLIA

Giardia lamblia infection, first recognized by Van Leeuwenhoek in 1681, is a cause of acute and persistent diarrhea and possibly malnutrition in children in many tropical and subtropical countries. It is also a well-recognized cause of travelers' diarrhea. In many cases it is self-limiting, but the course may be prolonged in immunoglobulin deficiencies. Asymptomatic infection is common. Diagnosis is by stool microscopy, although when this is negative and the clinical suspicion is strong, trophozoites may be detected in small intestinal fluid and mucosal biopsy specimens obtained by endoscopy (Figure 203.1). Fecal *Giardia* antigen enzyme-linked immunosorbent assays (ELISA) and PCR are now increasingly used in many routine diagnostic laboratories.

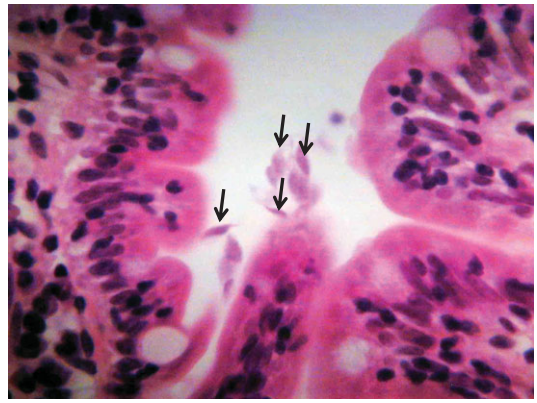

Figure 203.1 Trophozoites of *Giardia lamblia* in the lumen in a small intestinal biopsy (6-mm section stained with hematoxylin and eosin).

Several drugs are now available for the treatment of giardiasis but none are regarded as safe in pregnancy, and treatment failures are not uncommon, requiring a second and sometimes a third course of therapy. Five classes of chemotherapy are available (Table 203.3): nitroimidazoles (metronidazole and tinidazole), benzimidazoles (albendazole, secnidazole), nitazoxanide, nitrofurans (furazolidone), and paromomycin, which is the treatment of choice in pregnancy as it is not absorbed. If single agents fail repeatedly, combination therapy may be

Table 203.3 Drug treatment of giardiasis

Drug	Adult dosage	Child dosage	Efficacy
Metronidazole	500 mg TID for 3 d	5 mg/kg TID for 10 d (maximum 750 mg daily)	>90%
Tinidazole	2 g single dose	75 mg/kg single dose	>90%
Albendazole	400 mg daily for 5 d		>85%
Nitazoxanide	100–200 mg 2× daily		85%
Furazolidone	100 mg QID for 10 d	2 mg/kg TID for 10 d	>80%
Paromomycin	500 mg 3× daily for 5–10 d		

Table 203.4 Treatment of ciliophora, coccidia, and microsporidia

Organism	Drug regimen
Ciliophora	
Balantidium coli	Tetracycline, 500 mg QID for 10 d
Coccidia	
Cryptosporidium parvum	Nitazoxanide, 500 mg 2× daily for 3 d
Isospora belli	Trimethoprim–sulfamethoxazole, 1 DS tab PO QID for 10 d; Prophylaxis: 1 DS tab 3×/week
Sarcocystis species	As for *I. belli*
Cyclospora cayetanensis	Trimethoprim–sulfamethoxazole, 1 DS tab PO BID for 7 d
Microsporidia	
Enterocytozoon bieneusi	Fumagillin, 60 mg daily for 14 d
Encephalitozoon intestinalis	Albendazole, 400 mg BID for 14 d
Blastocystis hominis	The status of this organism as a pathogen is still the subject of controversy, so it is uncertain whether it requires treatment. It is our practice to attempt eradication with metronidazole, 750 mg TID for 10 d, when there are gastrointestinal symptoms and no other cause is apparent

tried, but there are few controlled data to guide drug choice, dose, or duration.

BALANTIDIUM COLI

Balantidium coli infection manifests as a severe, sometimes life-threatening, colitis indistinguishable from amebic dysentery. It is uncommon but occurs in Central and South America, Iran, Papua New Guinea, and the Philippines, usually in communities that live in close proximity to pigs, which are an important reservoir. Diagnosis is made by identification of the large trophozoites in feces or in rectal biopsies. Treatment is with tetracycline, 500 mg four times daily for 10 days (Table 203.4). Metronidazole and paromomycin are alternatives.

CRYPTOSPORIDIOSIS

Infection with *Cryptosporidium parvum* or *Cryptosporidium hominis* is likely to present as acute, self-limiting watery diarrhea in children or in travelers or as a waterborne epidemic. Most episodes require no specific therapy, but attention to fluid and electrolyte balance is important. Cryptosporidiosis is associated with persistent diarrhea, even in apparently immunocompetent children, and in human immunodeficiency virus (HIV)-infected individuals often persists until death. Cryptosporidiosis is also common in malnourished children in the tropics, irrespective of HIV infection. In patients with HIV-related diarrhea, cryptosporidiosis can be found in 10% to 30% of cases in industrialized countries and 10% to 40% of cases in tropical populations. However, since the introduction of highly active antiretroviral therapy (ART) with multidrug regimens, this infection is much less frequent in those regions where ART programs have been scaled up. It remains a significant clinical challenge in patients in the tropics, where patients often present with advanced AIDS or compliance is often poor. Diagnosis is usually made by microscopy of fecal smears using a modified Ziehl–Neelsen stain, which reveals the red-staining 5-μm oocysts, but ELISA and PCR tests are being adopted (Figure 203.2).

Although many drugs have been tried, only two have been shown to have any value in controlled trials: paromomycin and nitazoxanide. Hyperimmune bovine colostrum is a form of passive immunotherapy but is not in clinical use. Paromomycin (30 mg/kg/day in three doses)

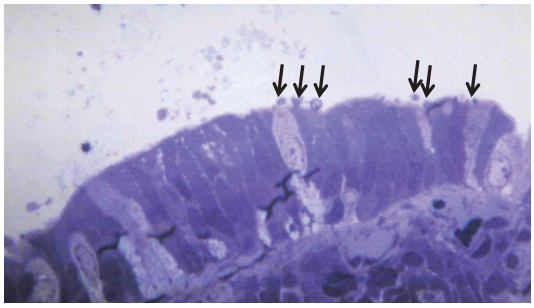

Figure 203.2 *Cryptosporidium* sp. trophozoites in small intestinal mucosa of an AIDS patient (semi-thin section stained with toluidine blue).

has been found to be of very limited efficacy. Nitazoxanide (1 g twice daily for 14 days) has been demonstrated to be effective in children and adults without AIDS in randomized controlled trials. Uncontrolled data from the US compassionate use program indicate that prolonged courses of 500 to 1500 mg nitazoxanide twice daily can be useful, but meta-analyses do not confirm this. There is still an urgent need for drugs which are effective in the severely immunocompromised host, and new drugs are in development. Interestingly, there is direct evidence that cryptosporidiosis can be prevented by simple measures: intensive hand washing reduced diarrheal disease, including cryptosporidiosis, in American AIDS patients, but to the author's knowledge this finding has not been replicated in a tropical setting.

ISOSPORA BELLI

Isospora belli is uncommon in industrialized countries but may be found in up to 40% of patients with HIV-related diarrhea in Africa. In HIV-infected individuals it causes a clinical syndrome of persistent diarrhea and wasting, which is indistinguishable from that attributed to other intracellular enteropathogenic protozoa (*C. parvum*, microsporidia). There were reports of isosporiasis before HIV infection appeared. Diagnosis rests on the identification in fecal smears of elongated, large sporocysts, which appear red with the modified Ziehl–Neelsen stain.

Trimethoprim–sulfamethoxazole (TMP–SMX) has been reported to be effective at a dosage of 160/800 mg four times daily for 10 days. In patients with AIDS, this needs to be followed with the same drug in a dose of 160/800 mg three times weekly indefinitely as prophylaxis against recurrence. Otherwise, recurrence is seen in 50% of patients with HIV infection at 2 months. An alternative drug is sulfadoxine–pyrimethamine (500/25 mg weekly) as secondary prophylaxis. Patients intolerant of sulfonamides could be given diclazuril, but only anecdotal evidence of its efficacy is available. In the author's experience it does not respond to nitazoxanide.

SARCOCYSTIS SPECIES

Sarcocystis infection, which may give rise to a persistent diarrhea, is treated in the same way as *I. belli*. This infection is uncommon.

DIENTAMOEBA FRAGILIS

Most infections with *Dientamoeba fragilis* are asymptomatic and do not require treatment. When required, treatment is as for amebiasis.

CYCLOSPORA CAYETANENSIS

Cyclospora cayetanensis is a newly recognized enteropathogen that causes travelers' diarrhea (especially in travelers to South America and Nepal) and foodborne outbreaks. In fecal smears, the oocysts resemble those of *C. parvum* in taking up carbol fuchsin in the modified Ziehl–Neelsen stain, but the oocysts are larger than *C. parvum* at 8–10 μm and they autofluoresce. Eradication is achieved using TMP–SMX (160/800 mg twice daily) for 7 days. If infection persists, then TMP–SMX should be continued for a further 3 to 5 days. In patients who are intolerant to TMP–SMX, ciprofloxacin can be used but it is less effective.

MICROSPORIDIA

Two microsporidia are pathogenic in the human gastrointestinal tract: *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis* (formerly known as *Septata intestinalis*). These organisms have recently been reclassified and are actually fungi, but we consider them here as their clinical manifestations are so similar to intracellular protozoal infections such as cryptosporidiosis and isosporiasis. They are intracellular parasites, which generally infect severely immunocompromised individuals. The most common manifestation is a persistent diarrhea associated with weight loss, but a syndrome of sclerosing cholangitis is also described. Diagnosis relies on detection of the parasite in duodenal biopsies obtained at

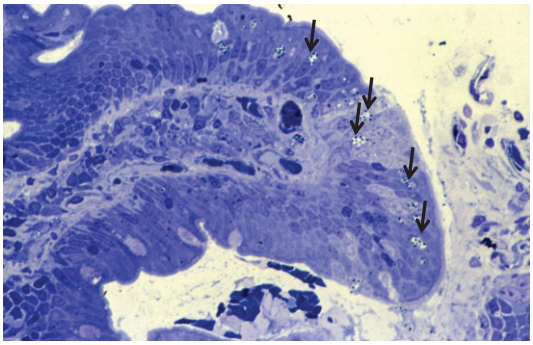

Figure 203.3 *Encephalitozoon intestinalis* in a small intestinal biopsy of an AIDS patient (semi-thin section stained with toluidine blue).

endoscopy (Figure 203.3) or on the finding of the spores in the feces using a variety of stains. *Encephalitozoon intestinalis* may cause a disseminated infection with renal spore excretion.

Treatment of *E. intestinalis* infection is with albendazole, 400 mg twice daily for 1 month, but maintenance treatment may be needed if relapse occurs following the cessation of therapy, although eradication may be achieved in some patients. *E. bieneusi* infection responds much less well, but fumagillin, 60 mg daily for 14 days, results in symptomatic improvement and parasite clearance in some patients. Fumagillin is toxic.

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204. Extraintestinal amebic infection

Robert Huang and Sharon L. Reed

Extraintestinal manifestations of invasive amebic disease, although far less common than amebic colitis, are still a significant cause of morbidity and mortality worldwide, accounting for approximately 50 000 deaths annually. The most common presentation, amebic liver abscess, can be diagnosed clinically by its characteristic presentation in conjugation with appropriate epidemiologic risks and supported by serologic, antigen-based, or molecular testing. Without treatment, amebic liver abscess is almost always fatal, but with prompt and appropriate therapy, a cure is predictable. Other, more rare, manifestations of invasive amebiasis also occur and will be discussed as well. The foundation of successful invasive amebiasis treatment has been metronidazole or the more recently US Food and Drug Administration (FDA)-approved and structurally related agent, tinidazole.

AMEBIC LIVER ABSCESS

In addition to amebic colitis and its complications, extraintestinal manifestations of invasive *Entamoeba histolytica* infections can occur, led in frequency by amebic liver abscesses. An estimated 10% of the worldwide 40 to 50 million symptomatic amebic infections will either present as or be complicated by amebic liver abscess. Adult men are 7 to 10 times more likely to have amebic liver abscess than women, but there is no difference between the sexes in children. The different gender rates in adults are likely to be due to the protective effects of estrogen in women as suggested by animal models. As with other invasive amebic infections, amebic liver abscesses occur predominantly in the developing world with endemic disease seen in Central and South America, Africa, and Asia. A single amino acid substution in the leptin receptor has been linked to a 4-fold increase in susceptibility to invasive amebiasis, a genetic polymorphism which is overrepresented in many of the endemic countries. Travelers to countries with endemic disease are at risk for developing amebiasis and liver disease. Longer stays are associated with increased risk; however, liver abscesses have been reported in visitors with exposure as short as 4 days. Men who have sex with men (MSM) are an at-risk population in developed countries as the overall risk of intestinal amebiasis is greater in this group versus the general population. Finally, those with cell-mediated immune defects including chronic steroid users, pregnant women, alcoholics, the malnourished, and those with malignancy may also be at increased risk of invasive *E. histolytica* infection and subsequent liver abscess.

The clinical presentation of amebic liver abscesses has been well described in several large reviews. Fever and right upper quadrant pain are the most frequent complaints and also the most consistent findings on examination (Table 204.1). The duration of disease influences the symptoms, as patients with symptoms for more than 2 weeks tend to be afebrile and have weight loss and more focal abdominal pain. The classic finding of point tenderness in the right upper quadrant or intercostal tenderness has been frequently noted in earlier literature but is likely neither sensitive nor specific. At most,

Table 204.1 Clinical findings for patients with amebic liver abscess

Clinical findings	%
Fever	85%–90%
Right upper quadrant pain	84%–90%
Hepatomegaly	30%–50%
Weight loss	33%–50%
Diarrhea	20%–33%
Cough	10%–30%
WBC count >12 000/μL	80%
Elevated level of alkaline phosphatase	70%

Abbreviation: WBC = white blood cell.
From Petri and Singh. *Clin Infect Dis.* 1999;29:1117–1125.

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only about one-third of patients have concomitant diarrhea or dysentery within the few weeks prior to their symptoms.

Approximately 80% of the liver abscesses are found in the right lobe of the liver, thus explaining the location of pain. The pain may also be located in the epigastrium, right lower chest, or the right shoulder tip (referred pain). Left-sided abdominal pain, corresponding to an abscess in the left lobe of the liver, is less common. Localized swelling or generalized hepatomegaly may be noted on exam depending on the size and location of the abscess or abscesses. Abscesses high in the right lobe of the liver may not result in hepatomegaly but, if of significant size, can lead to elevation of the right hemidiaphragm, which is evident on a chest radiograph.

Laboratory findings in a patient with amebic liver disease include leukocytosis (white blood cell [WBC] count $>12\,000/mm^3$), an elevated alkaline phosphatase, and, occasionally, elevated transaminases. It is uncommon to see an elevated bilirubin, and thus jaundice in a febrile patient with right upper quadrant pain should point the clinician toward another diagnosis. A mild degree of anemia (anemia of chronic disease) is present in many cases, particularly with symptoms for more than 2 weeks.

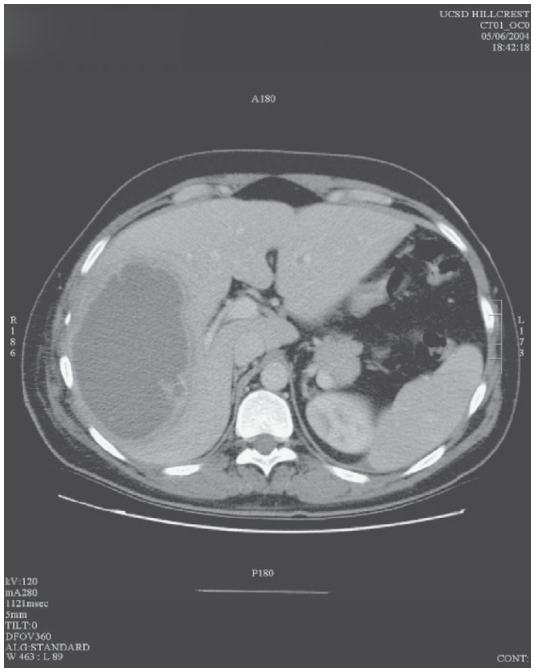

Figure 204.1 Contrast computed tomography (CT) scan image of an amebic liver abscess. The abscess appears as a hypoattenuating mass within the right lobe of the liver with an irregular, multiseptated rim with a thin rim of surrounding edema.

Diagnosis

Aspiration of a liver abscess is usually only indicated to rule out a pyogenic abscess or to prevent potential rupture as described below. Thus, the diagnosis of an amebic liver abscess is made in a patient with appropriate clinical symptoms, epidemiologic risk factors, and characteristic imaging findings confirmed by a positive serologic, antigen, or molecular test. Serologic testing for antibodies to *E. histolytica* is >80% sensitive in disease more than 1 week old, and nearly 99% sensitive in recovering patients. A negative test essentially rules out the diagnosis except in early infection (≤1 week). It is important to use an enzyme immunoassay (EIA) or agar gel dilution to test serology as an indirect hemagglutination often remains positive for years at high titer, and residents of an endemic region may have positive antibodies to *E. histolytica* that do not represent acute disease. Serum antigen detection tests to the *E. histolytica* Gal/GalNAc lectin gave a positive result in >95% of patients with amebic liver abscess in a study in Bangladeshi patients prior to treatment, comparing favorably to currently available serum antibody tests. Importantly, after treatment with metronidazole, circulating antigen levels were rarely detected (15%), making the test potentially useful for the diagnosis of acute disease in endemic countries. Molecular diagnosis using polymerase chain reaction (PCR) assays are highly sensitive and specific but remain primarily a research tool for the near future.

A number of imaging modalities are useful in supporting the diagnosis of amebic liver abscess. Chest radiographs in approximately 50% of patients with liver abscesses demonstrate an elevated right hemidiaphragm or other abnormality such as discoid atelectasis. Ultrasonography, computed tomography (CT) scanning, and magnetic resonance imaging (MRI) are all quite sensitive; however, the availability of these studies in amebiasis endemic areas is often limited. In the majority of cases, imaging demonstrates a single round or oval, homogeneous, hypoechoic lesion. Low-attenuation lesions with septations or an observable fluid level or debris may also be seen (see Figures 204.1 and 204.2). Unfortunately, although gallbladder and ductal abnormalities are seen more often in pyogenic liver abscess, there are really no specific radiographic features distinguishing

Table 204.2 Drug treatment of amebic liver abscess[a]

Drug of choice	Adult dose	Pediatric dose	Side effects
Metronidazole	750 mg IV/PO TID × 7–10 d	35–50 mg/kg/d in 3 doses × 7–10 d	Common: nausea, vomiting, metallic taste Occasional: peripheral neuropathy, vertigo, seizures, encephalopathy Disulfiram effect: nausea, vomiting with alcohol ingestion
Tinidazole[b]	2 g IV/PO qd × 5 d	60 mg/kg/d (maximum 2 g) × 5 d	Similar side effect profile as metronidazole: better tolerated with less nausea and vomiting

[a] All treatments should be followed by luminal amebicidal agent, described in text and detailed in Chapter 203, Intestinal protozoa.

[b] Used only as alternative to metronidazole.

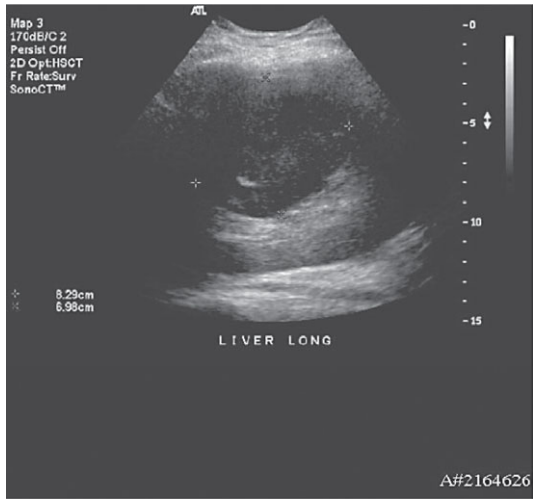

Figure 204.2 Ultrasound of the same amebic liver abscess as Figure 204.1.

pyogenic from amebic liver abscesses; therefore, imaging only serves as an aid to confirming the clinical suspicion of an intrahepatic process.

Aspiration of a liver abscess for the purpose of diagnosis is not generally recommended except in cases where immediate exclusion of a pyogenic abscess is clinically warranted. The classic gastronomic description of amebic pus as "anchovy paste" or "chocolate sauce" refers to the thick, acellular, proteinaceous debris consisting of necrotic hepatocytes and few polymorphonuclear cells obtained by successful aspiration. Amebic trophozoites are magenta colored by periodic acid–Schiff staining, making them easy to visualize, but finding trophozoites in an aspirate only occurs in 20% to 30% of cases, with a higher yield from the edge of the abscess.

The differential diagnosis of amebic liver abscesses includes pyogenic abscess, hepatocellular carcinoma, especially with necrosis, and echinococcal cyst. On imaging, the differential can often be narrowed to pyogenic abscess versus amebic liver abscess, with the clinical and radiographic findings being largely indistinguishable. Some epidemiologic differences may help to increase the likelihood of pyogenic liver abscess: age >50 years old, no sex predominance, underlying diabetes mellitus, biliary disease, and lack of travel to an endemic country. Nevertheless, these clues do not rule out amebic liver abscess, especially in a patient living in an endemic country.

Treatment

The treatment of amebic liver abscess worldwide has relied on the effective tissue amebicide, metronidazole. Metronidazole, a nitroimidazole compound, has been demonstrated in a number of trials to be effective in a dose of 750 mg three times daily for 7 to 10 days for adults and 35 to 50 mg/kg/day in three doses for 7 to 10 days for children (Table 204.2). Metronidazole is generally well tolerated but the disulfiram-like reaction to alcohol is important to mention to patients. Minor side effects such as nausea, vomiting, anorexia, and a metallic taste occur more frequently than rare neurologic adverse effects such as vertigo, seizures, and encephalopathy. The drug should be discontinued if these latter effects or, rarely, neutropenia occur. Long-term use of metronidazole is also known to cause peripheral neuropathy, but the duration of therapy for invasive amebic disease should not approach that at which this adverse event occurs.

The related imidazole compound, tinidazole, has been reported as effective as a single 2-g dose for treatment of liver abscess in South Africa. Tinidazole has now been approved by the FDA

after its use for years in other countries. The recommended dose for amebic liver abscess is 2 g/day for 3 to 5 days in adults and 50 mg/kg/day for 3 to 5 days in children. It is generally better tolerated than metronidazole and offers a shorter course; however, it is more expensive and less well studied. The imidazoles are more than 90% effective in the treatment of amebic liver abscess. Although clinical cases of resistance have been demonstrated in the related protozoa, *Giardia lamblia*, and resistance can be demonstrated in vitro, no clinical cases of metronidazole-resistant amebiasis have been documented. Treatment with these agents typically results in defervescence, decreased abdominal pain, and normalization of the WBC count within 3 days.

Therapeutic aspiration of amebic liver abscesses is now typically reserved for several specific circumstances. Disease not responding to 3 to 5 days of medical therapy with persistent fever or pain, imminent rupture of an abscess >15 cm, or a left lobe abscess that may rupture into the pericardium have all been cited as reasons to drain abscesses. Blind needling of the liver for the purposes of diagnosis or treatment is dangerous and ultrasonographic or CT-guided aspiration is recommended in all instances when available.

All treatment regimens with a tissue amebicide should be followed by treatment with a luminal amebicide to eliminate intestinal carriage of the organism that could lead to relapse if not treated. Paromomycin, a nonabsorbed aminoglycoside, taken for 7 days is the preferred luminal amebicide in the United States. It is safe in pregnancy, has minimal gastrointestinal side effects, and ototoxicity and nephrotoxicity rarely occur. Diloxanide furoate is also effective and well tolerated and has few side effects but is not commercially available in the United States. Iodoquinol is likewise effective but has some serious side effects such as optic neuritis and peripheral neuropathy, and requires a 20-day course. Nitazoxanide, a 5-nitrothiazolyl derivative, is active against a range of protozoa and is approved by the FDA for the treatment of diarrhea caused by *Cryptosporidium parvum* and *G. lamblia* in children. Its activity against *E. histolytica* has been demonstrated in vitro, and one double-blind, placebo-controlled trial suggested efficacy as well; however, it has not been directly compared to the standard luminal amebicides already mentioned.

The usual response to medical therapy of an amebic liver abscess is rapid resolution of fever and pain. There is no reason to get a follow-up ultrasound early in the course, as lesions may actually enlarge acutely, but they ultimately completely resolve within a year. Serology by EIA typically reverts to negative within 6 months.

AMEBIC PLEUROPULMONARY DISEASE

The most common pulmonary manifestation of invasive amebiasis is development of a serous, sympathetic effusion in the right pleural cavity due to a right-sided liver abscess. Rupture of a liver abscess into the chest cavity can lead to empyema, producing signs such as cough, dyspnea, and pleuritic chest pain. Thoracentesis will reveal the classic anchovy paste fluid described above. Classically, patients who develop bronchopleural fistula will expectorate the contents of the liver abscess. Although unpleasant, prior to amebicidal agents this occurrence was deemed a good prognostic sign, as it was an effective means of draining the abscess. In addition, hematogenous spread of amebic trophozoites can rarely cause disease in the lung parenchyma leading to consolidation and sometimes lung abscess. Treatment of pleuropulmonary disease involves the use of a tissue amebicide, such as metronidazole, and, in the case of empyema, drainage with a chest tube. Amebic pneumonia and lung abscesses from hematogenous spread are successfully treated with metronidazole alone.

AMEBIC PERICARDITIS

The most serious complication of a left-lobe amebic liver abscess is rupture into the pericardium leading to pericarditis and, potentially, cardiac tamponade. In one large series, the incidence of pericardial rupture was approximately 1% of all liver abscess cases. A left-lobe liver abscess threatening the pericardial sac may cause irritation and a serous effusion. The rapidity of leakage of amebic pus into the pericardial sac determines both the signs and symptoms that develop. A slow leak gives more insidious symptoms of gradually increasing shortness of breath, unmitigated fever, and patient deterioration, whereas a rapid rupture into the pericardium may cause cardiac tamponade and the associated chest pain, tachypnea, pulsus paradoxus, elevated neck veins, and hypotension.

The evaluation of amebic pericarditis begins with establishing the diagnosis of an invasive amebic infection with positive serologic testing in a patient with left-lobe liver abscess and a compatible epidemiologic history. An

electrocardiogram will show evidence of pericarditis, and chest radiography demonstrates an elevated and immobile left diaphragm. Confirming the diagnosis is only definitively accomplished by aspiration of the pericardium, which, along with effective tissue amebicides, is the treatment of choice. A concomitant large liver abscess should also be aspirated and repeat aspirations performed if needed to eliminate the risk of further pericardial accumulation. Fibrous constriction is unusual after the above treatment, and surgical treatment is unnecessary in most cases.

AMEBIC PERITONITIS

In about 2% of amebic liver abscesses, intraperitoneal abscess and peritonitis complicate the case. The associated physical exam findings of an acute abdomen are usually present. Compared to amebic peritonitis due to perforation of the colon from amebic colitis, patients with ruptured liver abscesses and peritonitis have better outcomes because there is not concomitant colonic bacterial flora contaminating the peritoneum. Treatment of amebic peritonitis due to liver abscess rupture is with metronidazole plus therapeutic paracentesis to drain infected collections.

OTHER MANIFESTATIONS OF INVASIVE AMEBIC DISEASE

Although very rare, amebic brain abscesses can occur by hematogenous seeding of trophozoites and may present with altered mental status, headache, and focal neurologic signs in a patient with known amebiasis. Computed tomography scanning of the head reveals often multiple space-occupying lesions, which, early in the course of disease, may be low-attenuation circumscribed areas without a clear rim or enhancement. Treatment involves an extended course of metronidazole, which has good central nervous system penetration, and possible surgical drainage depending on the size of the lesion(s) and severity of the symptoms.

Amebic splenic abscesses, also resulting from hematogenous spread of amebic trophozoites, can be visualized with ultrasound or CT scan and are treated medically with metronidazole. Splenectomy is occasionally required.

Urinary tract amebiasis, manifesting as perinephric abscesses, is again due to hematogenous spread of amebic trophozoites and treated with metronidazole. Genital amebiasis is more common in women than men, with vaginitis, vulvovaginal amebiasis, cervicitis, and salpingitis all having been reported. These cases may be sexually transmitted; consequently, ulcerative penile lesions in a sexual partner should be evaluated for possible amebiasis. Invasive carcinoma of the penis and carcinoma of the cervix are often initially suspected as the clinical appearance of the amebic ulcerative lesions mimics that of these malignancies. An epidemiologic study in Japan found a link between genital amebiasis and MSM engaging in anal sex with partners with amebic colitis. The treatment for these manifestations of the disease is again with metronidazole, and sexual partners should always be treated as well. Finally, cases of cutaneous amebiasis, presenting as painful ulcers, in both children and adults have also been described in the literature. These presentations are often, but not always, associated with intestinal amebiasis and respond to metronidazole.

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PART XXV

Antimicrobial therapy: general considerations

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205. Principles of antibiotic therapy

John S. Czachor

Over the last three decades, there has been the recognition of a very disturbing trend of antibiotic resistance amongst a wide variety of pathogens that are causing serious disease in patients residing in the community, in long-term care facilities, and in hospitals. Especially troublesome have been *Streptococcus pneumoniae* that may be resistant to penicillin and/or fluoroquinolones; *Staphylococcus aureus*, including all methicillin-resistant *S. aureus* (MRSA) variants, and rarely, those that may be resistant to vancomycin, linezolid, or daptomycin; *Enterococcus* spp. that are not susceptible to ampicillin, vancomycin, linezolid, or daptomycin; extended-spectrum β-lactamase-producing (ESBL) *Escherichia coli* and *Klebsiella pneumoniae* resistant to numerous agents; multidrug-resistant (MDR) *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, and *Acinetobacter* spp.; carbapenem-resistant *K. pneumoniae*, *E. coli*, and other Enterobacteriaceae; clindamycin-resistant *Bacteroides fragilis*; and *Mycobacterium tuberculosis* organisms resistant to all available drugs.

The pharmaceutical industry has responded to this grave concern and has developed a variety of agents, for example quinupristin–dalfopristin, linezolid, daptomycin, telavancin, and dalbavancin, which generally inhibit the growth of gram-positive bacteria; ceftaroline and ceftibiprole, which are cephalosporin class drugs that inhibit gram-positive organisms, including MRSA, and gram-negative bacteria; and tigecycline, which possesses inhibitory activity for a wide range of gram-positive, gram-negative, and anaerobic bacteria. As these antibiotics are used more frequently, it may be easier to precisely establish the indications for their use, their potential to cause toxicities and drug–drug interactions, and to identify *the* preferred agent for a specific infection.

Another event that has merited attention is the continuously evolving novel indications for antibiotics for both infectious and noninfectious disorders. The newer macrolides have anti-inflammatory properties, and their use in cystic fibrosis and emphysema continues to be delineated. The use of ampicillin combined with ceftriaxone has recently been championed to treat infective endocarditis caused by *Enterococcus faecalis* with high level reistance to aminoglycosides. Finally, there are a number of antimicrobial compounds that are prescribed for nonbacterial dermatologic conditions, such as dapsone for dermatitis herpetiformis.

When selecting an antibiotic, the clinician must reflect on a number of issues. Some of the more common factors that merit consideration include the patient's drug allergy history; the relative safety of the medication; the potential of the antibiotic to cause a significant drug–drug interaction; the mechanism of the drug's elimination from the body; the agent's historical "track record" in the therapy of the specific infection being treated; the route of administration of the antibiotic; and the cost of the medication. For the oral administration of antibiotics there are the additional concerns of patient compliance and adequate drug absorption.

PHARMACOKINETICS AND PHARMACODYNAMICS

The term pharmacokinetics refers to the disposition of an antibiotic throughout the human body. This encompasses such principles as absorption, bioavailability, distribution, protein binding, metabolism, and elimination. Pharmacodynamics refines the concept of pharmacokinetics by describing the interaction between the concentration of the antibiotic at the site of the infection over time and its subsequent effect on the infection itself. Pharmacodynamics is useful for establishing optimum dosing regimens. The absorption of most oral antibiotics occurs by passive diffusion in the small intestine. Some antibiotics, including

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vancomycin, aminoglycosides, and aztreonam, are not adequately absorbed when given orally. On occasion, this can be advantageous. Oral neomycin can be prescribed as a preoperative preparation prior to large bowel surgery or the treatment of hepatic encephalopathy, whereas the poorly absorbed oral vancomycin and fidaxomicin are used for the therapy of *Clostridium difficile*-related colitis. Other drugs, such as cefpodoxime proxetel and cefuroxime axetil, are administered as prodrugs to facilitate absorption. Food interferes with the absorption of some antimicrobials, for example, penicillin, ampicillin, cephalexin, tetracycline, and azithromycin.

A fundamental tenet of antimicrobial activity is that it must achieve therapeutic concentrations at the tissue source of the infection. Multiple factors influence the distribution of antibiotics from plasma to these sites: the nature of the capillary bed (those fenestrated by small pores versus those unfenestrated capillaries of the brain, leptomeninges, and vitreous humor), the lipid solubility, the degree of protein binding (as only unbound drug is antibacterially active and capable of diffusing across capillaries), and the presence of active transport pumps (located in the choroid plexus of the brain, retina, kidneys, and biliary ducts).

Antibacterial agents are eliminated from the body through hepatic and biliary excretion (ceftriaxone and piperacillin), hepatic metabolism (clindamycin, chloramphenicol, metronidazole, erythromycin, sulfonamides, some tetracyclines, isoniazid, rifampin, linezolid), and predominantly renal excretion (most penicillins and cephalosporins, imipenem, aminoglycosides, nitrofurantoin, most tetracyclines, ofloxacin, vancomycin, trimethoprim–sulfamethoxazole [TMP–SMX], daptomycin). It is essential that the clinician be aware of renal compromise from congestive heart failure, hypertension, diabetes, medication, and physiologic alteration with age, because this will mandate a dosage reduction for those compounds predominantly eliminated by renal excretion. The estimated glomerular filtration rate (GFR; using the Cockcroft–Gault equation or the Modification of Diet in Renal Disease [MDRD] equation) has traditionally been used to help determine appropriate drug doses for antimicrobials eliminated primarily by renal excretion when the measured creatinine clearance is not available. A newer formula, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), may be the best to estimate GFR.

Concentration-dependent antimicrobial agents function such that optimal bacterial killing occurs while the concentration of the antibiotic is above the minimum inhibitory concentration (MIC) of the organism. The aminoglycosides are one example of this type and are usually administered as once-daily dosing (unless prescribed for synergistic purposes), taking advantage of the observation that the ratio of the maximum peak drug concentration to organism MIC (8 to 12) correlates with clinical response. Other concentration-dependent antimicrobials include fluoroquinolones, daptomycin, and metronidazole. Alternatively, those compounds that are concentration independent or time dependent measure their success by the percentage of time the drug concentration exceeds the MIC of an organism. Drugs in this class include vancomycin, clindamycin, the macrolides, and the β-lactam group. There may be some benefit for continuous intravenous administration of the β-lactam antibiotics, thereby maintaining sustained drug levels above the MIC of the pathogen, particularly in the severely ill or immunocompromised patient.

The postantibiotic effect (PAE) is another pharmacodynamic concept that may impact antimicrobial choice. This refers to the persistent suppression of bacterial regrowth following limited exposure to an antibiotic and can be considered the time it takes for the organism to recover from this exposure. Classically, drugs that affect protein synthesis or nucleic acid synthesis, such as the fluoroquinolones, aminoglycosides, tetracyclines, macrolides, chloramphenicol, and rifampin, have significant PAEs against gram-negative organisms, although the only β-lactam antibiotics that share this property are the carbapenems.

SELECTION OF THERAPY

Table 205.1 delineates some of the more important host and drug features that influence antibiotic selection. Additional concerns relate to adherence to the therapeutic regimen and cost of the medication. Antibiotics that can be administered infrequently lend themselves to out-of-hospital administration. Daptomycin, ertapenem, televancin, and ceftriaxone can usually be infused as infrequently as once a day. Dalbavancin is a new once-weekly administered drug for skin and soft-tissue infections. The development of newer oral antimicrobial agents that can be given as infrequently as once or twice per day achieves

Table 205:1 Selection of therapy

Host factor	Special antibiotic concern
Drug allergy	Safety record
Site of infection	Success record
Pregnancy	Most likely organism(s) and
Epidemiologic information	susceptibility
Renal function	Bactericidal/bacteriostatic
Recent antibiotic exposure	Penetration into privileged sites
Infection acquisition	(CNS, endocardium)
(community/ECF/hospital)	Potential to cause major
Concomitant medication	untoward event

Abbreviations: CNS = central nervous system; ECF = extended care facility.

Table 205.2 Combination therapy

Tuberculosis
Disseminated *Mycobacterium avium* complex
Helicobacter pylori
Endocarditis (α-hemolytic streptococcus, enterococcus)
Life-threatening infection caused by *Pseudomonas aeruginosa*
Empiric treatment -Pneumococcal meningitis until susceptibility confirmed -Febrile, severely neutropenic host -Polymicrobic infection -Life-threatening infection with inapparent source

enhanced compliance. Compounds such as the fluoroquinolones, metronidazole, and linezolid have excellent absorption, resulting in high serum levels without the need for intravenous administration. Some medications, although still available, including chloramphenicol and erythromycin estolate, are infrequently prescribed, having fallen out of favor due to adverse effects, unfavorable pharmacokinetics and/or pharmacodynamics, or a limited spectrum of activity.

Antibiotic combinations are sometimes used to manage selected infections (Table 205.2). There are potential disadvantages, however, to the administration of antibiotic combinations such as increased untoward events, heightened costs, and suprainfection.

PRACTICE GUIDELINES AND ANTIBIOTIC STEWARDSHIP

In the past, with few exceptions, choosing an antibiotic has been left to the whims of clinicians. Seldom has the optimal duration of antibacterial treatment been defined by evidence-based medicine. Practice guidelines have emerged in response to questions regarding the quality, consistency, and the expense of medical care. Guidelines are generally created based upon the best available scientific evidence melded with expert opinion, cohesively assembled in a usable format for practitioners. Selected medical societies and organizations, as well as easily accessible websites, have become the repositories for the recommended information. Access to these guidelines has helped to transform how medicine is practiced today. Guidelines for various infectious conditions already exist, whereas others are being created and refined.

Just as important as the guidelines has been the recognition of the need for optimal, cost-effective, and rational use of antibiotics. Stewardship has evolved from guidelines to encompass antimicrobial utilization for all conditions and can be found in hospitals, long-term care facilities, long-term acute care facilities, ambulatory surgical centers, dialysis centers, and other medical settings. Institutions employing stewardship are coordinating interventions, often in conjunction with pharmacy assistance, to promote appropriate antibiotic selection, as well as their proper dose, duration, and route of administration. Benefits of antibiotic stewardship include improved clinical outcomes, reduced medical costs, fewer toxic and adverse effects, and decreased selection of antibiotic-resistant microorganisms.

SPECIAL POPULATIONS

The pregnant patient

Physiologic changes in the urinary tract and complications of parturition predispose the pregnant woman to urinary tract infections, as well as chorioamnionitis and endometritis. Antibiotic selection for the pregnant woman must take into consideration the potential for drug-induced toxicities for both the woman and her developing fetus. Animal studies and epidemiologic data (generated from pregnant women who were exposed to antibacterial agents because of clinical need) suggest that penicillins, including those in combination with a β-lactamase inhibitor, cephalosporins, aztreonam, erythromycin, azithromycin, clindamycin, and metronidazole have not demonstrated human fetal risk. Sulfonamides should be avoided late in pregnancy because of the potential to develop neonatal kernicterus. Chloramphenicol should not be administered to

Table 205.3 Adverse drug reaction

Drug	Untoward event
Aminoglycoside	Nephrotoxicity, ototoxicity
Amoxicillin–clavulanate (chronic administration)	Hepatotoxicity
TMP–SMX	Blood dyscrasias, hyperkalemia
Fluoroquinolone	Seizure
Doxycycline	Esophageal stricture/ulcer
Nitrofurantoin (chronic administration)	Pulmonary fibrosis, hepatitis, agranulocytosis

Abbreviation: TMP–SMX = trimethoprim–sulfamethoxazole.

Table 205.5 Drugs requiring dosage alteration during CRRT[a]

Amikacin	Penicillin
Ampicillin/sulbactam	Piperacillin
Cefazolin	Piperacillin–tazobactam
Ciprofloxacin	Ticarcillin–clavulanate
Daptomycin	Tobramycin
Gentamicin	TMP–SMX
Levofloxacin	Vancomycin

[a] Dose reduction as compared to normal renal function.
Abbreviations: CRRT = continuous renal replacement therapies; TMP–SMX = trimethoprim–sulfamethoxazole.

the mother near term as the newborn does not possess the appropriate liver enzyme to metabolize this drug, and hence the "gray baby" syndrome can result. The aminoglycosides gentamicin, tobramycin, and amikacin should not be administered to pregnant women, especially eclamptic women, unless there is a compelling reason. If they must be prescribed, serum concentrations must be monitored carefully.

The fluoroquinolones are not recommended for use in pregnancy because of their adverse effects on developing cartilage seen in animal studies. Tetracyclines are contraindicated in pregnant women because these compounds can interfere with normal development of teeth and bones in the fetus and have caused hepatorenal failure and death, particularly when administered intravenously to treat pyelonephritis, in pregnant women.

The elderly patient

There are a number of factors that distinguish the administration of antibiotics in elderly patients: concern about compliance with the medication because of poor memory, impaired vision, diminished hearing, or difficulty in opening child-resistant containers; the decrease of renal function with normal aging, and the need to make appropriate dosage adjustment of medications to prevent antibiotic-related toxicities; the potential for drug–drug interactions, as many geriatric patients take numerous medications daily; and the presence of concomitant medical disorders that can adversely influence antibiotic distribution and penetration. Elderly patients appear to experience adverse drug reactions from antibacterial compounds more frequently than younger patients do (Table 205.3).

Table 205.4 Drugs not requiring dosage alteration during continuous renal replacement therapies

Aztreonam	Linezolid
Azithromycin	Meropenem
Cefepime	Metronidazole
Ceftriaxone	Moxifloxacin
Clindamycin	Oxacillin
Doxycycline	Quinupristin–dalfopristin
Gatifloxacin	Rifampin
Imipenem	

ANTIBIOTIC USE IN CONTINUOUS RENAL REPLACEMENT THERAPY

For critically ill patients with infection, acute renal insufficiency often develops. Acute renal failure is associated with increased morbidity and mortality in patients with sepsis. Continuous renal replacement therapy (CRRT), an alternative to traditional hemodialysis and better tolerated by hemodynamically unstable patients, decreases the incidence of adverse biomarkers. Appropriate dosing of antimicrobial agents for patients receiving CRRT remains poorly defined, as the pharmacokinetics of drug removal in critically ill patients undergoing CRRT is complex. Those antibiotics with low protein-binding capacity and/or poor tissue penetration have enhanced removal. Mechanical or operational factors associated with CRRT play a role in antibiotic therapy in these patients as well, and increasing the blood flow or dialysate flow rate of CRRT may increase drug clearance. Tables 205.4 and 205.5 list antibiotic dose alterations for patients with CRRT.

ROUTE OF ADMINISTRATION

Antibiotics are administered intravenously when the patient has systemic perfusion issues (septic shock, hypotension), has bacterial infection at a

unique or protected site (e.g., leptomeninges, endocardium, a deep neck infection, epiglottitis, endophthalmitis, myopericarditis, mediastinitis, septic thrombophlebitis), has an infection that is imminently life endangering (e.g., meningococcemia, Rocky Mountain spotted fever, plague, bacteremia), has an infection that precludes oral administration because of nausea/vomiting or impaired function of the gastrointestinal tract (peritonitis, appendicitis, ascending cholangitis, pancreatic abscess), or has an infection that cannot be managed with an oral compound. Traditionally, physicians have prescribed an intravenous antibiotic simply because a patient was admitted to the hospital. However, the decision to hospitalize a patient does not automatically dictate that the antibacterial therapy must be administered intravenously. Unless one of the indications previously listed is present, some serious infections can be successfully managed by oral antibiotics.

ADVERSE REACTIONS

Antibiotic-induced untoward events are a concern not only because they result in host injury but also because these adverse events interrupt and complicate treatment, thereby requiring the administration of alternative and often more expensive and potentially toxic medication. Antibiotic-induced untoward events can also serve as a source of medical litigation.

Adverse events attributed to antibiotics are usually caused by three mechanisms: exaggerated response to the known pharmacologic effects of the drug, immunologic reactions to the drug or its metabolites, and toxic effects of the medication or its metabolites. Many of the antibiotic-related adverse events are initiated by an extension of the drug's normal pharmacology, and these events are often avoided by appropriate dosage adjustment.

In addition to the direct influence of the antibiotic, host factors such as genetic constitution, integrity of drug elimination mechanisms, and concomitant medical disorders can affect the frequency and severity of antibiotic-induced untoward events. For example, with human immunodeficiency virus (HIV)-infected patients, TMP–SMX causes more non-dose-related gastrointestinal intolerance, fever, and altered liver function, while ampicillin-induced rash is more common in those patients with infectious mononucleosis.

The penicillin family of drugs is usually well tolerated, but on occasion these drugs can cause hypersensitivity events, including fever, rash (maculopapular and urticarial), anaphylaxis, exfoliative dermatitis, erythema multiforme, serum sickness, and hemolytic anemia. When administered intravenously in high doses, particularly to patients with renal impairment, they have the potential to cause central nervous system toxicity, manifested by myoclonic jerks, seizures, and coma.

The most notorious side effects of clindamycin are diarrhea and *C. difficile*-related colitis. This drug has rarely caused drug fever, blood dyscrasias, and hepatotoxicity. Doxycycline has caused diarrhea and, on occasion, photosensitivity, rash, hepatitis, and, particularly in elderly patients, esophageal ulcerations and strictures.

Uncommon adverse events attributed to vancomycin include rash, fever, nephrotoxicity, ototoxicity, and reversible, transient hematopoietic toxicity. The most dramatic side effect is the red man syndrome, a nonimmunologically mediated reaction consisting of pruritis and erythema with or without hypotension, which appears to be dependent on dose, frequency of administration, and rate of infusion. With regard to the newer antibiotics designed to manage gram-positive infections caused by vancomycin-resistant organisms, quinupristin–dalfopristin can cause severe arthralgias and myalgias; chronic administration of linezolid has produced myelosuppression, optic neuropathy, and peripheral neuropathy; infusion of daptomycin has elicited myopathy and paresthesias/dysesthesias, and rarely, eosinophilic pneumonitis; and tigecycline has been associated with nausea, vomiting, and headache. Gastrointestinal symptoms are the most common untoward events attributed to the administration of the new semisynthetic lipoglycopeptide dalbavancin.

Rash, fever, and gastrointestinal adverse events are the most common side effects produced by TMP–SMX. Additional rare untoward events include nephrotoxicity, hyperkalemia, hematologic derangements (neutropenia, thrombocytopenia, agranulocytosis, aplastic anemia, megaloblastic anemia), hepatitis, and central nervous system events, including headache, insomnia, vertigo, ataxia, and aseptic meningitis.

Adverse events attributed to the macrolides have included nausea, vomiting, abdominal pain, diarrhea, and rarely antibiotic-associated colitis, pancreatitis, cholestatic jaundice, acute hepatitis,

and reversible ototoxicity. Azithromycin and clarithromycin have demonstrated the propensity to prolong the QTc interval, resulting in cardiac arrhythmias and sudden death.

The most common adverse events associated with the administration of the fluoroquinolones are gastrointestinal symptoms, nervous system toxicity (headache, dizziness, insomnia, agitation, hallucinations), and allergic reactions, including pruritis and rash. Rare adverse events attributed to the quinolones include seizures, elevation of liver enzymes, and tendinopathy. Administration of the fluoroquinolones has been associated with an increased risk of dysglycemia.

There has been renewed interest in the old antibiotic, polymyxin E (colistimethate sodium), as therapy for patients with life-endangering infections caused by drug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. This agent has the potential to elicit both neurotoxic side effects and nephrotoxicity.

ANTIBIOTIC ALLERGY

Antibiotic-induced allergic reactions are immunologically mediated and most commonly involve the skin as pruritus, a maculopapular eruption, or urticaria. More significant antibiotic-induced allergic reactions include erythema multiforme major (Stevens–Johnson syndrome), toxic epidermal necrolysis, exfoliative dermatitis, angioedema, and anaphylaxis. Antibiotic-induced allergic reactions are not confined to the skin: amoxicillin–clavulanate and macrolides have caused cholestatic liver injury, and high-dose administration of penicillins and cephalosporins have caused hemolysis and cytopenias.

Among the most feared allergic reactions to penicillins and cephalosporins are angioedema and anaphylaxis. These events are usually attributed to drug-specific immunoglobulin E (IgE) antibodies from prior drug administration, but these serious untoward events can also result from direct release of mast-cell mediators following the first dose of antibiotic. Vancomycin and fluoroquinolones can also cause direct mast cell release in the absence of drug-specific IgE antibodies. Skin testing has been very accurate for identifying penicillin-related IgE antibodies and for determining the risk for patients experiencing an immediate reaction (see Chapter 210, Hypersensitivity to antibiotics).

If a patient has a history of a presumed IgE-mediated reaction to a penicillin (angioedema, anaphylaxis), it may be best to avoid a cephalosporin, although rates of cross-reactivity are approximately 2% and the risk lessens as the compounds go from first generation to fourth generation. It is noteworthy to remember that any drug desensitization can be complicated by severe allergic reactions. Although structurally similar to the β-lactam antibiotics, aztreonam can be safely administered to patients who have experienced an anaphylactic reaction following the administration of a member of the penicillin family. It is considered potentially harmful to administer a carbapenem to patients with a history of immediate hypersensitivity to penicillins; however, recent investigation suggests that those patients with negative skin testing to imipenem–cilastatin can safely be offered this antibiotic.

DRUG–DRUG INTERACTIONS

Drug–drug interactions can be subtle or life-endangering, and they occur when one drug modifies the pharmacokinetics (absorption, distribution, metabolism, or excretion) or pharmacodynamics of another drug. Magnesium antacid reduces the absorption of nitrofurantoin, food diminishes the absorption of azithromycin, and antacids, sucralfate, ferrous sulfate, and zinc alter the bioavailability of oral tetracyclines and quinolones. Oral antacids lower the plasma concentrations of cefditoren. The angiotensin-converting enzyme inhibitor quinapril has a high concentration of magnesium, and it impedes the absorption of the quinolones. Suppression by oral tetracyclines, erythromycin, or TMP–SMX of upper intestinal bacteria that inactivate digoxin can result in digoxin-induced toxicity. Administration of doxycylcine has been associated with failure of oral contraceptive preparations. Alcohol ingestion in patients receiving metronidazole can result in a disulfiram-like reaction.

Drug–drug interactions have not been a major concern for patients receiving the penicillins, carbapenems, aztreonam, and the cephalosporins. Theophylline and cyclosporine can reduce the threshold for seizures in patients receiving imipenem, and meropenem decreases the serum concentrations of valproic acid to subtherapeutic levels in patients with seizure disorders. There is the potential for enhanced aminoglycoside-induced nephrotoxicity and/or ototoxicity when patients receive vancomycin, amphotericin B, cyclosporine, cisplatin, and ethacrynic acid.

Ciprofloxacin has the potential to inhibit the metabolism of theophylline through its effect on the enzymes of the cytochrome P450 system and

produce theophylline toxicity. Ciprofloxacin can also alter cyclophosphamide pharmacokinetics in patients with non-Hodgkin's lymphoma. There is a potential concern when fluoroquinolones are used to treat patients taking medications (antipsychotics, tricyclic antidepressants, and antiarrhythmics) that predispose to the development of torsades de pointes. Levofloxacin and moxifloxacin have been associated with enhancement of the effect of warfarin.

Macrolides are extensively metabolized by cytochrome P450 3A isozymes (CYP3A), and when these antibiotics are coadministered with medications that are strong inhibitors of CYP3A, such as azole antifungal drugs, diltiazem, verapamil, and protease inhibitors, sudden cardiac death can occur. Coadministration of sirolimus and erythromycin in transplant recipients increases the blood concentrations of the immunosuppressant. Clarithromycin is oxidized by the cytochrome P450 system, and this compound results in decreased clearance of those other agents given concurrently that are metabolized by the same enzyme system. Administration of clarithromycin to a patient taking a statin (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor) other than pravastatin can result in rhabdomyolysis. Coadministration of digoxin and clarithromycin can result in digitalis intoxication.

The serotonin syndrome (fever, agitation, mental status changes, myoclonus, and tremors) has been associated with the coadministration of linezolid and medications that increase concentrations of serotonin in the central nervous system, such as the selective serotonin reuptake inhibitors. If the patient's infection requires linezolid therapy, the selective serotonin reuptake inhibitor should be discontinued, and the patient monitored for the serotonin syndrome. Coadministration of TMP–SMX with phenytoin, glipizide, methotrexate, and thiazide diuretics has caused phenytoin toxicity, enhanced hypoglycemia, bone marrow suppression, and severe hyponatremia, respectively. TMP–SMX can enhance warfarin-induced anticoagulation and ganciclovir-induced bone marrow suppression, and it can diminish cyclosporine concentrations, resulting in a transplant rejection. Neutropenia and thrombocytopenia can occur in renal allograft recipients who receive azathioprine and more than 3 weeks of treatment with TMP–SMX. When prescribed to patients receiving a potassium-sparing diuretic, TMP–SMX has caused hyperkalemia.

Quinupristin–dalfopristin is a potent inhibitor of CYP3A4, and it should be used with caution when patients are receiving drugs that are substrates of 3A4, such as cyclosporine, nifedipine, protease inhibitors, and statins.

DRUG MONITORING

Monitoring the adequacy of antibiotic treatment involves the physician critically assessing the patient's response on a regular basis, as determined by the resolution of both the systemic and local inflammatory response and, in part, measured by results obtained from laboratory studies, microbiology data, and radiologic exams. In general, antibiotic concentrations in blood are not routinely measured. Aminoglycoside antibiotics are an exception, however, because serum concentrations of these compounds are performed to ostensibly reduce the risk of nephrotoxicity and ototoxicity and to ensure appropriate therapeutic levels. Better outcomes for treating patients with gram-negative bacteremia are noted if peak levels of gentamicin and tobramycin exceed 5 μg/mL and peak amikacin concentrations exceed 20 μg/mL. Avoiding elevated aminoglycoside levels may result in decreased ototoxic and nephrotoxic effects. Serial audiometric testing to assess ototoxicity should be considered for those patients receiving long-term administration of aminoglycosides and vancomycin. Some practitioners also measure vancomycin troughs to assist their choice of dosage interval and drug amount, and appropriate levels may reduce the incidence of ototoxicity.

Outpatient parenteral antibiotic therapy

Outpatient parenteral antibiotic therapy is designed either to avoid hospitalization or to continue treatment initiated in the hospital and to provide therapy that is therapeutically equivalent to the inpatient setting, while enhancing the patient's quality of life and achieving significant cost savings. The decision to initiate outpatient parenteral antibiotic therapy is influenced by the following factors: availability of an adequate oral treatment; the patient's clinical status and acceptance of this form of treatment; the home environment and support systems; the potential for treatment plan compliance; the availability of competent, professional follow-up; and the reimbursement status. Outpatient parenteral antibiotic therapy has been a safe and effective form of treatment for patients with a wide array of

infectious diseases, and antibiotics such as ceftriaxone, vancomycin, daptomycin, ertapenem, and aminoglycosides lend themselves to outpatient parenteral antibiotic therapy because these compounds can be administered infrequently. In addition to antibiotic-related adverse events, outpatient intravenous antibiotic infusion poses the risk of vascular access-related complications, such as venous thrombosis and catheter-related bloodstream infections.

Switch (step-down) therapy

The availability of numerous safe and effective oral antimicrobials that are well absorbed and can be administered infrequently provides the opportunity for switch or step-down therapy. This approach, available to the patient who has stabilized and appears to be "turning the corner," as manifested by resolution of fever with improved appetite and strength as well as the reduction of the signs and symptoms caused by the infection, has been successfully used to treat patients with the most commonly identified community-acquired infections. Switch therapy frees the patient from the inconvenience, discomfort, and risks of intravenous access, results in considerable cost savings, and permits earlier hospital discharge. Switch therapy requires patient compliance with the medication and adequate intestinal absorption of the antimicrobial, coupled with the appropriate follow-up from the clinician.

ANTIBACTERIAL PROPHYLAXIS

Appropriately administered antibiotic prophylaxis is the standard of care for patients who undergo selective surgical procedures. The ideal prescribed agent should cause minimal untoward events, should not select for virulent organisms, achieves adequate local tissue levels, is relatively inexpensive, demonstrates inhibitory activity for the bacteria anticipated to cause postoperative infection, and should be infused (usually 30–60 minutes before the surgery begins) so that therapeutic concentrations are present prior to the initial operative incision (see Chapter 114, Surgical prophylaxis).

In addition to their indication for the prevention of postoperative infections, antibacterial agents have been effective for the prevention (primary/secondary) of a number of nonsurgical disorders, including rheumatic fever, syphilis, travelers' diarrhea, tuberculosis, invasive meningococcal disease, pertussis, diphtheria, plague, and recurrent cystitis in women. Although no definite studies have confirmed that antibiotic prophylaxis provides protection against the development of endocarditis during bacteremia-producing procedures, it is currently recommended that patients with certain cardiac conditions receive antibiotic prophylaxis when subjected to selective dental, respiratory tract, gastrointestinal tract, and genitourinary tract bacteremia-producing procedures (see Chapter 113, Nonsurgical antimicrobial prophylaxis, and Chapter 37, Endocarditis of natural and prosthetic valves: treatment and prophylaxis).

ANTIMICROBIAL FAILURE

When a patient is not responding to antimicrobial therapy, there is a temptation to administer an alternative compound with an extended spectrum of activity. This approach is often valid, particularly for the seriously ill patient. It is essential, however, for the clinician to establish an accurate diagnosis, because noninfectious disorders often masquerade as infection. For example, hypersensitivity to an insect bite, acute gout, a fixed drug reaction, Lyme disease, necrotizing fasciitis, and anaerobic myonecrosis can initially resemble traditional bacterial cellulitis; Charcot joint in the diabetic simulates osteomyelitis; pulmonary infarction, lung cancer, acute respiratory distress syndrome, aspiration of gastric contents, drug-induced pneumonitis, and congestive heart failure can imitate an infectious pneumonia; and vasculitis can resemble endocarditis. There should be consideration given to those factors that have the potential to impede successful antibiotic treatment (obstruction, necrotic tissue, undrained abscess, or an infected prosthetic device), the possibility of a polymicrobic infection, the development of drug resistance or a superinfection, or infection in a "privileged site," such as meningitis, endocarditis, or chronic bacterial prostatitis, disorders that require antimicrobials with unique penetration properties.

The clinician should also consider drug compliance and adequacy of drug dosage and recognize that selective infections, such as bacterial endocarditis, bacterial meningitis, and life-threatening infections in granulocytopenic hosts, require a bactericidal antibiotic. An additional factor that can impact antibiotic treatment for patients is the recognition that numerous patients self-prescribe antibiotics prior to their first encounter with physicians. This practice can alter

the anticipated microbiologic cause, the manifestations of the infection, and the clinical response of the infection.

In addition to antibiotics, survival of seriously ill, hospitalized infected patients often requires early institution of adjunctive treatments. Therapies that merit consideration include vigorous fluid administration (goal-directed therapy), cardiovascular support with a vasopressor or an inotropic agent, oxygen delivery via lung-protective ventilation, and CRRT.

INAPPROPRIATE ADMINISTRATION

There are no convincing scientific data to support the administration of antibiotics to otherwise healthy patients who experience rhinitis and nonbacterial pharyngitis, laryngitis, acute bronchitis, or acute sinusitis. These infections are predominantly self-limited viral disorders. Antibiotic administration to these patients will serve only to add to healthcare-related costs, promote the spread of antibiotic-resistant organisms, and place patients at risk of adverse drug reactions. Additional disorders for which antibiotics are not indicated include witnessed aspiration pneumonia, colonized noninfected wounds, and asymptomatic bacteriuria, unless the latter condition is identified in a pregnant woman.

Antibiotic therapy is not appropriate treatment for the patient with persistent unexplained fever. These patients merit a thorough evaluation, consisting of a comprehensive medical history and physical examination, complemented with the judicious application of laboratory and radiographic studies. Empiric administration of an antibiotic to the patient with protracted fever may serve to obscure and/or delay the correct diagnosis and result in untoward drug-induced events.

When making decisions regarding the administration of antibiotics, clinicians should be guided by accurate susceptibility data for those clinically significant isolates recovered from appropriately collected specimens, as well as expert consultation, and evidence-based medicine as published in the practice guidelines.

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206. Antibacterial agents

Richard R. Watkins

The discoveries of penicillin by Fleming in 1928 and sulfonamides by Domagk in 1932 originated the modern era of effective antibacterial therapy. Since then, over a dozen different classes of antibacterial agents have been developed. This chapter describes the various antibacterial agents, emphasizing their mechanisms of action, clinical indications, and mechanisms of bacterial resistance (Table 206.1).

Table 206.1 Overview of antibacterial agents

Penicillins and monobactams
Cephalosporins
Carbapenems
Aminoglycosides
Quinolones
Tetracyclines
Macrolides
Glycopeptides, lipopeptides, and streptogramins
Oxazolidinones
Sulfonamides
Metronidazole and clindamycin
Rifamycins
Polymyxins
Miscellaneous agents
Chloramphenicol
Nitrofurantoin
Pivmecillinam
Fosfomycin
Topicals

PENICILLINS AND MONOBACTAMS

The core structure of the penicillins consists of a thiazolidine ring attached to a β-lactam ring and an R-group side chain. The thiazolidine–β-lactam ring provides antibacterial activity, while the side chain determines the antimicrobial spectrum and pharmacologic characteristics. Penicillins are bactericidal agents that inhibit penicillin-binding proteins (PBPs), which are involved in the synthesis of peptidoglycan. PBPs vary in their concentrations among bacteria and in their binding affinity for β-lactam antibiotics. This largely explains why β-lactam antibiotics differ in their efficacy and antibacterial spectrum. One type of PBP is β-lactamase, which hydrolyzes and inactivates the β-lactam ring. The penicillins may be conveniently grouped into the following classes: natural penicillins, penicillinase-resistant penicillins, aminopenicillins, and extended-spectrum penicillins. In addition, some of the penicillins have been combined with β-lactamase inhibitors including clavulanic acid, sulbactam, and tazobactam, which widen their antibacterial spectrum of activity.

The natural penicillins, penicillin G and penicillin V, are so named because they can be purified directly from cultures of the mold *Penicillium*. Penicillin G is unstable in acid and inactivated by gastric contents. It is administered by intramuscular, subcutaneous, intrathecal, or intravenous injection. Benzathine penicillin G, the treatment for primary, secondary, and latent syphilis, is slowly absorbed from tissue after intramuscular injection and detectable in serum for up to 30 days. However, levels are inadequate for treating neurosyphilis and intravenous formulations should be used. Most bacteria have developed resistance to the natural penicillins. Those that remain susceptible include *Streptococcus pyogenes*, viridans group streptococci, some enterococci, some *Streptococcus pneumoniae*, *Listeria monocytogenes*, *Neisseria meningitidis*, some *Haemophilus influenzae*, *Clostridium* (except *Clostridium difficile*), *Actinomyces israelii*, and *Leptospira*. Penicillin V is only available for oral use and treats most of the same organisms as penicillin G, although it is less active against *Haemophilus* and *Neisseria*. Nafcillin, a penicillinase-resistant penicillin, is active against methicillin-sensitive *Staphylococcus aureus*, penicillin-susceptible strains of *S. pneumoniae*, and most anaerobic gram-positive cocci. Importantly, nafcillin does not treat enterococcus and *Listeria*. Oral formulations of penicillinase-resistant penicillins include

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dicloxacillin (which is frequently used for skin and soft-tissue infections [SSTIs]) and cloxacillin. The aminopenicillins, ampicillin and amoxicillin, have improved activity against enterococci compared to penicillin G. Amoxicillin is better orally absorbed than ampicillin, while the latter is effective in treating meningitis due to *L. monocytogenes*, *N. meningitidis*, and group B streptococci. Ampicillin has been combined with the β-lactamase inhibitor sulbactam and is often given for mixed bacterial infections, such as intra-abdominal infections and obstetric and gynecologic infections. Amoxicillin–clavulanate is an oral formulation that is also given when multiple organisms need to be treated, such as animal or human bite wounds. The extended-spectrum penicillins include piperacillin, ticarcillin, and carbenicillin. Piperacillin is almost always given in combination with the β-lactamase inhibitor tazobactam. It has a wide range of activity including streptococci, anaerobes, enterococci, many Enterobacteriaceae as well as *Pseudomonas aeruginosa*. Piperacillin–tazobactam is utilized for many serious infections including hospital-acquired pneumonia, neutropenic fever, polymicrobial SSTIs, intra-abdominal infections, complicated urinary tract infections (UTIs), and often empirically for sepsis. Of note, use of piperacillin–tazobactam has been identified as a risk factor for *Candida glabrata* and *Candida krusei* fungemia. Ticarcillin–clavulanate is another parenteral broad-spectrum agent with similar indications as piperacillin–tazobactam, although less active against enterococci.

Monobactams consist of a single β-lactam ring with side chains. Currently the only commercially available monobactam is aztreonam. Monobactams are active exclusively against gram-negative aerobic bacteria. Aztreonam is not absorbed from the gastrointestinal tract and is usually given by the intravenous route. It is the only β-lactam that can be given to patients with allergies to penicillin or other β-lactam antibiotics since there is no cross-reactivity between them. An inhaled formulation of aztreonam has been developed for chronic use in cystic fibrosis patients with endobronchial *P. aeruginosa* infection.

Bacteria employ a number of resistance mechanisms against the penicillins and monobactams. The most common is the production of β-lactamase, which covalently reacts with and lyses the β-lactam ring. Four different classes of β-lactamases have been identified, designated A through D. Other mechanisms include efflux pumps which push penicillin out across the bacterial outer membrane, porins which do not allow passage of penicillins into the cytoplasm, and production of low-affinity PBPs.

CEPHALOSPORINS

The second major group of β-lactams, cephalosporins, are widely used in clinical practice. Currently there are over 20 cephalosporins available worldwide. They are composed of a β-lactam ring fused to a six-member dihydrothiazine ring. This structure bestows more intrinsic resistance against β-lactamases compared to the five-member ring of penicillin. Cephalosporins are commonly classified according to generation, with agents in each generation having a similar antibacterial spectrum of activity. Successive generations gain activity against aerobic gram-negative bacteria. Enterococci are intrinsically resistant to cephalosporins, although the new methicillin-resistant *S. aureus* (MRSA)-active cephalosporins have lower minimum inhibitory concentrations (MICs) against ampicillin-sensitive strains. The mechanism of action of cephalosporins is similar to other β-lactam agents, namely binding to and inhibiting PBPs, which in turn prevents peptidoglycan synthesis. Cephalosporins are bactericidal drugs and cause persistent suppression of bacterial growth for several hours, called post-antibiotic effect (PAE), in gram-positive bacteria, but not in gram-negative organisms. Their rapidity of bacterial killing is determined by the amount of time that the drug concentration exceeds the MIC, with maximal killing at four times the MIC.

The first-generation cephalosporins include cefazolin, cefadroxil, and cephalexin with the first administered parenterally and the latter two orally. Cefazolin is commonly used for infections caused by methicillin-sensitive staphylococci and streptococci, such as SSTIs, endocarditis from susceptible strains, and surgical prophylaxis for foreign-body insertion and other clean and clean-contaminated surgical procedures with a high risk for infection. The oral first-generation agents have good oral bioavailability and are effective for many SSTIs. They are often used to transition to oral therapy after parenteral cefazolin or in the outpatient setting. They are not active against *H. influenzae* or *Moraxella catarrhalis* and should not be used for respiratory infections. Second-generation cephalosporins are divided into two groups, the true cephalosporins (cefuroxime) and the cephamycins (cefoxitin and cefotetan). Cefuroxime was frequently used in the

past for respiratory tract infections, but its poor activity against penicillin-resistant *S. pneumoniae* has now limited its effectiveness. The cephamycins have good activity against aerobic gram-negative and anaerobic organisms and are first-line agents for intra-abdominal, gynecologic, and mixed skin infections. The parenteral third-generation cephalosporins (ceftriaxone, cefotaxime, ceftazidime, and ceftizoxime) have a number of important clinical indications. Ceftriaxone and cefotaxime are active against penicillin-resistant pneumococcus and are recommended for treatment of community-acquired pneumonia (combined with azithromycin) and meningitis. Ceftriaxone is the drug of choice for gonococcal infections and is combined with doxycycline to treat pelvic inflammatory disease. Both ceftriaxone and cefotaxime are active against *Borrelia burgdorferi* and are effective for neurologic Lyme disease. Also, these agents have good activity against Enterobacteriaceae, although caution should be used with monotherapy against *Citrobacter*, *Serratia*, and *Enterobacter* species as they can develop inducible resistance through chromosomal β-lactamase production. Ceftazidime has excellent activity against *P. aeruginosa* but limited activity against *S. aureus*. Several oral third-generation cephalosporins are available (cefpodoxime, cefixime, cefdinir, and cefditoren) and are commonly prescribed for respiratory infections, sinusitis, and otitis media. Currently the only available fourth-generation cephalosporin in the United States is cefepime. This drug has an enhanced spectrum of activity against gram-negative organisms including those with reduced sensitivity to third-generation drugs. Cefepime is recommended as monotherapy for patients with neutropenic fever, although it is often combined with an aminoglycoside. Ceftaroline and ceftobiprole are advanced-generation cephalosporins with broad gram-positive and gram-negative in vitro activity and comparable efficacy to vancomycin against MRSA. They are also active against ampicillin-sensitive enterococci but not against *P. aeruginosa* or *Acinetobacter* species. Ceftaroline has been approved in the United States to treat community-acquired pneumonia and SSTIs, including those caused by methicillin-sensitive and -resistant *S. aureus*.

CARBAPENEMS

Among the most broad-spectrum antibiotics, carbapenems are often reserved for serious infections. There are four available agents in this class: ertapenem, meropenem, imipenem, and doripenem. Their chemical structure is slightly different from other β-lactams in that the sulfur is replaced by a methylene group and the ring contains a double bond. Imipenem is a substrate for the kidney enzyme dehydropeptidase-1. It is coadministered with cilastin, a dehydropeptidase-1 inhibitor. Carbapenems have a similar mechanism of action, i.e., binding to high-molecular-weight PBPs, and are not hydrolyzed by most penicillinases. All have excellent activity against many gram-positive cocci. Penicillin-susceptible *Enterococcus faecalis* is susceptible to imipenem with MICs less than or equal to 2 μg/mL but resistant to the other carbapenems. *Enterococcus faecium* is resistant to all carbapenems, as are methicillin-resistant staphylococci. *Neisseria* species, *Haemophilus* species, and Enterobacteriaceae are all highly susceptible to carbapenems. Doripenem is the most active against *P. aeruginosa*, while ertapenem is inactive. Ertapenem also has poor activity against *Acinetobacter*. *Stenotrophomonas maltophilia* and *Burkholderia cepacia* are intrinsically resistant to all four carbapenems. As a class, carbapenems are highly active against anaerobic bacteria.

Because of their activity against many gram-positive, gram-negative, and anaerobic bacteria, carbapenems treat a wide range of infections. Moreover, they are often a good choice for patients who have recently received other antibiotics or for empiric coverage of severe sepsis. From an antibiotic stewardship perspective, carbapenems are advantageous since they can replace multiple antibiotics with one drug. For instance, ertapenem, with its long half-life that permits once-daily dosing, is often given to treat polymicrobial infections. However, the convenience of carbapenems must be carefully balanced against the potential for the emergence of resistance. Adverse events are similar to other β-lactams, although as a class there is an increased risk for seizures, particularly with imipenem.

Resistance to carbapenems usually occurs through overproduction of efflux pumps, altering PBPs, diminished outer membrane permeability, or production of β-lactamases. Several species of Enterobacteriaceae carry the plasmid-borne carbapenemases KPC-1, KPC-2, and KPC-3 which are capable of degrading carbapenems. *P. aeruginosa* also has a distinct efflux pump that is capable of removing numerous antibiotics, including meropenem, doripenem, and ertapenem but not imipenem. The recently emerged carbapenemase NDM-1 (New Delhi metallo-β-lactamase-1) has

quickly spread worldwide. It is a class B carbapenemase (also called a metallolactamase) that requires zinc at its active site.

AMINOGLYCOSIDES

The first aminoglycoside to be produced was streptomycin in 1944. It was followed by neomycin, then gentamicin, tobramycin, and lastly amikacin in 1972. They are bactericidal agents that exhibit concentration-dependent killing. Aminoglycosides bind to the 30S subunit of the prokaryotic ribosome, preventing protein synthesis from mRNA. This occurs through penetration of the bacterial cytoplasmic membrane by an oxygen-dependent active transport mechanism. Because of this action, aminoglycosides work poorly in anaerobic environments such as abscesses. These agents demonstrate a significant PAE, which increases with the peak serum concentration. Aminoglycosides are rarely used as single agents and are usually combined with another antimicrobial, such as a β-lactam or vancomycin. This helps prevent the emergence of resistance and gains the benefit of synergy. In cases of endocarditis, gentamicin should be administered using multiple daily dosing. However, for other types of infections there are several advantages of once-daily administration over multiple daily dosing. Animal studies have shown a lower rate of drug-related toxicities as well as a more robust PAE with once-daily dosing. Studies in humans have also demonstrated that once-daily dosing is efficacious, causes less nephrotoxicity, and is more cost-effective compared to multiple daily dosing regimens. The toxicities of aminoglycosides are well established and include nephrotoxicity (incidence 5%–10%), ototoxicity, vestibular toxicity, and neuromuscular blockade. Therefore, these agents should be used cautiously in patients with myasthenia gravis, electrolyte abnormalities such as hypocalcemia and hypomagnesemia, or with concurrent drugs that interfere with neuromuscular transmission, such as calcium channel blockers. Renal failure associated with aminoglycosides is usually reversible and often resolves once the drug is discontinued. Ototoxicity is more likely to be permanent.

Among their clinical indications, aminoglycosides have in vitro activity against strains of methicillin-susceptible *S. aureus* (MSSA), although resistance can develop quickly unless used in combination with another active drug. Gentamicin is active against species of *Enterococcus*, but tobramycin and amikacin are not. Pneumococci and all other streptococci are resistant to aminoglycosides, as are anaerobic bacteria. Certain aminoglycosides have activity against mycobacteria, for instance streptomycin inhibits *Mycobacteria tuberculosis* and amikacin inhibits *Mycobacteria avium-intracellulare*. Most species of Enterobacteriaceae, *P. aeruginosa*, *Serratia*, and *Acinetobacter* remain susceptible to amikacin, gentamicin, and tobramycin but resistance rates vary between institutions. Of note, *Stenotrophomonas maltophilia* and *Burkholderia cepacia* are resistant to these drugs. Streptomycin is effective therapy for *Yersinia pestis* and *Francisella tularensis*, and gentamicin plus doxycycline is used to treat brucellosis.

Overall, the prevalence of bacterial resistance to the aminoglycosides remains low. There are three main mechanisms for resistance to these agents: (1) point mutations in 16S ribosomal RNA; (2) efflux pumps that prevent accumulation of the drug; and (3) bacterial enzymes that modify the drug to bind poorly to ribosomes. Enterococci are intrinsically resistant due to their facultative anaerobic metabolism. Additionally, extended-spectrum β-lactamases (ESBL) are on plasmids that carry multiclass resistance genes including for aminoglycosides.

QUINOLONES

The first quinolone, nalidixic acid, was generated as a by-product during the production of chloroquine. Investigators discovered it had activity against certain gram-negative bacteria. Modifications of the compound including the addition of fluorine led to further quinolones with aerobic gram-positive, additional aerobic gram-negative, and some anaerobic activity. The most commonly used quinolones include ciprofloxacin, levofloxacin, ofloxacin, moxifloxacin, and gemifloxacin. They are rapidly bactericidal agents that stop bacterial DNA synthesis by inhibiting two enzymes, topoisomerase IV and DNA gyrase. Like aminoglycosides, quinolones cause PAE against gram-negative bacilli, lasting approximately 2 to 6 hours. The bioavailability of quinolones is high (close to 100%), making for an easy transition from the intravenous to oral route. They have a high distribution in tissues including lung, bile, prostate, and stool. Except for moxifloxacin, concentrations in the kidney and urine are high. Although bone concentration is less than serum, quinolones have been successfully used to treat osteomyelitis and prosthetic joint infections, especially when combined with rifampin in the latter.

Table 206.2 Characteristics of quinolones

Drug	Principle route of metabolism	Common clinical indications and uses
Ciprofloxacin	Renal	UTIs, prostatitis, atypical pneumonia, HAP, travelers' diarrhea, gastroenteritis, peritonitis prophylaxis with cirrhosis, chronic osteomyelitis; excellent activity against gram negatives including *P. aeruginosa*
Levofloxacin	Renal	AECOPD, CAP, HAP, *P. aeruginosa* infections
Moxifloxacin	Hepatic	Aspiration pneumonia, AECOPD, CAP, abdominal infections, mixed anaerobic infections
Ofloxacin	Renal	UTIs, prostatitis, travelers' diarrhea
Gemifloxacin	Renal	AECOPD, CAP

Abbreviations: UTI = urinary tract infection; CAP = community-acquired pneumonia; HAP = hospital-acquired pneumonia; AECOPD = acute exacerbations of chronic obstructive pulmonary disease.

The clinical uses for quinolones are presented in Table 206.2. Common toxicities associated with this class include gastrointestinal upset, dizziness, delirium (especially in the elderly), and rashes, while prolongation of the QT interval, arrhythmias, and tendonitis are rare but potentially serious. They should not be given with dairy products or metals like aluminum, calcium, or magnesium as these can reduce absorption of the drugs. Likewise, caution should be used in patients concurrently on warfarin, with close monitoring of prothrombin times as an increased risk of bleeding has been reported.

Bacterial resistance to quinolones occurs mainly from spontaneous mutations in genes that code for DNA gyrase or topoisomerase IV. Less commonly, resistance mutations occur in genes that encode membrane porin channels, leading to reduced diffusion, as well as overexpression of efflux pumps. Studies have shown an increased risk for the development of resistance while on therapy in *P. aeruginosa* and *S. aureus*.

TETRACYCLINES

Originally derived from soil microorganisms, tetracyclines have broad-spectrum activity against gram-positive and gram-negative bacteria, intracellular bacteria, and some parasites. They are bacteriostatic agents, have anti-inflammatory properties, and inhibit protein synthesis by binding to the 30S subunit of the bacterial ribosome. Currently there are three tetracyclines available for clinical usage: doxycycline, minocycline, and tetracycline. A similar class is the glycylcyclines, which are derivatives of minocycline and have a modified side chain at position 9. Tigecycline is currently the only available glycylcycline. Both doxycycline and minocycline have high bioavailability, while the bioavailability of tetracycline is reduced when taken with food. Like quinolones, their absorption is decreased by multivalent cations like calcium and magnesium. The routes of elimination differ between the agents, with tetracycline cleared through the urine, doxycycline through the feces, minocycline through the liver, and tigecycline through the biliary/fecal route and to a lesser extent the urine. Toxicities are uncommon and include gastrointestinal upset, esophageal ulcers, rashes, and photosensitivity reactions. Minocycline can cause vertigo, more often in women. Tetracyclines should be avoided in pregnant women and children under age 8 because of teeth staining. Patients should be encouraged to take oral tetracyclines with a full glass of water and remain upright for at least 30 minutes to decrease the risk for esophageal irritation.

Tetracyclines have a multitude of clinical uses. Doxycycline is included in the Infectious Diseases Society of America guidelines for the management of community-acquired pneumonia for monotherapy in outpatients and in combination with a β-lactam for inpatients. Given recent reports associating arrhythmias with macrolides and quinolones, doxycycline seems to be a safe and effective alternative. It is often used to treat mild MRSA SSTIs. Moreover, doxycycline has been associated with a lower risk for *C. difficile* infection than other antibiotics. Tetracyclines are first-line therapy for Lyme disease, Rocky Mountain spotted fever, Q fever, cat scratch disease, anaplasmosis, ehrlichiosis, bartonellosis, brucellosis, pelvic ulcer disease, and in combination therapy for *Helicobacter pylori*. They also serve as alternative therapy for several conditions when patients are allergic or otherwise intolerant to first-line agents, including syphilis, leptospirosis, and Whipple's disease. Tigecycline is a broad-spectrum antibiotic with activity against MRSA, vancomycin-resistant enterococci (VRE), and many gram-negative bacilli including multidrug-resistant strains of *Acinetobacter*. However, it does not treat "the three P's" *Pseudomonas*, *Proteus*, and *Providencia*, or *Morganella*. Tigecycline is indicated to treat intra-abdominal

Table 206.3 Characteristics of macrolides

Drug	Mechanism of action	Common clinical uses	Adverse reactions
Erythromycin	Binds bacterial 50S ribosome and inhibits RNA-dependent protein synthesis	*Bordetella pertussis* Atypical respiratory pathogens Prokinetic agent for gastroparesis	Nausea, vomiting, rashes, ototoxicity (high doses), QT prolongation
Azithromycin	Binds bacterial 50S ribosome and inhibits RNA-dependent protein synthesis	Pharyngitis Bacterial sinusitis CAP Otitis media MAC treatment and prophylaxis NGU Q fever SSTIs	Diarrhea, nausea, abdominal pain, cholestatic hepatitis, arrhythmias
Clarithromycin	Binds bacterial 50S ribosome and inhibits RNA-dependent protein synthesis	Pharyngitis Bacterial sinusitis CAP Otitis media *H. pylori* MAC and other mycobacterial infections (except MTb) Q fever SSTIs	Diarrhea, nausea, abdominal pain, arrhythmias
Fidaxomicin	Inhibits bacterial RNA polymerase	*C. difficile* infection; lower relapse rate compared to vancomycin except with NAP1/B1/027 strain	Nausea, vomiting, abdominal pain, gastrointestinal hemorrhage

Abbreviations: CAP = community-acquired pneumonia; MAC = *Mycobacterium avium* complex; MTb = *Mycobacterium tuberculosis*; NGU = nongonococcal urethritis; SSTIs = skin and soft-tissue infections.

infections, community-acquired pneumonia, and SSTIs. Approximately 25% of patients develop nausea, which may necessitate discontinuation of therapy.

Tetracycline resistance occurs mainly by acquisition of exogenous genes for efflux pumps and ribosomal protection proteins. Tigecycline has a higher affinity for ribosomes and can overcome ribosomal protection proteins, although it remains susceptible to multidrug-resistance pumps.

MACROLIDES

The macrolide group of antibiotics includes erythromycin, azithromycin, clarithromycin, and the new agent fidaxomicin (previously OPT-80), which was approved by the US food and Drug Administration (FDA) in May 2011. The first three drugs are used to treat a wide range of infections, while fidaxomicin is only used to treat *C. difficile* (Table 206.3). In addition to their primary indications, macrolides are often used as alternative agents for several conditions, such as Lyme disease in pregnancy and streptococcal pharyngitis in penicillin-allergic patients.

The first macrolide to be discovered, erythromycin, previously had good activity against many gram-positive organisms, but resistance has decreased its clinical efficacy. Erythromycin still maintains excellent activity against *Bordetella pertussis* and atypical respiratory pathogens. It is also used as a prokinetic agent for gastroparesis. However, gastrointestinal side effects and frequent dosing limit its use. Azithromycin has been the most commonly prescribed antibiotic in the United States for adults in recent years. It is better tolerated than erythromycin and, for many of its indications, is taken once a day for a 5-day course. Unfortunately, azithromycin has been associated with an increased risk of cardiovascular death, estimated at 47 additional cardiovascular deaths per 1 million courses.

All macrolides exhibit anti-inflammatory and immunomodulatory properties. Evidence suggests they are beneficial in certain chronic noninfectious illnesses such as cystic fibrosis and bronchiectasis. Their role in cardiovascular disease is controversial and requires further clarification.

Resistance to erythromycin, azithromycin, and clarithromycin is mediated through efflux pumps, mutations in genes for 50S ribosomal

proteins, and enzymatic inactivation by phosphotransferases. A single strain of *C. difficile* with an elevated fidaxomicin MIC taken from a cured patient was found to have a single mutation in the β subunit of the RNA polymerase.

GLYCOPEPTIDES, LIPOPEPTIDES, AND STREPTOGRAMINS

Vancomycin, derived from the word "vanquish," was the first glycopeptide introduced for clinical use. The other glycopeptide is teicoplanin, which is available in Europe and Asia but not the United States. Glycopeptides are bactericidal agents that inhibit cell wall synthesis in dividing bacteria by binding to precursors of the peptidoglycan chain. Vancomycin has activity against most strains of staphylococci (including MRSA), streptococci, and enterococcus. Most strains of *L. monocytogenes* are susceptible although some with high MICs have been reported. *Leuconostoc*, *Lactobacillus*, and *Pediococcus* are intrinsically resistant. Vancomycin is used for many serious infections including meningitis, endocarditis, MRSA pneumonia, cellulitis, osteomyelitis, and gram-positive bacteremia. Oral vancomycin, which is not systemically absorbed, is used to treat moderate to severe *C. difficile* infections and recurrences. Adverse reactions to the drug are uncommon and include infusion-related reactions such as rash (red man syndrome), neutropenia, thrombocytopenia, ototoxicity, and nephrotoxicity. Resistance in enterococci is mediated by the *van* genes, which are found mostly in *E. faecalis* and can be transmitted to other bacteria such as staphylococci. It is increasingly common for strains of *S. aureus* to exhibit rising MICs to vancomycin (so-called "MIC creep"). Indeed, high rates of clinical failure with vancomycin have been observed with MRSA bacteremia when the vancomycin MIC is 2 μg/mL or greater.

Telavancin is a semisynthetic lipoglycopeptide derived from vancomycin. It has a bactericidal concentration-dependent method of killing and a dual mechanism of action, inhibiting cell wall synthesis and disrupting membrane integrity. Telavancin exhibits potent in vitro activity against many gram-positive organisms, including staphylococcus, streptococcus, both vancomycin-susceptible and -resistant enterococcus, and gram-positive anaerobes. In the United States, telavancin is approved for the treatment of patients with complicated SSTIs. Women of childbearing age should have a pregnancy test prior to starting telavancin because of possible teratogenicity. Dalbavancin is another lipoglycopeptide with broad gram-positive activity, recently approved for skin and skin structure infections. It has a long half-life and is given once weekly for two doses.

The lipopeptide daptomycin is a rapidly acting, bactericidal agent that forms calcium-dependent ion channels in the cytoplasmic membrane of gram-positive organisms, causing loss of intracellular potassium and cell death. Daptomycin has a similar spectrum of activity as vancomycin and can be used to treat SSTIs, *S. aureus* bloodstream infections and right-sided endocarditis, osteomyelitis, and septic arthritis. Pulmonary surfactant inactivates daptomycin and it should not be used for pneumonia. It is usually well tolerated but reversible myopathy can occur. Therefore, monitoring of creatine phosphokinase (CPK) should be done weekly and concurrent statin therapy should be avoided. Resistance to daptomycin has been associated with MRSA strains with decreased susceptibility to vancomycin. Many bacteria with elevated daptomycin MICs demonstrate phenotypic changes in their cell membranes.

The streptogramins consist of two different macrocyclic compounds that each bind to the 50S subunit of the bacterial ribosome, inhibiting protein synthesis. Currently quinupristin–dalfopristin is the only streptogramin available in the United States. It is active against most gram-positive organisms (except *E. faecalis*) and a few gram-negatives including *Neisseria gonorrheae*, *N. meningitidis*, *M. catarrhalis*, and *H. influenzae*. Resistance occurs through conformational changes in the 50S subunit, enzymatic inactivation, and production of efflux pumps. The clinical use of quinupristin–dalfopristin has been limited by its frequent side-effects (arthralgias, myalgias, hyperbilirubinemia), many drug interactions, and because it needs to be administered through a central line due to frequent thrombophlebitis and pain when given peripherally.

OXAZOLIDINONES

Linezolid is the first of the oxazolidinones, a completely synthetic class of antibacterial agents with broad gram-positive activity. Unlike vancomycin, daptomycin, and quinupristin–dalfopristin, linezolid is available in both intravenous and oral formulations. It is a bacteriostatic agent that inhibits protein synthesis by binding to 23S rRNA in the catalytic site of the 50S ribosome. It is

approved for the following indications: (1) VRE infections, including bacteremia; (2) nosocomial pneumonia caused by MSSA, MRSA, and *Streptococcus pneumoniae*; (3) complicated skin and skin structure infections, including diabetic foot infections without concurrent osteomyelitis, caused by MSSA, MRSA, *Streptococcus pyogenes*, or *Streptococcus agalactiae*; (4) uncomplicated skin and skin structure infections caused by MSSA or *S. pyogenes*; (5) community-acquired pneumonia caused by MSSA or *S. pneumoniae*. Adverse events are uncommon and usually mild, including headache, nausea, and diarrhea. More serious ones can also occur, usually if linezolid is given for greater than 28 days. These include anemia, thrombocytopenia, lactic acidosis, optic neuritis, and peripheral neuropathy. It is therefore recommended that a weekly complete blood count be done while on therapy. Linezolid can cause serotonin syndrome when taken concurrently with selective serotonin reuptake inhibitors (SSRIs) and should be avoided. Resistance to linezolid has been observed in strains of MRSA and VRE with mutations in the 23S ribosomal RNA domain V region and is usually associated with prior exposure to the drug. Once-daily tedizolid phosphate has recently been approved, and other oxazolidinones are in various stages of development.

SULFONAMIDES

The first class of antibacterials in clinical use, sulfonamides are still widely prescribed. There are two agents currently available: trimethoprim–sulfamethoxazole (TMP–SMX) and dapsone. They are bacteriostatic and inhibit folic acid synthesis, stopping bacterial growth. Trimethoprim is a dihydrofolate reductase inhibitor that potentiates the activity of sulfonamides but also has antibacterial properties itself. Sulfonamides have broad in vitro activity against many gram-positive and gram-negative bacteria. TMP–SMX is most often used to treat UTIs, including pyelonephritis, cystitis, and prostatitis. It can also be given as prophylaxis for patients with recurrent UTIs. Furthermore, TMP–SMX is effective for treating SSTIs due to community-associated MRSA, with >90% of strains currently susceptible. It is first-line therapy for patients with *Pneumocystis jirovecii* pneumonia (PCP), as well as PCP prophylaxis. Intravenous TMP–SMX is often used in severe cases. Dapsone is the treatment of choice for leprosy and for PCP prophylaxis in patients intolerant of TMP–SMX. Hemolytic anemia can occur on dapsone especially in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency, so a G6PD level should be obtained before therapy is started. Adverse reactions associated with TMP–SMX include rashes (rarely Stevens–Johnson syndrome), fever, gastrointestinal upset, hepatitis, cytopenias, and hyperkalemia.

Because of long-standing usage (>70 years), widespread resistance to the sulfonamides has developed. It is mediated by overproduction of para-aminobenzoic acid (PABA) or structural changes in dihydropteroate synthetase, or by plasmids that code for the production of drug-resistant enzymes or decreased bacterial cell wall permeability.

METRONIDAZOLE AND CLINDAMYCIN

Developed in the 1950s, metronidazole is commonly used for parasitic and anaerobic infections. It is bactericidal and acts by interfering with electron transport proteins via reduction of its nitro group, leading to free radical formation and cell death. Oral metronidazole is well absorbed and serum levels are comparable to intravenous therapy. Metronidazole is active against nearly all gram-negative anaerobic bacteria, including *Bacteroides fragilis*, gram-positive anaerobes such as *C. difficile*, *H. pylori*, and parasites such as *Giardia*, *Entamoeba*, and *Trichomonas vaginalis*. Clinically it is used to treat a variety of anaerobic infections such as brain abscesses, bacteremia, endocarditis, bacterial vaginosis, bone and joint infections, and infections of the head and neck. Oral metronidazole is effective against mild *C. difficile* infection, although recurrences are common (approximately 25%). Of note, it should not be used as a single agent in treating lung abscesses because of the frequent presence of aerobic gram-positive cocci, against which it lacks activity. Adverse reactions associated with metronidazole include gastrointestinal upset, rashes, neutropenia, neurologic complaints such as headache, dizziness, and peripheral neuropathy. Alcohol should be avoided as it can lead to a disulfiram-like reaction. Resistance is rare and results from a decreased capacity of the electron transport chain to reduce the nitro group of metronidazole. Certain strains of *H. pylori* acquire resistance from mutational inactivation of the *rdxA* gene.

Clindamycin is a chemical modification of lincomycin, the original member of the lincosamide group. Similar to the macrolides, clindamycin binds to the 50S subunit of the bacterial ribosome

and inhibits protein synthesis. It has in vitro activity against many aerobic gram-positive bacteria, including staphylococci and streptococci, and anaerobes, although resistance is becoming more common. In particular, approximately 25% of clinical strains of *B. fragilis* are resistant to the drug. Clindamycin is used to treat lung abscesses, intra-abdominal and gynecologic infections, and gas gangrene from *Clostridium perfringens*. Topical formulations are effective for acne vulgaris and vaginal ones for bacterial vaginosis. It has good activity against MSSA but less so with MRSA. A D test should be done on strains of MRSA or *S. pyogenes* resistant to erythromycin; a positive D test indicates resistance to clindamycin will also occur. It can also be given as an adjunctive agent to bind toxins produced by *S. pyogenes* and *S. aureus*. Finally, clindamycin can serve as an alternative to penicillin or macrolides for most indications for patients with drug allergies. The major toxicity associated with clindamycin is *C. difficile* infection, which is not infrequent and now limits its clinical usage. Resistance to the drug occurs mainly through 50S ribosomal modification and enzymatic inactivation.

RIFAMYCINS

A versatile class of drugs, the rifamycins have many indications but are usually used in combination with other antibiotics. There are four drugs currently available: rifampin, rifabutin, rifapentine, and rifaximin. Rifamycins act by inhibiting the β-subunit of bacterial RNA polymerase. They are potent inducers of the cytochrome P450 system. This leads to many drug interactions including human immunodeficiency virus (HIV) medications, warfarin, cardiovascular drugs such as beta-blockers and statins, and immunosuppressive agents such as tacrolimus and glucocorticoids. Rifamycins are also associated with many adverse reactions. They cause an orange-red discoloration of tears and other secretions. Gastrointestinal symptoms such as nausea, vomiting, and diarrhea are common, while rashes, hepatitis, cytopenias, uveitis, and a lupus-like syndrome can also occur.

There are different clinical indications for each of the rifamycins. Rifampin is the oldest and most commonly used. It can be given as an alternative to isoniazid for treatment of latent tuberculosis, as one of the four drugs to treat active tuberculosis, in combination with dapsone for leprosy, as monotherapy for prophylaxis against meningococcal disease, or in combination therapy for prosthetic valve endocarditis or osteomyelitis (especially with foreign bodies) from *Staphylococcus*. Furthermore, rifampin can be used to eradicate MRSA colonization along with another drug such as doxycycline. Rifabutin and rifapentine are mainly used to treat mycobacterial infections. Rifaximin is poorly absorbed and is indicated for travelers' diarrhea. Moreover, it is sometimes used for recurrent or refractory *C. difficile* infection, usually for 2 weeks after finishing a standard course of oral vancomycin. Rifaximin is also effective for treating and preventing hepatic encephalopathy.

Resistance to rifamycins occurs mainly through single-step mutations in the gene that codes for RNA polymerase. Because this process occurs rapidly, rifamycins are not used to treat infections by themselves, except for the few indications noted above.

POLYMYXINS

First discovered in the 1940s, polymyxins were used to treat serious gram-negative infections until around 1980, when safer agents with less nephrotoxicity became available. They have reemerged in recent years, often as agents of last resort, due to the ongoing spread of multidrug-resistant bacteria. The two drugs in this class currently available are polymyxin B and colistin. They are rapidly bactericidal and act like a detergent by punching holes in the bacterial cell membrane. Polymyxins have broad activity against aerobic gram-negative bacteria, including most strains of *P. aeruginosa* and *Acinetobacter baumannii*. However, *Proteus*, *Serratia*, *Providencia*, *Burkholderia*, *Moraxella*, *Vibrio*, *Morganella*, *Helicobacter*, and *Edwardsiella* are resistant. Colistin is often used parenterally to treat serious multidrug-resistant gram-negative bacterial infections such as ventilator-associated pneumonia. Aerosolized colistin is also available and mainly given to treat colonization or infection of the bronchial system in patients with cystic fibrosis. A dose-related nephrotoxicity is a common side effect and is usually reversible with discontinuation of the drug. Also, neurologic side effects can occur, such as paresthesias, peripheral neuropathy, and muscle weakness. Resistance to polymyxins develops through modification of lipopolysaccharides on the bacterial cell wall.

MISCELLANEOUS AGENTS

Chloramphenicol is rarely used in North America and Europe, although an inexpensive oral formulation is widely available in underdeveloped countries. It has excellent activity against aerobic gram-positive and gram-negative bacteria, anaerobes (including *Clostridium* and *B. fragilis*), and atypical bacteria. However, serious toxicities limit its clinical utility. Most common is reversible bone marrow suppression. Development of aplastic anemia from chloramphenicol is rarer but can be irreversible. Because of these, it should only be used for serious, life-threatening infections (e.g., bacterial meningitis) when alternative drugs are contraindicated.

Nitrofurantoin is an oral agent used to treat and prevent UTIs. It is bactericidal and acts by inhibiting translation and pyruvate metabolism. Over 90% of *Escherichia coli* and *Citrobacter* strains are susceptible, and it has excellent activity against group B streptococci, *Staphylococcus saphrophyticus*, and enterococci including VRE. However, most other strains of Enterobacteriaceae are resistant. For uncomplicated cystitis, a 10-day course of therapy is usually given as shorter courses have been associated with suboptimal cure rates. Daily nitrofurantoin (100 mg) is effective therapy for both young and postmenopausal women with asymptomatic and symptomatic bacteriuria. Toxicities include gastrointestinal symptoms, pulmonary reactions including fibrosis, hepatitis, hemolytic anemia, and peripheral neuropathy. Patients on long-term prophylaxis should be monitored for these conditions.

Pivmecillinam is a β-lactam antibiotic with activity against Enterobacteriaceae, including ESBL-producing strains. It is used to treat lower UTIs and is orally administered. The drug has good clinical efficacy but high rates of persistent bacteriuria have been found. Pivmecillinam is primarily used in Scandinavian countries and currently is not available in the United States.

Fosfomycin is another oral agent for lower UTIs whose usage has been increasing in recent years because of bacterial resistance to other agents. It is bactericidal and inhibits cell wall synthesis through inactivation of the bacterial enzyme MurA. Resistance occurs through mutations in the bacterial membrane transporter for the drug. Fosfomycin has broad-spectrum antibacterial activity. Among susceptible pathogens are *E. coli* (including ESBL-producing strains), *Citrobacter*, *Proteus*, and *Enterococcus* (including VRE). Rates of susceptibility vary in *Klebsiella* and *Enterobacter*, while strains of *Pseudomonas* are often resistant. Fosfomycin is given as a one time mega-dose that is formulated as a powder and dissolved in a glass of water. It can also be given as a prophylactic agent for recurrent UTIs once every 10 days.

TOPICALS

Topical antibiotics are important agents for both treating and preventing infections of the skin, as well as to eradicate chronic carriage of certain pathogens such as MRSA. The introduction of antisepsis techniques by Dr. Joseph Lister in the nineteenth century was a seminal event in medicine, and skin disinfection for surgery remains a crucial procedure to prevent infection. The two most common agents used for this purpose are povidone-iodine and chlorhexidine, with the latter becoming more widely available and popular in recent years.

Available topical antibacterials include silver sulfadiazine, which is mainly used as a burn wound dressing. Activated silver has broad-spectrum antimicrobial activity and some anti-inflammatory properties. Silver sulfadiazine decreases colonization of wounds but there is no clear evidence it treats infections or improves wound healing. Bacitracin is active against many gram-positive bacteria including staphylococci, streptococci, and clostridia. It is effective for treating impetigo but may also lead to slower wound healing. Mupirocin is another agent with in vitro activity against gram-positive organisms, especially MRSA. It is used to treat impetigo, folliculitis, infected wounds and ulcers, and to decolonize the nares in patients colonized with *S. aureus*. Unfortunately, the development of mupirocin resistance in MRSA is becoming increasingly common. Neomycin is an aminoglycoside with activity against both gram-positive and gram-negative organisms including *S. aureus*, *S. pyogenes*, *E. coli*, *Proteus*, and *Serratia* while *P. aeruginosa* is usually resistant. It can cause contact sensitivity and resistance may develop. Neomycin is not recommended for patients with decreased renal function as it can be systemically absorbed, leading to ototoxicity. Polymyxin B is bactericidal against several aerobic gram-negative organisms including *P. aeruginosa* but not species of *Proteus*, *Serratia*, and *Providencia*. It is often used in combination with another agent such as bacitracin. Fusidic acid is another topical with only gram-positive activity.

It gets good tissue penetration and is useful for treating boils. Retapamulin has in vitro activity against staphylococci (including MRSA) and streptococci and exhibits a potent post-antibiotic effect lasting 3 to 4 hours. It is indicated for treating impetigo in adults and children.

FUTURE DIRECTIONS

The spread of antibiotic-resistant bacteria presents a major challenge to public health in the twenty-first century. Indeed, some experts believe we will soon enter the post-antibiotic era. In order to forestall this dire prediction, judicious usage of antibiotics should be a salient intervention, as well as novel infection control methods that reduce the spread of multidrug-resistant pathogens. Ongoing efforts at drug development by the pharmaceutical industry should be actively supported by all relevant stakeholders, including payers, professional societies, and government agencies.

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207. Antifungal therapy

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This chapter focuses on the use of drugs that treat systemic mycoses (Table 207.1). Treatment of cutaneous fungal infections is discussed in Chapter 26, Superficial fungal diseases of the hair, skin, and nails.

AMPHOTERICIN B

Amphotericin B is a polyene antifungal synthesized by *Streptomyces nodosus*. Its chemical structure confers it with amphoteric properties that are essential for the drug's ability to form channels through the cytoplasmatic membrane. The pores formed from preferential binding of amphotericin B to ergosterol, the primary fungal cell sterol, result in an increase in membrane permeability, leading to a loss of essential elements such as potassium and other molecules that impairs fungal viability. Amphotericin B binds with less affinity to cholesterol, the primary cell sterol of mammalian cells, which are therefore less affected by amphotericin B than is the fungal target.

Amphotericin B is commercially available as a complex with sodium deoxycholate: commercial vials contain amphotericin B, 50 mg, sodium deoxycholate, 41 mg, and a sodium phosphate buffer, 25.2 mg. The clinical pharmacology of amphotericin B is characterized by extensive binding to plasma proteins (>95%) and wide distribution to the peripheral compartment with preferential accumulation in liver and spleen, with lesser amounts in kidney and lung. Intravenous administration of therapeutic doses results in peak plasma levels of 1.0 to 1.5 μg/mL falling to 0.5 to 1.0 μg/mL 24 hours later. At therapeutic doses, less than 5% of the drug is excreted in the urine. The elimination of amphotericin B is not altered in patients with renal or liver dysfunction and does not require dose adjustment in patients who are anephric or undergoing hemodialysis. Cerebrospinal fluid (CSF) levels are low, although higher concentrations occur in brain tissue. Amphotericin B also diffuses poorly into other body fluids such as saliva, amniotic fluid, aqueous humor, and vitreous humor. However, drug concentrations in inflamed pleura, peritoneum, aqueous humor, and joint spaces are roughly two-thirds of the trough plasma concentration.

For clinical administration, amphotericin B is diluted in 5% dextrose (at a concentration of ≤0.1 mg of amphotericin B per milliliter of diluent) and infused intravenously over 2 to 4 hours at dosages of 0.5 to 1.5 mg/kg/day. The most common side effects of amphotericin B treatment are acute infusion-related reaction and nephrotoxicity. The acute infusion-related reaction consists of a syndrome of chills/rigors, fever, and tachypnea that typically occurs 30 to 45 minutes after beginning the first infusion and may last for 2 to 4 hours. Premedication with acetaminophen (650 mg given orally or rectally), hydrocortisone (25 to 50 mg given intravenously or mixed with the amphotericin B infusion solution), and diphenhydramine (50 mg given orally or rectally) can diminish the frequency and severity of these reactions. Chills and rigors may be terminated by the administration of meperidine (50 mg given intravenously). The acute symptoms associated with amphotericin B infusion can be serious. The occurrence of severe infusion reactions is considered an indication for use of lipid-associated amphotericin B preparations, which are usually significantly better tolerated (see below).

The other major side effect of amphotericin B is the development of nephrotoxicity, which occurs through a decrease in the glomerular filtration rate as a result of a direct vasoconstrictive effect on afferent renal arterioles, reducing glomerular and renal tubular blood flow, and by direct effects on the distal tubules resulting in the loss of cations. The nephrotoxicity may be exacerbated by other nephrotoxic agents. There is evidence that renal vasoconstriction is partially reversible

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Table 207.1 Antifungal agents: therapeutic options

	Therapy	
DISEASE	PRIMARY	ALTERNATIVE
Aspergillosis: invasive	Voriconazole 6 mg/kg IV q12h for 2 doses then 4 mg/kg or 200–300 mg PO q12h	Liposomal formulations of AmB (see Table 207.3 for dosage) Caspofungin 70 mg IV × 1 dose, then 50 mg IV/d AmB, 1.0–1.5 mg/kg/d IV Posaconazole 300 mg BID on day 1 then 300 mg QD (tablet and IV); 800 mg/d in 2–4 doses (oral suspension) Itraconazole 400 mg/d PO (oral solution preferred)
Blastomycosis	Itraconazole, 200–400 mg/d PO for 6 mo; or AmB or L-AmB	Fluconazole, 400–800 mg/d for at least 6 mo
Candidiasis		
Candidemia	Caspofungin, 70 mg IV × 1 dose then 50 mg IV/d, or micafungin, 100 mg IV/d, or anidulafungin, 200 mg IV × 1 dose then 100 mg IV/d, followed by fluconazole 400–800 mg/d IV/PO (for susceptible organisms) or voriconazole when clinically stable to complete 14-d course after last positive blood culture If neutropenic, longer courses – until neutropenia resolves – may be necessary	Fluconazole 400–800 mg/d IV/PO for less seriously ill In patients who fail to respond or deteriorate, lipid formulations may be necessary Avoid fluconazole in patients with recent azole exposure, or if *Candida krusei* likely
Hepatosplenic candidiasis	L-AmB 3–5 mg/kg/d or Fluconazole, 800 mg/d IV	AmB lipid complex (ABLC), 5 mg/kg/d
Coccidiomycosis		
Nonmeningeal (AIDS and non-AIDS)	Fluconazole, 400–800 mg/d PO for 12–18 mo	Itraconazole, 200 mg BID PO × 12–18 mo, or AmB, 0.6–1.0 kg/d IV; total dose, ≥2.5 g In HIV, suppressive treatment with fluconazole, 200–400 mg/d PO, or itraconazole, 200–400 mg/d PO Posaconazole, voriconazole investigational
Meningeal (AIDS and non-AIDS)	Fluconazole, 400–800 mg/d PO indefinitely	L-AmB/AmB IV as for nonmeningeal Posaconazole, voriconazole investigational
Cryptococcosis		
Nonmeningeal	AmB, 0.7 mg/kg/d IV ± 5-FC 25 mg/kg PO q6h until response, then fluconazole, 400 mg/d PO for 8–10 wk, or Lipid AmB 3–5 mg/kg/d IV ± 5-FC as above	Fluconazole 400–800 mg/d IV Posaconazole, voriconazole investigational
Meningeal	AmB, 0.7 mg/kg/d IV ± 5-FC, 25 mg/kg PO q6h for 2 wk, then fluconazole, 400 mg/d PO for 8–10 wk, or fluconazole, 400 mg/d PO for 8–10 wk (for less severely ill patients)	Oral fluconazole less favorable success rates; Posaconazole, voriconazole investigational
Histoplasmosis		
Non-AIDS	Itraconazole, 400 mg/d PO for 9 mo; if life threatening, AmB, 0.7–1.0 mg/kg/d or lipid AmB 3–5 mg/kg/d IV × 14 d, followed by itraconazole, 400 mg/d × 8–10 wk if clinical response	
Disseminated/ AIDS	AmB, 0.7–1.0 mg/kg/d IV or lipid AmB 3–5 mg/kg/d × 14 d, followed by itraconazole, 400 mg/d × 8–10 wk, then begin suppressive treatment with itraconazole 200 mg/d PO	Itraconazole, 300 mg BID PO × 3 d, then 200 mg BID PO × 12 wk, or 400 mg/d × 12 wk, then 200 mg/d PO (less seriously ill)
Mucormycosis	Surgery plus lipid AmB 5–7.5 mg/kg/d IV	Posaconazole, AmB 0.8–1.5 mg/kg/d IV
Sporotrichosis		
Lymphocutaneous	Itraconazole, 200 mg/d PO × 6 mo	Potassium iodide solution (SSKI), 10–15 gtt TID × 6–12 wk
Extracutaneous	AmB or L-AmB (may require adjunctive intra-articular therapy or surgery)	Itraconazole, 200–300 mg PO BID × 6 mo, then 200 mg PO BID long term

Note: Dosages and duration of therapy given are approximations based on clinical response and underlying condition in the host. Individual responses and therapeutic requirements may vary.

Abbreviations: AmB = amphotericin B; 5-FC = flucytosine; AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus.

by salt loading with 500 to 1000 mL of normal saline before each infusion. Other renal effects include potassium and bicarbonate wasting and decreased erythropoietin production. Permanent loss of renal function can occur if the drug is continued in the setting of worsening renal function. Other chronic toxicities include nausea and vomiting, anorexia, normocytic normochronic

anemia (with the hematocrit rarely falling below 20% to 25%), and, rarely, thrombocytopenia, leukopenia, and peripheral vein phlebitis.

Amphotericin B is active against most fungal pathogens that cause systemic or deep-seated infections. Despite its significant dose-limiting toxicities, amphotericin B remains an option for many mycoses because of its broad spectrum of activity and fungicidal activity, although the availability of better tolerated and effective alternative agents (including lipid formulations of amphotericin B, the extended-spectrum azoles, or the echinocandins) have limited indications for the use of amphotericin B deoxycholate. Recommendations for appropriate dosages of amphotericin B and for duration of therapy remain poorly defined for most infections. In the past, total doses of 1 to 2 g for serious infections (which is approximately 15 to 30 mg/kg over a 6-week period) were usually recommended. However, the dosage and duration of amphotericin B depend largely on response of infection to therapy and resolution of underlying host immunodeficiency (e.g., resolution of neutropenia). Increasingly, a therapeutic approach that includes aggressive "induction" courses of amphotericin B followed by "consolidation" therapy with an azole, which can be administered orally, is used. This strategy has been evaluated most thoroughly in cryptococcal meningitis, but clinical reports have documented success of sequential amphotericin B to azole therapy in candidemia (using oral fluconazole), invasive aspergillosis (with an oral anti-*Aspergillus* azole such as voriconazole, posaconazole, or itraconazole), and endemic fungi (coccidioidomycosis and histoplasmosis with fluconazole and itraconazole, respectively). Generally, a 2-week (or until signs of infection have resolved or significantly improved) course of amphotericin B can be followed by azole therapy although none of the azoles are licensed for use in that manner.

Local instillation is rarely indicated due to the advances in alternative agents. Historically, itrathecal amphotericin B was a mainstay of therapy for coccidioidal meningitis, but the use of intrathecal amphotericin B is associated with substantial toxicity; consequently, that approach is now usually reserved for patients in whom systemic therapy fails, including high dosages of an azole. In other cases, local instillation of amphotericin B into the bladder via a Foley catheter has been used for urinary tract candidiasis, but systemic azole therapy, usually with fluconazole, is well tolerated and effective for that indication.

Lipid preparations of amphotericin B have been developed in an attempt to reduce the nephrotoxicity of the conventional form of amphotericin B deoxycholate. The administration of such liposomal forms modifies the pharmacokinetic and toxicologic properties of amphotericin B and as such these preparations have largely replaced amphotericin B deoxycholate for recommended use in serious fungal infections. Characteristics of the commercially available lipid amphotericin B preparations, liposomal amphotericin B (L-AMB, AmBisome), amphotericin B lipid complex (ABLC, Abelcet), and amphotericin B colloidal dispersion (ABCD, Amphotec), are shown in Table 207.2, although the use of ABCD is limited due to the increased toxicity associated with that formulation. Serum levels of L-AMB are higher than those achieved with standard amphotericin B, but serum levels of ABLC and ABCD are similar to those of amphotericin B deoxycholate. The advantage of the administration of amphotericin B in lipid complexes or in liposomes is the reduced rate of nephrotoxicity, allowing the delivery of larger amounts of the drug. Although few direct comparisons of the preparations have been performed, the fewest infusion reactions appear to occur with L-AMB with slightly more reactions, including chills and fevers, associated with ABLC. The highest incidence of infusion-related toxicities, including hypoxia, has been reported with ABCD. Infusions of L-AMB have been associated with anxiety, nervousness, restlessness, and chest pain, which have been described as a feeling of impending doom.

The lipid amphotericin B formulations have shown efficacy in many indications, including their use as salvage therapy for patients who fail amphotericin B deoxycholate or who are intolerant to it. In addition, L-AMB was shown to have fewer adverse events and to reduce breakthrough invasive fungal infections when used as empiric therapy for persistent fever in febrile neutropenic patients, although no change in overall outcome was noted. However, despite the improved therapeutic index of these amphotericin B formulations as compared with amphotericin B deoxycholate, they have not been shown superior in efficacy. The use of these preparations in patients with severe fungal infection who have baseline renal insufficiency or who are at very high risk for nephrotoxicity (e.g., allogenic bone marrow transplant recipients receiving nephrotoxic medications) is recommended. In addition, in patients who have infections that respond poorly

Table 207.2 Amphotericin B lipid formulations

Amphotericin B lipid formulations	Structure	Indications	Dosages
Amphotericin B lipid complex (ABLC) (Abelcet)	Ribbonlike structures of a bilayered membrane formed by combining a 7:3 mixture of dimyristoyl phosphatidylcholine and dimyristoyl phosphatidylglycerol with amphotericin B (drug/lipid ratio of 1:1)	Invasive fungal infections in patients refractory or intolerant to amphotericin B deoxycholate	5 mg/kg/d as single infusion
Amphotericin B cholesteryl sulfate complex colloidal dispersion (ABCD), (Amphotec)	Disklike structures of cholesterol sulfate complexed with amphotericin B in equimolar concentration	Treatment of patients who either failed or are intolerant to amphotericin B deoxycholate; increased toxicity noted	3–4 mg/kg/d (up to 6 mg/kg/d)
Liposomal amphotericin B (Ambisome)	Small unilamellar liposomes about 55–75 nm in diameter made up of a bilayer membrane of hydrogenated soy phosphatidylcholine and distearoyl phosphatidylglycerol stabilized by cholesterol and combined with amphotericin B in a 2:0.8:1:0.4 ratio	Treatment of patients with *Aspergillus* species, *Candida* species, and/or *Cryptococcus* species infection refractory to amphotericin B deoxycholate, or in patients in whom renal impairment or toxicity precludes the use of amphotericin B deoxycholate; empirical treatment for presumed fungal infection	3–5 mg/kg/d as single infusion

Data from Hiemenz JW, Walsh TJ. Lipid formulations of amphotericin B: recent progress and future directions. *Clin Infect Dis.* 1996;22(Suppl 2):5133.

to amphotericin B, including infections caused by members of the order *Mucorales*, *Fusarium* species, and other invasive molds such as *Aspergillus*, it is possible that high doses of lipid formulations of amphotericin B will improve outcome. Although increases in the doses of lipid formulations are also associated with increased toxicity, their increased therapeutic index has largely resulted in replacement of amphotericin B deoxycholate for invasive fungal infections.

AZOLES

Similar to the polyenes, azole antifungal agents also target ergosterol albeit through an alternative mechanism of action. By binding to lanosterol 14-α-demethylase, these agents inhibit ergosterol biosysnthesis, resulting in disruption of the fungal cell membrane. The primary members of this class used in the treatment of invasive mycosis are fluconazole, itraconazole, voriconazole, and posaconazole.

Fluconazole is commercially available in both an oral and an intravenous preparation. Following oral administration, fluconazole is nearly completely absorbed with a bioavailability >90% and is widely distributed into the tissues, including the CSF (concentrations in CSF and urine concentrations are 70% to 90% of those found in the plasma). The half-life of fluconazole is approximately 30 hours, and its primary route of elimination is as unchanged drug in the urine. Doses may need to be adjusted in renal failure.

Itraconazole is available in oral capsule and solution formulations. Unlike fluconazole, itraconazole capsules have low and erratic bioavailability due to poor water solubility, which may be influenced by gastric pH. An oral solution and intravenous itraconazole formulation are available, both of which utilize hydroxy-propyl-β-cyclodextrin as an excipient to overcome the insolubility of itraconazole in aqueous solution. The oral solution has improved the bioavailability and consistency of plasma levels of itraconazole. Due to its high lipophilicity itraconazole is extensively distributed to the tissues. Itraconazole is highly protein bound (>99%) and is extensively metabolized by cytochrome P450 3A4, with less than 1% of drug found unchanged in the urine. The half-life of itraconazole is 24 hours. Due to the extensive hepatic metabolism, the oral formulations do not require dose adjustments in renal failure.

Voriconazole is available as an oral and intravenous preparation. Following oral administration, the bioavailability of voriconazole is approximately 90%. Voriconazole undergoes extensive hepatic metabolism primarily by cytochrome P450 2C19 and, to a lesser extent, 2C9 and 3A4 isoenzymes. The bioavailability of voriconazole may be influenced by polymorphisms in 2C19, with homozygous poor metabolizers having peak plasma concentrations and overall

exposures, as measured by the plasma area under the curve, 4-fold higher than those of homozygous extensive metabolizers. Compared to the other azoles, the half-life of voriconazole is variable, ranging between 6 hours and 24 hours. Significant intra- and interpatient variability has also been reported with voriconazole and may be the result of drug interactions as well as differences in metabolism between patients due to polymorphisms in the cytochrome P450 enzyme 2C19. At higher doses voriconazole demonstrates nonlinear kinetics in adults due to saturable metabolism and is distributed extensively to the tissues. The intravenous formulation contains a cyclodextrin excipient (sulfobutyl ether β-cyclodextrin), which may accumulate with decreased renal function.

Although posaconazole was previously available only PO, now an oral tablet and an intravenous formulation are available. The bioavailability of the oral suspension is greatly enhanced when coadministered with a high-fat meal. In addition, agents that increase the gastric pH (e.g., proton pump inhibitors and H_2 blockers) or motility (e.g., metoclopramide) also significantly reduce the bioavailability of the oral suspension. Posaconazole has a large volume of distribution, suggesting extensive tissue distribution, and is extensively protein bound (99%). Unlike itraconazole and voriconazole, posaconazole does not undergo phase I metabolism (mediated by cytochrome P450 enzymes) but instead is metabolized via glucuronidation (phase II metabolism). The half-life of posaconazole is 25 hours, and the majority of elimination occurs in the feces as unchanged drug.

The azole antifungals are generally well tolerated, with a mild side-effect profile consisting of nausea, vomiting, headache, dizziness, rash, pruritus, and anorexia, but these agents can also have more serious dose-limiting toxicities such as hepatic toxicity, serious dematologic effects, visual toxicities, central nervous system (CNS) side effects, and cardiovascular effects. The milder dose-related toxicities are uncommon, occurring in fewer than 5% of patients, but vary according to specific agents. Fluconazole is generally the best-tolerated agent of the class although alopecia with long-term high doses can occur. Notably, itraconazole oral solution may be associated with significant gastrointestinal adverse effects, including nausea, vomiting, and osmotic diarrhea, due to the cyclodextrin component. In addition, administration of itraconazole at doses greater than 400 mg/day can cause hypokalemia, hypertension, and pedal edema. Voriconazole has been associated with several adverse effects, including visual disturbances, CNS toxicity, hepatotoxicity, and cutaneous phototoxicity. Some of these adverse effects have been shown to be concentration dependent, particularly the CNS toxicities and/or visual disturbances. Visual disturbances, which may manifest as photophobia or abnormal vision, are transient, have not resulted in long-term toxicity, and abate with continued treatment. Posaconazole has been associated with few systemic toxicities, most commonly gastrointestinal intolerance, although this may reflect the poor bioavailability and low systemic exposures with the oral solution.

Each member of this class can cause hepatotoxicity although fluconazole is rarely associated with dose-limiting liver abnormalities. Typically, the liver dysfunction is characterized by asymptomatic elevation of transaminases in the range of two to three times the upper limit of normal. Mild, asymptomatic transaminase elevations can be managed without drug discontinuation and close follow-up. Symptomatic liver dysfunction, however, requires discontinuation of treatment. Enzyme elevations are reversible but may take months to normalize. However, cases of fatal hepatotoxicity have been reported with itraconazole, voriconazole, and posaconazole, although the latter appears to be associated with less hepatotoxicity due to its lack of hepatic metabolism.

Due to similarities between ergosterol and cholesterol biosynthesis, drug interaction can occur via inhibition of cytochrome P450 enzymes by azole antifungals. In addition, itraconazole, voriconazole, and, to a lesser extent, fluconazole are also substrates of cytochrome P450 enzymes. Although posaconazole does not undergo phase I metabolism, it is an inhibitor of cytochrome P450 3A4. In addition, posaconazole is a substrate for P-glycoprotein efflux. Thus, coadministration of azoles with drugs that are substrates, inhibitors, or inducers of these enzymes may result in significant drug interactions (Table 207.3). Therefore, careful consideration is required prior to the addition or removal of an azole to or from an existing drug regimen. Monitoring patients for signs and symptoms of toxicity or subtherapeutic effects, and when possible measuring concentrations of coadministered drugs, may also be necessary. The clinician is advised to seek out detailed drug interactions, which are available in several updated extensive on-line databases including www.drugs.com, Micromedex®

Table 207.3 Antifungal drug–drug interaction

Drug	CYP 2C19	CYP 2C9	CYP 3A4	Other selected interactions
Fluconazole	Minimal inhibitor	Moderate inhibitor	Moderate inhibitor	• Reduced concentrations with inducers of CYP enzymes
Itraconazole		Minimal inhibitor	Strong inhibitor; substrate	• Reduced concentrations with inducers of CYP enzymes • Reduced absorption with proton pump inhibitors, H_2 blockers, metoclopramide
Posaconazole			Strong inhibitor	• Reduced concentrations with rifampin/rifabutin, phenytoin, efavirenz coadministration • Reduced absorption with proton pump inhibitors, H_2 blockers, metoclopramide
Voriconazole	Strong inhibitor; substrate	Moderate inhibitor; substrate	Moderate inhibitor; substrate	• Reduced concentrations with inducers of CYP enzymes
Caspofungin				• Reduced concentrations with rifampin, phenytoin, efavirenz, dexamethasone, nevirapine, or carbamazepine coadministration • May reduce tacrolimus concentrations
Micafungin				• Increased sirolimus or nifedipine concentrations when coadministered
Flucytosine				• Nephrotoxicity from amphotericin B may lead to toxic levels of flucytosine

Note: The clinician is advised to seek out detailed drug interactions which are available in several updated extensive on-line databases including www.drugs.com, Micromedex® (www.micromedexsolutions.com), Lexicomp® (www.uptodate.com), the Aspergillus website (www.aspergillus.org.uk), and others.

Fluconazole has been used extensively in the treatment of systemic yeast infections, including primary therapy for candidemia, particularly that caused by *Candida albicans* but also other yeasts, including *Candida tropicalis, Candida parapsilosis*, and *Candida glabrata*. Only *Candida krusei* is inherently resistant to fluconazole, although resistance may develop to fluconazole and other azoles in *C. glabrata*. Fluconazole is also effective in the therapy of cryptococcal infections, including meningitis, with most use for consolidation therapy after initial therapy with amphotericin B and for long-term suppressive therapy in immunosuppressed patients, including those with acquired immunodeficiency syndrome (AIDS). Fluconazole is an alternative, when appropriate, to amphotericin B in the management of *Coccidioides immitis* meningitis. In addition, fluconazole is indicated for the prophylaxis of yeast infection in patients with chemotherapy-induced neutropenia.

Itraconazole is indicated for the therapy of endemic mycoses, including histoplasmosis, blastomycosis, and sporotrichosis, usually used after amphotericin B in severely ill patients or as primary therapy in patients with less extensive infection. It may be used for sequential therapy following initial amphotericin B in invasive aspergillosis, as primary therapy in less immunosuppressed patients with less extensive infection, and as prophylaxis in patients with chemotherapy-induced neutropenia and in allogeneic stem cell transplant recipients with graft-versus-host disease receiving corticosteroids. In addition, itraconazole is effective in cutaneous and systemic infection resulting from dematiaceous fungi, including *Exserohilum* species, *Exophiala* species, and *Bipolaris/Curvularia* species.

Voriconazole has a broad spectrum of activity against *Aspergillus* species, including *Aspergillus terreus*, *Candida* species, including those resistant to fluconazole (*C. krusei*), *Pseudallescheria boydii/Scedosporium apiospermum*, and *Fusarium* species. In vitro activity has also been demonstrated against *Cryptococcus neoformans*, *Blastomyces dermatitidis, C. immitis*, and *Histoplasma capsulatum*. Voriconazole has become the drug of choice for the primary treatment of invasive aspergillosis and infections caused by *P. boydii/S. apiospermum* and *Fusarium* species. It is also indicated for invasive candidiasis and esophageal candidiasis, including fluconazole-resistant species, although cross-resistance (particularly in *C. glabrata*) can occur as it can with posaconazole and the other azoles. Voriconazole has also been shown to be effective as early or pre-emptive therapy for presumed *Aspergillus* infections.

Posaconazole has been shown to be effective for the salvage treatment of invasive aspergillosis and invasive candidiasis, although it is only licensed in Europe for the former and has a limited role in serious *Candida* infections due to the lack of an intravenous formulation. Similar to voriconazole, posaconazole has a broad spectrum of activity against a wide range of both yeast and filamentous fungi, including *Aspergillus* and *Candida* species, the dimorphic fungi *C. immitis/posadasii*, *H. capsulatum*, and *B. dermatitidis*, and *Cryptococcus* species. However, unlike voriconazole, posaconazole also has in vitro and in vivo activity against members of the order *Mucorales*. Studies have also demonstrated the potential utility of this agent in the treatment of invasive infections caused by *Fusarium* species. Excellent efficacy of posaconazole has also been demonstrated as antifungal prophylaxis both in neutropenic patients and in allogeneic stem cell transplant recipients post-engraftment with graft-versus-host disease.

Monitoring of antifungal concentrations within biologic fluids has gained attention, and this practice is routinely used by some institutions. The majority of antifungal therapeutic drug monitoring is with the azoles voriconazole, posaconazole, and itraconazole. Several groups have reported associations between voriconazole concentrations and both clinical efficacy and toxicity. For voriconazole, trough concentrations within the bloodstream of <1 μg/mL have been associated with clinical failure in patients with invasive fungal infections, while toxicities have been reported with elevated levels (>5.5 μg/mL in one study). Although an exact range of safe and effective voriconazole concentrations has not been definitively set, a therapeutic range with a high probability of success and low probability of toxicity may be between 1.5 and 4.5 μg/mL. For posaconazole, the exact threshold associated with clinical efficacy for the treatment of invasive fungal infections remains unknown. However, as prophylaxis, studies have suggested that concentrations of 0.5 to 0.7 μg/mL may be used as a target level. Therapeutic drug monitoring may also be performed with itraconazole. However, the interpretation of these results is dependent upon the assay used for measurement of drug concentrations. When measured by analytical assays, such as high performance liquid chromatography (HPLC) or liquid chromatography mass spectrometry (LC/MS), levels of 0.5 μg/mL have been reported to be associated with improved prophylactic efficacy. Some laboratories still use a bioassay to measure itraconazole concentrations. This method is unable to distinguish between itraconazole and the active metabolite hydroxy-itraconazole, resulting in concentrations that are higher than that reported by analytical means. Unfortunately, levels measured by bioassay may be between 2 and 10 times higher than those measured by HPLC or LC/MS.

ECHINOCANDINS

The echinocandins anidulafungin, caspofungin, and micafungin are large, cyclic, semisynthetic lipopeptides. Through noncompetitive inhibition of glucan synthase, these agents deplete β-1,3-glucan, a primary component of the cell wall of many pathogenic fungi, including *Aspergillus* and *Candida* species.

Due to their high molecular weight and poor bioavailability, each member of this class is available only for intravenous administration. Each echinocandin contains a hexapeptide nucleus. However, differences in the *N*-acyl side chain are responsible for variability in the physiochemical properties among these agents. Anidulafungin is not metabolized but rather undergoes spontaneous chemical degradation to an open-ring peptide following intravenous administration. This echinocandin is also extensively protein bound (range 97% to 99%). The majority of the plasma concentration–time profile is characterized by a half-life of approximately 26 hours, followed by a long terminal half-life (52 hours). Caspofungin does undergo phase I metabolism (hydrolysis and *N*-acetylation) as well as some spontaneous chemical degradation to an open-ring peptide. However, distribution to the tissues, not excretion or metabolism, is the primary determinant of plasma clearance. Similar to anidulafungin, a half-life between 9 and 11 hours characterizes the majority of the plasma concentration–time profile, followed by a long terminal half-life of 40 to 50 hours. Caspofungin is also extensively protein bound (97%). Micafungin does undergo limited phase I metabolism. However, the primary route of elimination is as unchanged drug in the feces. Similar to anidulafungin and caspofungin, micafungin is also extensively protein bound (99.5%), with an elimination half-life between 13 and 15 hours.

Due to their inhibition of glucan synthase, a fungal-specific target without a mammalian homolog, the echinocandins are very well tolerated with few clinically significant drug

interactions. The primary adverse effects reported in clinical trials are generally mild to moderate in severity and include rash, headache, nausea, vomiting, diarrhea, and infusion-related reactions and in clinical use are rarely dose-limiting. Mild elevations in transaminases and alkaline phosphatase have also been reported. None of the members of this class act as inhibitors or inducers of cytochrome P450 isoenzymes, nor do they undergo extensive metabolism by these enzymes. Table 207.3 lists potential drug–drug interactions associated with the echinocandins.

Therapeutic uses

The echinocandins have a broad spectrum of activity against *Candida*, including non-albicans species and isolates resistant to fluconazole, and *Aspergillus* species. However, these agents lack activity against *Cryptococcus* species, *Fusarium* species, and the *Mucorales*. Each member of this class has been shown to be effective in the treatment of candidemia, invasive candidiasis, and esophageal candidiasis. In addition, caspofungin and micafungin have also been shown to be effective in the treatment of invasive aspergillosis, including in patients with refractory infections, although only caspofungin is licensed for that indication. Caspofungin has also been shown to be effective in the setting of febrile neutropenia, whereas micafungin is efficacious as prophylaxis in patients with neutropenia.

FLUCYTOSINE

The clinical usefulness of flucytosine (5-FC) is limited by its narrow spectrum of activity, frequent emergence of resistance, and toxicity. Flucytosine is usually administered at a dosage of 150 mg/kg/day in four divided doses, although 100 mg/kg/day in four divided doses may be used in combination with amphotericin B for cryptococcal meningitis. More than 90% of the drug is excreted unchanged in the urine, and patients with renal insufficiency require dosage reduction. As an approximation, the total daily dose should be reduced to 75 mg/kg with a creatinine clearance of 26 to 50 mL/min and to 37 mg/kg when the creatinine clearance is 13 to 25 mL/min. In azotemic patients, blood levels should be measured and dosage should be adjusted so that serum levels do not exceed 50 to 100 μg/mL. The drug readily diffuses to the CSF and achieves concentrations of about 74% of serum. Flucytosine is usually well tolerated and results in minor and uncommon adverse effects, such as rash, diarrhea, and mild hypertransaminasemia. The presence of azotemia or the concomitant use of amphotericin B might exacerbate the toxicity, resulting in severe leukopenia, thrombocytopenia, and enterocolitis. These complications seem to occur in many, but not all, patients with blood levels exceeding 100 μg/mL.

Flucytosine has been used extensively to treat chromomycosis. It is not used alone because of the rapid development of resistance and the availability of other less toxic agents, although it has activity in candidiasis and cryptococcosis. Importantly, 5-FC has been shown to have synergistic effects in combination with amphotericin B against most isolates of *Candida, C. neoformans*, and possibly *Aspergillus*. The combination of amphotericin B and 5-FC has been proved useful in the treatment of cryptococcal meningitis in terms of more rapid sterilization of CSF and possibly in reducing rate of relapse. Flucytosine has been used with amphotericin B for invasive *Aspergillus* infections as well as in the therapy of refractory candidemia, although its benefit in these infections has not been shown in controlled trials. Flucytosine has also been used in combination with fluconazole in both cryptococcal infections and against *Candida*.

NEW THERAPIES

Investigational azoles

New azoles are in various stages of development, including isavuconazole (BAL4815 and the oral prodrug BAL8557) and ravuconazole. Isavuconazole has been shown to have a broad spectrum of activity against *Candida* species, *C. neoformans*, *Aspergillus* species, and other opportunistic molds and yeasts. Results from a clinical trial comparing isavuconazole to voriconazole for invasive aspergillosis have recently been released suggesting similar efficacy of the agents. A similar broad spectrum of activity has been demonstrated for ravuconazole, including the *Mucorales*, although clinical development is uncertain.

Other agents

The fungal Cyp51 inhibitors VT-1129 and VT-1161 inhibit the biosynthesis of ergosterol. These agents are highly selective for fungal Cyp51 compared to mammalian cytochrome P450 enzymes,

thus there is the potential for fewer drug interactions compared to the azoles. Both agents demonstrate potent activity against yeasts, including *Candida* and *Cryptococcus* species, and VT-1161 is currently in early clinical trials. T-2307 is an aromatic diamidine with some structural similarities to pentamidine. Although the mechanism of action is not fully understood, this agent demonstrates potent activity against *Candida* species, including azole-resistant isolates, *C. neoformans*, and *Aspergillus fumigatus*. E1210 inhibits inositol acylation early in the glycosylphosphatidylinositol biosynthesis pathway in fungi but not in humans. This agent has potent, broad-spectrum activity against fungi, including *Candida*, *Aspergillus*, *Fusarium*, and *Scedosporium* species. However, E1210 is inactive against *Candida krusei* and members of the order *Mucorales*. One novel strategy that is currently being evaluated targets the epigenetic regulation in fungi. MGCD290 is a fungal deacetylase inhibitor that has been shown in vitro to act in synergy with fluconazole, voriconazole, and posaconazole, including isolates that are usually resistant to these azoles. When combined with fluconazole, synergy was observed against *Candida* species, including *C. krusei*, as well as some *Aspergillus* species, and with voriconazole, synergy was observed against most *Mucorales* isolates. Nikkomycin Z (VFS-1), which targets the synthesis of the cell wall component chitin, has shown activity against *C. immitis* and *B. dermatitidis* alone and against *Candida* species, *C. neoformans*, and *A. fumigatus* in combination with azoles.

FUTURE DIRECTIONS

Despite the increasing number of antifungal agents, treatment of fungal diseases still remains unsatisfactory. In many cases, host factors such as neutropenia, immunosuppression associated with transplantation, uncontrolled hematologic malignancy, or other causes of underlying immunosuppression play a pivotal role as important risk factors for the acquisition of fungal infections as well as for response to therapy. Future research efforts should be aimed at reducing risk of acquiring fungal infections as well as improving host defenses against these opportunistic pathogens. In addition, the development of improved diagnostics are needed to allow early and targeted therapy for specific mycoses, including drug-resistant pathogens. Finally, combination therapy may be a means for improving overall outcomes in these difficult-to-treat infections.

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208. Antiviral therapy

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Successful antiviral therapy continues to be one of the most difficult challenges facing the healthcare provider today. Certain intrinsic characteristics of the major human viral pathogens contribute to this challenge. Because all viruses parasitize host cell enzymes and structures to varying degrees, designing or discovering drugs that specifically target the virus without toxicity is difficult. Additionally, many viruses establish a latent infection in the host, during which time they are essentially quiescent. Elimination of such latent viruses from the host has not been possible to date. Some of the most serious viral infections today stem from the reactivation of latent viruses during periods of impaired cell-mediated immunity. Additionally, an ongoing challenge in antiviral therapy is the development of drug resistance due to mutating viruses and/or transmission of resistant viruses.

Most of the currently available antiviral agents target the virus by exploiting differences in viral and host replication processes. Many viruses have their own specific DNA polymerases, which are more susceptible to inhibition by specific drugs than the cellular DNA replication enzymes. Thus many antiviral agents are nucleoside/nucleotide analogs. In addition, some of these compounds accumulate preferentially in virus-infected cells or are activated by virus-encoded enzymes, increasing their specificity. Nevertheless, unlike many antibacterial agents, most antiviral agents remain far from being "magic bullets" and can have considerable dose-related toxicities.

This chapter describes the US Food and Drug Administration (FDA)-approved antiviral drugs, their primary uses, their pharmacokinetics and potential interactions, and the major toxicities associated with their administration (Table 208.1).

Antiretrovirals associated with the treatment of human immunodeficiency virus (HIV) are discussed in Chapter 99, HIV infection: antiretroviral therapy.

Table 208.1 FDA-approved antiviral drugs

Acyclovir
Adefovir
Amantadine
Boceprevir
Cidofovir
Docosanol
Entecavir
Famciclovir
Foscarnet
Ganciclovir
Imiquimod
Interferons
Lamivudine
Oseltamivir
Palivizumab
Penciclovir
Ribavirin
Rimantadine
Telaprevir
Telbivudine
Tenofovir
Valacyclovir
Valganciclovir
Vidarabine
Zanamivir

ACYCLOVIR

Acyclovir, a guanine derivative, has in vitro activity against herpes simplex virus (HSV) types 1 and 2, varicella-zoster virus (VZV), Epstein–Barr virus (EBV), and cytomegalovirus (CMV), but it is used primarily in HSV and VZV infections. Acyclovir is preferentially taken up by

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HSV-infected cells and is phosphorylated by HSV thymidine kinase, which is necessary for conversion to the active triphosphate form. It inhibits viral DNA polymerase and causes DNA chain termination when incorporated into replicating DNA. Valacyclovir (discussed later in this chapter) is a prodrug of acyclovir.

Acyclovir may be used for primary episodes of genital herpes to reduce the time of viral shedding and time to healing at a dose of 200 mg orally five times per day for 10 days. It can also be used for treatment of recurrent episodes with 200 mg orally five times a day for 5 days at the first sign of a recurrence. Acyclovir can be used as chronic suppressive therapy to decrease the incidence of recurrent genital herpes at 400 mg orally twice daily. Therapy should be evaluated periodically to reassess the need for chronic suppression. An ointment is available for primary herpes genitalis, but its impact on the natural course of the infection is marginal. Many physicians use acyclovir for the treatment of herpes labialis in a fashion similar to the treatment of genital herpes.

Acyclovir reduces mortality in HSV encephalitis and should be used at high dosages (10–15 mg/kg intravenously [IV] every 8 hours) for 14 to 21 days. Severe mucosal and cutaneous infections in immunocompromised patients may require IV therapy (5 mg/kg every 8 hours) for 7 days. HIV-1-infected patients often require oral suppression to prevent recurrences. Refractoriness to therapy in such patients may indicate the development of acyclovir resistance.

Acyclovir is also active against VZV, but treatment of VZV infections requires higher dosages than treatment of uncomplicated HSV infections. Acyclovir, 800 mg five times daily for 7 to 10 days, should be used in patients with herpes zoster (shingles) to prevent dissemination and in an attempt to shorten the time to healing. In immunocompromised patients, the recommended dose is 10 mg/kg IV every 8 hours for 7 days. Such treatment does not convincingly alter the subsequent development of postherpetic neuralgia, however. Ophthalmic zoster, involving the first branch of the trigeminal nerve, warrants evaluation by an ophthalmologist and immediate therapy, which may be given orally. VZV has also been associated with the syndrome of acute retinal necrosis, which should be treated as a medical emergency.

Acyclovir 800 mg orally every 6 hours for 5 days is effective in the treatment of primary varicella or chickenpox, shortening the duration and severity of illness when begun within 24 hours after the onset of rash. The recommended dose for the treatment of immunocompromised patients is 10 mg IV every 8 hours for 7 to 10 days. Chickenpox in pregnant women may be life threatening, particularly when varicella pneumonia develops. Acyclovir treatment of neonates with VZV or HSV infection is also indicated.

Oral acyclovir, 400 mg five times a day, or IV therapy is effective in preventing mucocutaneous HSV infections in both solid organ and bone marrow transplant patients. It may be given longer term (6 months) to decrease the incidence of VZV infections in bone marrow transplant recipients.

Acyclovir may be of some benefit in EBV-induced lymphoproliferative disease in immunocompromised patients, but it is not clinically useful in EBV disease such as mononucleosis. Incidentally, acyclovir is of no utility in the treatment of chronic fatigue immune dysfunction syndrome (CFIDS)/chronic fatigue syndrome (CFS), because this syndrome has no causal association with EBV infection. Acyclovir is active and has been clinically useful against *Herpesvirus simiae*, or B virus, an endemic herpesvirus of certain primate species, which, when transmitted to humans has resulted in severe neurologic disease and death.

Pharmacokinetics

Acyclovir has poor water solubility and hence poor oral bioavailability (10%–15%) but good tissue distribution; the low oral bioavailability necessitates frequent administration which is partly resolved by using either the IV formulation or valacyclovir. The serum half-life is 2.5 to 3 hours. Acyclovir is excreted renally and dose adjustment is necessary in patients with impaired renal function.

Major toxicities

Central nervous system (CNS) effects range from confusion to seizures and coma, especially in the settings of renal insufficiency, underlying altered mental status, and old age. Renal failure may occur from precipitation in the renal tubules. When administering high IV doses, it is important to ensure adequate hydration of the patient. Acyclovir is potentially teratogenic, but inadvertent or therapeutic administration during pregnancy has occurred without obvious adverse effects.

Drug interactions

Acyclovir may potentiate or be potentiated by drugs that decrease renal function or compete for active tubular secretion. Coadministration of acyclovir with cimetidine, mycophenolate mofetil, or probenecid may increase acyclovir exposure although dose adjustment is usually not necessary because of the wide therapeutic index of acyclovir. Acyclovir may increase cyclosporine and theophylline exposure.

ADEFOVIR

Adefovir dipivoxil is a nucleotide analog that inhibits reverse transcriptase. It is indicated for the treatment of chronic hepatitis B infection with active viral replication and either elevated serum aminotransferases (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) or histologically active disease. Adefovir competitively inhibits hepatitis B virus (HBV) DNA polymerase, causing DNA chain termination. The recommended dose of adefovir is 10 mg daily. HIV resistance may emerge in chronic hepatitis B patients treated with adefovir but with unrecognized or untreated HIV infection.

Pharmacokinetics

Following oral intake, adefovir dipivoxil is readily converted to adefovir. It is renally excreted by both glomerular filtration and tubular secretion. The dosing interval should be adjusted in patients with renal impairment.

Major toxicities

Associated adverse events include asthenia, headache, abdominal pain, gastrointestinal (GI) upset, pruritus, lactic acidosis, hepatitis, hepatomegaly with steatosis, and nephrotoxicity with prolonged use. An exacerbation of hepatitis can occur when treatment is discontinued.

Drug interactions

Adefovir may potentiate or be potentiated by drugs that decrease renal function or compete for active tubular secretion.

AMANTADINE

Amantadine hydrochloride (1-adamantanamine hydrochloride) is used to treat Parkinson's disease and as an antiviral agent that prevents uncoating of influenza A virus after host cell entry. In 2008/2009, it was determined that widespread resistance exists to amantadine, among circulating influenza A strains. It is therefore no longer recommended for prevention or treatment.

BOCEPREVIR

Boceprevir and telaprevir (discussed later) represent the first orally administered direct-acting antivirals (DAA) against hepatitis C virus (HCV). Both are HCV NS3/4A serine protease inhibitors; boceprevir is indicated for patients with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy, including prior null responders, partial responders, and relapsers. When initiating therapy with boceprevir, patients should receive a 4-week lead-in period with pegylated interferon (peginterferon alfa) and ribavirin followed by the addition of boceprevir 800 mg three times daily with food. Treatment is for 24 and 32 weeks in those who are treatment naïve and treatment experienced, respectively. The need for continued peginterferon/ribavirin treatment is then determined by virologic response (response-guided therapy) at week 4 (i.e., after the lead-in period), 8, and 24 as well as prior treatment history, and presence or absence of cirrhosis upon liver biopsy.

Pharmacokinetics

Boceprevir is formulated as a 1:1 mixture of two diastereomers. In plasma, a 2:1 ratio is observed favoring the active diastereomer. It is rapidly absorbed and food increases its exposure. Metabolism of boceprevir is via aldo-keto reductase (AKR) to inactive ketones. The average terminal elimination half-life of boceprevir is 3.4 hours.

Major toxicities

Associated adverse events for the combination of boceprevir, peginterferon, and ribavirin include fatigue, anemia, nausea, headache, and dysgeusia. Patients should be closely monitored for anemia, hypersensitivity, and neutropenia.

Drug interactions

Boceprevir is a substrate and potent CYP3A inhibitor. Coadministration of boceprevir with alfuzosin, cisapride, drospirenone, pimozide, rifampin, St. John's wort (*Hypericum perforatum*),

ergot derivatives (i.e., dihydroergotamine, ergonovine, ergotamine, or methylergonovine), certain anticonvulsants (i.e., carbamazepine, phenobarbital, or phenytoin), certain HMG-CoA reductase inhibitors (i.e., lovastatin or simvastatin), certain phosphodiesterase type 5 inhibitors when used in the treatment of pulmonary hypertension (i.e., sildenafil and tadalafil), or certain sedative/hypnotics (i.e., oral midazolam or triazolam) is contraindicated. It is not recommended to coadminister boceprevir and the following medications: dexamethasone, rifabutin, salmeterol, inhaled corticosteroids, and certain HIV protease inhibitors (i.e., atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir). The dose of colchicine or phosphodiesterase type 5 inhibitor when used for erectile dysfunction (e.g., sildenafil, tadalafil, or vardenafil) should be adjusted when coadministered with boceprevir.

CIDOFOVIR

Cidofovir is an acyclic nucleoside derivative with antiviral activity. Cidofovir was designed to minimize the resistance that develops in response to nucleoside analogs that require phosphorylation by viral enzymes, such as acyclovir and ganciclovir. Although cidofovir must be diphosphorylated to become active, it does not require phosphorylation by viral kinases. Rather, cidofovir is activated by cellular enzymes. Cidofovir is more active against herpesvirus DNA polymerases than cellular DNA polymerases and thus has selective antiviral activity.

Cidofovir is primarily used for the treatment of CMV retinitis in acquired immunodeficiency syndrome (AIDS) patients. Its use in other CMV infections and in other immunocompromised patients has not been adequately evaluated. Cidofovir has been effective in delaying the progression of CMV retinitis in AIDS patients, including those who have failed ganciclovir or foscarnet therapy. Ganciclovir-resistant strains of CMV, which carry mutations in the UL97 phosphokinase gene, generally remain susceptible to cidofovir. However, other ganciclovir-resistant mutants, especially those carrying mutations in the DNA polymerase gene may be cross-resistant to cidofovir. CMV strains resistant to ganciclovir, foscarnet, and cidofovir have also been described.

Intravenous cidofovir is administered with probenecid to prevent rapid secretion of the drug by the renal tubules. Creatinine clearance should be estimated by calculation or directly measured before initiating therapy with cidofovir. The nephrotoxic potential of cidofovir is such that a creatinine clearance less than 55 mL/min, a serum creatinine greater than 1.5 mg/dL, or 2+ proteinuria is a contraindication to its use. Induction therapy with cidofovir is initiated at a dosage of 5 mg/kg once weekly for 2 weeks, followed by the same dose once every 2 weeks as maintenance therapy. Intravenous saline prehydration with 1 L of normal saline immediately before cidofovir infusion is mandatory to prevent nephrotoxicity. If possible, an additional liter of saline should be administered with and after cidofovir over a 1- to 3-hour period. In addition, great care should be taken to monitor renal function with both urine and serum measurements, and the importance of taking the probenecid should be emphasized. Probenecid is administered as follows: 2 g 3 hours before infusion and 1 g at 2 and 8 hours after infusion.

Pharmacokinetics

Approximately 70% of cidofovir is eliminated unchanged by the kidneys. Its plasma half-life is approximately 2.5 hours, but it has a long-lasting antiviral effect. The latter is the result of the intracellular persistence of its active phosphorylated metabolite.

Major toxicities

As described, the major toxicity of cidofovir is its nephrotoxicity. Neutropenia has occurred in approximately 20% of cidofovir recipients in clinical trials.

Drug interactions

The most important drug interactions are those leading to additional nephrotoxicity. Additive or synergistic nephrotoxic effects with other drugs known to result in nephrotoxicity, such as aminoglycosides or amphotericin B, have not been studied. In addition, the potential for probenecid effects on the metabolism and disposition of other drugs must be considered.

DOCOSANOL

Docosanol is a saturated fatty alcohol that can reduce the duration of cold sores associated with HSV. Its mechanism of action is not entirely known but may involve inhibition of fusion between the viral envelope and human host cell.

Docosanol 10% is available over the counter and is applied topically to the cold sore five times a day for up to 10 days. The most commonly reported side effects include headache and local skin irritation.

ENTECAVIR

Entecavir is a nucleoside analog that works by inhibiting HBV polymerase. It is indicated for the treatment of chronic hepatitis B infection in adults with evidence of active viral replication and either persistently elevated serum aminotransferases (ALT or AST) or histologically active disease. For the treatment of chronic hepatitis B infection in adults and adolescents (16 years old or older) who are nucleoside treatment naïve, the dosing is 0.5 mg daily. For patients with hepatitis B viremia also being treated with lamivudine or who have lamivudine and/or telbivudine resistance, the dose is 1 mg daily. Dose adjustment is necessary for patients with decreased renal function. Like adefovir, HIV resistance may emerge in chronic hepatitis B patients treated with entecavir but with unrecognized or untreated HIV infection.

Pharmacokinetics

Entecavir has a bioavailability of 100% following oral administration when the patient is fasting. It is predominantly eliminated by the kidney as unchanged drug. It undergoes both glomerular filtration and tubular secretion.

Major toxicities

Commonly reported side effects include headaches, fatigue, dizziness, and GI upset. Severe acute exacerbations of hepatitis have occurred when treatment has been discontinued.

Drug interactions/precautions

Entecavir may potentiate or be potentiated by drugs that decrease renal function or compete for active tubular secretion.

FAMCICLOVIR

Famciclovir, a diacetyl 6-deoxy analog of penciclovir (9-[4-hydroxy-3-hydroxymethylbut-1-yl] guanine), is a nucleoside analog that has a spectrum of activity similar to that of acyclovir. Famciclovir is an inactive prodrug of penciclovir. After oral administration, famciclovir is rapidly metabolized to active penciclovir, which is phosphorylated by viral thymidine kinase and has a mechanism of action similar to acyclovir. Famciclovir is more bioavailable than acyclovir and has a prolonged intracellular half-life, which permits thrice-daily dosing. Famciclovir is approved for treatment of herpes zoster (500 mg three times daily for 7 days) and is similar to acyclovir in ameliorating the course of the acute attack. It is also claimed, on the basis of two studies, that famciclovir shortens the duration of postherpetic neuralgia. It is also indicated for the treatment and suppression of recurrent genital HSV (treatment: 1000 mg every 12 hours for 1 day; suppression: 250 mg every 12 hours for up to 1 year) and recurrent herpes labialis in immunocompetent patients (1500 mg as a single dose). For the treatment of orolabial or genital herpes in HIV-infected patients, it is recommended that famciclovir 500 mg be given every 12 hours for 7 days.

Pharmacokinetics

Famciclovir is excreted renally. The serum half-life is 2.5 to 3 hours, but the intracellular half-life is 10 to 20 times longer. Dose adjustment is necessary in patients with reduced renal function.

Major toxicities

In clinical trials, no major adverse effects have been reported to date. No adverse effects were observed on embryo–fetal development in animal testing. However, no adequate and well-controlled studies have been conducted in pregnant women. Testicular toxicity was observed in animal models, and decreased fertility was observed in male rats after 10 weeks of administration at 1.9 times the human dosage.

Drug interactions

Probenecid may lead to increased famciclovir levels. Famciclovir may lead to increased digoxin levels.

FOSCARNET

Foscarnet (phosphonoformic acid) binds to pyrophosphate binding sites on viral DNA polymerases and reverse transcriptases. This compound does not bind to cellular DNA polymerases at virus-inhibitory concentrations. Foscarnet is active against all herpesviruses and has some

direct activity in vitro against HIV-1. Foscarnet is used in AIDS patients with CMV retinitis who cannot tolerate or worsen on ganciclovir. Foscarnet is not curative but delays progression to greater than 3 months versus less than 1 month without therapy. Induction treatment is given at 60 mg/kg IV every 8 hours for 2 to 3 weeks, followed by maintenance therapy at 90 mg/kg once daily. Foscarnet is also used in resistant VZV and HSV infections in AIDS patients.

Pharmacokinetics

Foscarnet is excreted renally. Its half-life is variable and highly dependent on renal function, which is invariably impaired by foscarnet. Thus, close monitoring of renal function with dosage adjustment is mandatory in all patients.

Major toxicities

The major toxicity of foscarnet is impairment of renal function. In addition, hypocalcemia, hypophosphatemia, hyperphosphatemia, hypomagnesemia, and hypokalemia may occur.

Drug interactions

Foscarnet may interact with pentamidine, increasing the risk of fatal hypocalcemia, and may have additive effects on anemia due to zidovudine.

GANCICLOVIR

Ganciclovir (9-[1,3-dihydroxy-2-propoxymethyl] guanine, a guanine derivative) is a major antiviral agent used against CMV. It is the active form of the prodrug valganciclovir (discussed later). Ganciclovir is phosphorylated by viral and then cellular kinases and preferentially accumulates in CMV-infected cells. It competitively inhibits viral DNA polymerase and is incorporated into DNA, acting as a chain terminator. Ganciclovir is used primarily in AIDS-associated CMV retinitis, colitis, pneumonitis, and disseminated disease. Efficacy in AIDS is clearly established only for retinitis, in which it slows progression and is not curative. Retinitis is treated with an induction phase (5 mg/kg every 12 hours for 14 to 21 days) followed by maintenance at the same dose once a day. Rarely maintenance may also be given orally as 1000 mg three times daily with food. Patients who fail while receiving maintenance therapy may be "reinduced" or changed to foscarnet. Ganciclovir tablets can also be used for the prevention of CMV disease in patients with advanced HIV infection. The recommended dose for this indication is 1000 mg three times a day with food.

An intravitreal ganciclovir implant for the treatment of CMV retinitis is available. Because such local therapy does not prevent the development of CMV disease elsewhere, most importantly in the contralateral eye, combination therapy with systemic ganciclovir has been studied. A large-scale study demonstrated that oral ganciclovir, albeit at a dosage of 4.5 g/day, prevented the development of retinitis in the unaffected eye almost as well as did IV ganciclovir. CMV retinitis is much less common since the advent of highly active antiretroviral therapy (HAART), and prophylaxis may be unnecessary in those patients achieving immune reconstitution. However, CMV retinitis often occurs in patients in whom antiretroviral therapy has already failed.

Ganciclovir prevents CMV disease in high-risk transplant patients when given for 7 to 14 days at the same dosages as for induction therapy. The duration of maintenance therapy depends on the intensity of immunosuppression and should be given for at least 100 days after the transplant in the case of bone marrow transplant patients. Treatment of established CMV pneumonia in bone marrow transplant patients is effective when combined with IV immunoglobulin.

Pharmacokinetics, major toxicities, and drug interactions

Ganciclovir is excreted renally. Dose reductions based on creatinine clearance are necessary in patients with impaired renal function. The major toxicity of ganciclovir is hematologic, often causing anemia, neutropenia, and thrombocytopenia. All cytotoxic drugs that inhibit cell replication have the potential to significantly increase the marrow toxicity of ganciclovir. These include chemotherapeutic agents, trimethoprim–sulfamethoxazole, dapsone, zidovudine, and other nucleoside analogs. Other adverse events associated with ganciclovir use include renal insufficiency, fever, diarrhea, anorexia, vomiting, and sweating. Cyclosporin, amphotericin B, and other nephrotoxic agents should be used with caution because of the increased risk of combined nephrotoxicity. Probenecid may lead to increased ganciclovir levels.

Ganciclovir has demonstrated teratogenic and carcinogenic effects in animal studies.

IMIQUIMOD

Imiquimod is a topical agent that may be used for the treatment of condyloma acuminata. It can also be used to treat actinic keratosis and superficial basal cell carcinoma. Its mode of action is unknown but it appears to act as an immune response modifier. Imiquimod induces mRNA encoding cytokines, including interferon-α, at the application site. Human papillomavirus (HPV) L1 mRNA and HPV DNA levels decrease significantly following treatment. It has no direct antiviral activity. Systemic absorption appears to be minimal, and local reactions appear to be the major toxicity. However, its long-term effects and safety have not been evaluated.

INTERFERONS

Interferons are naturally occurring glycoproteins with antiviral, antitumor (antiproliferative), and immunomodulatory activities. They are induced by viral infection, especially double-stranded RNA viruses. Interferon-α is primarily synthesized by B lymphocytes and interferon-β by fibroblasts and other cells. Interferon-α and interferon-β are closely related. Interferon-α is actually a heterogeneous family of proteins encoded by multiple similar genes. Interferon-γ is produced by T lymphocytes and is induced by mitogenic stimuli, such as antigen-presenting cells and antigen. Interferon-γ also has macrophage-activating functions and other interleukin activities, modulating the function of other lymphocytes. *Interferon alfacon-1* is not found in nature, but its structure was derived by combining the sequences of various naturally occurring interferons and produced by recombinant DNA technology.

The mechanism(s) of action of interferons is varied. Their antiviral effect is partly mediated by inducing cellular enzymes that lead to a shutdown of protein synthesis in virus-infected cells, as well as activating RNA degradation.

Route of administration and major toxicities

Administration is subcutaneous, intramuscular (IM), or intralesional. Major toxicities commonly observed are flu-like symptoms, fever (in almost all patients treated), myalgias, fatigue, and alopecia. Exacerbation of some autoimmune diseases and psoriasis with interferon has been observed. Depression has been associated with administration of some interferons. Ophthalmologic side effects such as retinal hemorrhages have been rarely reported concomitantly with interferon therapy.

Interferon-α2a

Interferon-α2a (recombinant human protein made in *Escherichia coli*) may be used in the treatment of the following conditions: (1) AIDS-associated Kaposi's sarcoma (the response correlates with extent of HIV-1 progression more than the severity of Kaposi's sarcoma) and (2) chronic hepatitis C (see the following section).

Interferon-α2b

Interferon-α2b (recombinant human protein made in *E. coli*) is used in the treatment of the following conditions:

- Condyloma acuminata: Interferon-α2a is injected intralesionally for the treatment of condyloma acuminata. Injection of 1 million units per lesion is performed with a tuberculin syringe on alternate days, three times a week for 3 weeks. The product literature should be consulted for other details regarding administration and dosage.
- AIDS-associated Kaposi's sarcoma: The dosage is 30 million units/m^2 three times a week, administered IM or subcutaneously. If tolerated, treatment may be continued until resolution of tumors.
- Chronic hepatitis C: Interferon treatment decreases transaminase levels and may lead to sustained virologic response. The benefit extends beyond the period of therapy. Relapse may be treated with combination ribavirin and interferon therapy. Interferon-naïve patients may also be treated with combination therapy. The dosage is 3 million units subcutaneously three times weekly. The optimal duration of therapy in different situations remains to be defined.
- Chronic hepatitis B: A virologic response with loss of eAg (and sAg in some patients) and improved transaminases may occur. Lasting remission may also be occasionally obtained. Interferon-α2b has been administered as 5 million units daily or 10 million units three times a week for this indication.

Interferon-α3n

Interferon-α3n is a purified natural human leukocyte interferon. It is produced by infecting human leukocytes with Sendai virus and then purifying the induced interferon. It is used intralesionally for condyloma acuminata.

Interferon alfacon-1

Interferon alfacon-1 is used in the treatment of chronic hepatitis C. A dose of 9 μg is administered subcutaneously three times a week for 24 weeks.

Peginterferon-α2a

Peginterferon-α2a is a covalent conjugate of interferon-α2a and a PEG (polyethylene glycol) moiety. Pegylation lowers the systemic clearance of interferon-α2a 100-fold, thereby increasing the mean terminal half-life after subcutaneous dosing from 5.1 hours to 80 hours. Peginterferon-α2a is indicated as monotherapy and in combination with ribavirin for the treatment of chronic hepatitis C infection in patients with compensated liver disease. Efficacy, defined by achieving sustained virologic response, is greater with the use of peginterferon-α2a compared to interferon-α2a. The recommended dose for the treatment of chronic hepatitis C in monotherapy and in combination therapy with ribavirin is 180 μg subcutaneously weekly. The side-effect profile is similar to that of interferon-α2a.

Peginterferon-α2b

Peginterferon-α2b is a covalent conjugate of interferon-α2b and monomethoxypolyethylene glycol (PEG). Its use is indicated for the treatment of chronic hepatitis C, as monotherapy and in combination with ribavirin in patients with compensated liver disease. Virologic response rates are superior with the use of peginterferon-α2b compared to interferon-α2b in patients with hepatitis C genotype 1. The superiority is less clear in the treatment of other hepatitis C genotypes. When used as monotherapy, the recommended dose is 1.0 μg/kg/week, subcutaneously. When used in combination with ribavirin, peginterferon-α2b is dosed 1.5 μg/kg/week. The side-effect profile is similar to that of interferon-α2b with the exception of a higher incidence of injection site reactions/inflammation with the pegylated agent.

LAMIVUDINE

Lamivudine is a pyrimidine analog most commonly used as part of combination regimens for treatment of HIV-1 infection. Lamivudine also inhibits hepatitis B DNA polymerase and may be used as treatment for chronic hepatitis B infection. Treatment with 100 mg daily has been shown to result in serologic conversion, virologic response, and histologic improvement. Treatment has been associated with the development of lamivudine-resistant mutants. Treatment of HIV-1-positive patients with lamivudine alone is not recommended because it is likely to result in rapid appearance of lamivudine-resistant HIV-1 strains. Lactic acidosis with severe hepatomegaly and steatosis are rare side effects of lamivudine. The majority of lamivudine is excreted unchanged in the urine.

Pharmacokinetics

Lamivudine is rapidly absorbed after oral intake. It is phosphorylated intracellularly. The incorporation of monophosphorylated lamivudine into viral DNA by HBV polymerase causes chain termination. The majority of lamivudine is eliminated unchanged in the urine. The mean elimination half-life is between 5 and 7 hours. Dose adjustment is necessary in patients with impaired renal function.

Adverse events

Serious adverse events reported with the use of lamivudine in patients with chronic hepatitis B infection include lactic acidosis, hepatic steatosis, pancreatitis, and post-treatment exacerbation of hepatitis B.

Drug interactions

As lamivudine is mainly eliminated by active organic cationic secretion into the urine, the possibility exists of interactions with other drugs eliminated by a similar mechanism. However, no clinically relevant interactions are known that would require dose adjustments.

OSELTAMIVIR

Oseltamivir phosphate is a neuraminidase inhibitor. It is indicated for the treatment of uncomplicated influenza in patients at least 1 year old. It is also indicated for the prophylaxis of influenza in

this same population. By inhibiting influenza virus neuraminidase, it is believed to alter viral particle aggregation and release. For the treatment of influenza in adults and adolescents, oseltamivir is dosed 75 mg twice daily for 5 days. Treatment should be started within the first 2 days of the commencement of symptoms. For prophylaxis of influenza, oseltamivir should be prescribed 75 mg once daily for a minimum of 7 days. The treatment should be started within 2 days of exposure.

Pharmacokinetics

Oseltamivir is absorbed by the GI tract and is converted to the carboxylate salt by hepatic esterases. Oseltamivir carboxylate is eliminated in the urine by both glomerular filtration and tubular secretion. The product package insert should be reviewed for information regarding plasma concentrations following various dosing schedules in renally impaired patients.

Drug interactions

Clinically significant drug interactions are unlikely to occur.

Common toxicities

Associated adverse events include GI upset, bronchitis, abdominal pain, dizziness, headache, insomnia, and fatigue.

PALIVIZUMAB

Palivizumab is a monoclonal antibody directed against the F protein of respiratory syncytial virus (RSV). It is used for the prevention of RSV infection in high-risk pediatric patients by passive immunization. Palivizumab is a "humanized" monoclonal antibody. It is produced in vitro and was developed using recombinant technology. It is genetically composed of 95% human and 5% murine sequences. It is administered as an IM injection at a dose of 15 mg/kg of body weight. Its efficacy has been demonstrated in children with bronchopulmonary dysplasia (BPD) and premature infants born at less than 35 weeks' gestation. Use of the monoclonal antibody resulted in a 55% decrease in the rate of hospitalization due to RSV infections. However, the severity of infection occurring despite prophylaxis did not appear to be significantly affected.

Pharmacokinetics and major toxicities

The mean half-life in pediatric patients was 20 days. Although no major toxicities have been observed, the potential for local and anaphylactic reactions may exist with this preparation, as with all protein injections.

PENCICLOVIR

Penciclovir is a nucleoside analog similar to ganciclovir in structure. It has activity similar to that of acyclovir and is available only as a topical preparation for recurrent herpes labialis. Famciclovir is an oral prodrug of penciclovir. In clinical trials, penciclovir shortened the duration of symptoms by half a day, if applied within 1 hour of the beginning of symptoms and again every 2 hours while awake. Thus, its unimpressive performance is similar to that of all topical preparations available for the treatment of herpes infections, other than in the eye.

RIBAVIRIN

Ribavirin is a synthetic nucleoside that interferes with viral RNA transcription, but its complete mechanism of action may be more complex. Ribavirin has a broad spectrum of activity against RNA viruses, including RSV, hepatitis C, measles virus, Lassa fever virus, and hantaviruses.

A major use for ribavirin is as combination therapy with interferon-α against chronic hepatitis C. Oral ribavirin combined with injected interferon-α (see below) has been shown to produce a sustained virologic response when used either as initial therapy or after relapse in patients previously treated with interferon-α alone. Oral dosage is based on body weight and is 400 mg in the morning and 600 mg in the evening daily for those weighing less than 75 kg. For those weighing more than 75 kg, the dosage is 600 mg twice a day. For previously untreated patients, treatment should be administered for 24 to 48 weeks. Discontinuation of therapy should be considered in those who have not responded by 24 weeks. For patients who have relapsed after interferon therapy, the recommended duration is 24 weeks. Ribavirin is administered as an aerosol for confirmed, severe, lower respiratory (RSV) infection in infants or the immunosuppressed adult host. Because ribavirin has in vitro activity against Lassa fever virus and hantaviruses, it has been used intravenously in Lassa fever cases, in hemorrhagic fevers, and in the recent hantavirus

pulmonary syndrome outbreak in the United States. Management of these rare and often fatal infections mandates contact with the Centers for Disease Control and Prevention (Atlanta, Georgia).

Pharmacokinetics

Ribavirin is rapidly absorbed after oral administration and undergoes first-pass metabolism. The elimination half-life of ribavirin is more than 300 hours after multiple dosing. Ribavirin thus accumulates over the long term in vivo. Aerosolized ribavirin is absorbed systemically with a plasma half-life greater than 9 hours.

Major toxicities

Ribavirin is potentially mutagenic, teratogenic, and embryotoxic. Documentation that a female patient is not pregnant and two methods of contraception while receiving therapy and for 6 months after treatment is therefore recommended. It is also recommended that similar precautions be observed if the male partner is being treated. Hematologic side effects, principally hemolytic anemia, are common, and the recommendations for dosage adjustment and discontinuation vary depending on whether the patient has known cardiac disease. Ribavirin by the aerosol route may lead to respiratory failure in chronic obstructive pulmonary disease (COPD) and asthma. Of note, the drug may precipitate in the mechanical ventilator and lead to an inability to ventilate the patient.

Drug interactions

It is not recommended to coadminister didanosine with ribavirin due to increased exposure to didanosine.

RIMANTADINE

Rimantadine hydrochloride (α-methyltricyclo-[3.3.1.1/3.7]decane-1-methenamine hydrochloride) is a structural analog of amantidine. It has essentially the same indications as amantadine, the prevention and treatment of influenza A. Similar to amantadine, due to widespread resistance among circulating influenza A strains, rimantadine is no longer recommended for the prevention or treatment of influenza.

TELAPREVIR

Telaprevir is a DAA that inhibits the NS3/4A serine protease of HCV. It is indicated for patients with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy, including prior null responders, partial responders, and relapsers. The treatment regimen is telaprevir 750 mg three times daily with food coadministered with peginterferon alfa and ribavirin for 12 weeks, followed by a response-guided regimen of either 12 or 36 additional weeks of peginterferon alfa and ribavirin depending on viral response and prior response status. HCV RNA should be monitored regularly as an inadequate viral response could lead to the development of resistance. Therefore, treatment discontinuation is recommended when HCV RNA levels exceed 1000 IU/mL at week 4 or 12, or upon confirmed detectable HCV RNA levels at week 24.

Pharmacokinetics

Telaprevir binds primarily to alpha 1-acid glycoprotein and albumin in a concentration-dependent manner. It is primarily metabolized by CYP3A but aldo-keto reductases and other non-CYP enzymes may also be involved.

Major toxicities

The most common adverse events associated with telaprevir are rash, pruritus, anemia, nausea, hemorrhoids, diarrhea, anorectal discomfort, dysgeusia, fatigue, vomiting, and anal pruritus. Telaprevir is associated with hypersensitivity including Stevens–Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS), and toxic epidermal necrolysis (TEN). Fatal cases have been reported in patients with progressive rash and systemic symptoms who continued to treatment with telaprevir after a serious skin reaction was identified, therefore serious skin reactions, including rash with systemic symptoms or a progressive severe rash, warrant immediate discontinuation of peginterferon alfa, ribavirin, and telaprevir; discontinuation of other medications known to be associated with serious skin reactions should be considered. Patients should be promptly referred for urgent medical care.

Drug interactions

Telaprevir is a substrate and potent inhibitor of CYP3A and P-glycoprotein. Coadministration of telaprevir with alfuzosin, cisapride, pimozide,

rifampin, St. John's wort (*Hypericum perforatum*), ergot derivatives (i.e., dihydroergotamine, ergonovine, ergotamine, or methylergonovine), certain HMG-CoA reductase inhibitors (i.e., lovastatin or simvastatin), certain phosphodiesterase type 5 inhibitors when used in the treatment of pulmonary hypertension (i.e., sildenafil and tadalafil), or certain sedative/hypnotics (i.e., oral midazolam or triazolam) is contraindicated. It is not recommended to coadminister telaprevir and the following medications: rifabutin, salmeterol, certain corticosteroids (i.e., fluticasone, budesonide, prednisone, or methylprednisolone), and certain HIV protease inhibitors (i.e., darunavir/ritonavir, fosamprenavir/ritonavir, or lopinavir/ritonavir). The dose of colchicine or phosphodiesterase type 5 inhibitor when used for erectile dysfunction (e.g., sildenafil, tadalafil, or vardenafil) should be adjusted when coadministered with telaprevir.

TELBIVUDINE

Telbivudine is a nucleoside analog with activity against HBV DNA polymerase. It is indicated for the treatment of chronic hepatitis B infection in adult patients with evidence of viral replication and either persistently elevated aminotransaminases or histologically active disease. The recommended dosage is 600 mg once daily. The optimal duration of treatment has not yet been determined.

Pharmacokinetics

Telbivudine is phosphorylated by cellular kinases to the active triphosphate form (telbivudine 5′-triphosphate), which competes with thymidine 5′-triphosphate. When telbivudine 5′-triphosphate is incorporated by the viral DNA, it causes chain termination. Telbivudine is primarily eliminated by renal excretion as unchanged drug. Patients with moderate to severe renal impairment require modification of the dosing interval.

Adverse events

In clinical studies, telbivudine was well tolerated. However, lactic acidosis and severe hepatomegaly with steatosis have been reported. Severe exacerbations of hepatitis can occur after discontinuing therapy with telbivudine. No teratogenic toxicity has been seen in animal studies.

Drug interactions

No clinically remarkable drug–drug interactions are known.

TENOFOVIR

Tenofovir disoproxil fumarate is a nucleotide analog that inhibits reverse transcriptase. Tenofovir is indicated for the treatment of chronic hepatitis B infection and is commonly used for the prevention and treatment of HIV. The recommended dose of tenofovir disoproxil fumarate is 300 mg (245 mg tenofovir disoproxil) daily.

Pharmacokinetics

Following oral intake, tenofovir disoproxil fumarate is readily converted to tenofovir. It is renally excreted by both glomerular filtration and tubular secretion. The dosing interval should be adjusted in patients with renal impairment.

Major toxicities

Associated adverse events include asthenia, headache, abdominal pain, GI upset, pruritus, lactic acidosis, hepatitis, hepatomegaly with steatosis, and nephrotoxicity with prolonged use. An exacerbation of hepatitis can occur when treatment is discontinued.

Drug interactions

Tenofovir may potentiate or be potentiated by drugs that decrease renal function or compete for active tubular secretion.

TRIFLURIDINE

Trifluridine (trifluorothymidine) is a fluorinated pyrimidine analog that interferes with DNA synthesis and is used topically for the treatment of HSV keratitis. Trifluridine may cause local irritation and palpebral edema.

VALACYCLOVIR

Valacyclovir is a valyl ester of acyclovir that is metabolized to acyclovir after oral administration, resulting in plasma levels of acyclovir similar to those achieved with IV acyclovir. However, such higher bioavailability is expected to be dependent on factors such as GI absorption and hepatic function. Valacyclovir given at a dosage

of 1 g three times daily has been shown to reduce time to healing and postherpetic neuralgia in herpes zoster and to do so more effectively than acyclovir. Valacyclovir may also be used in primary (1 g twice daily for 10 days) and recurrent (500 mg three times per day) genital herpes. In patients with normal immune function, valacyclovir 1 g daily can be used as suppressive therapy of recurrent genital herpes. Herpes labialis can be treated with valacyclovir 2 g every 12 hours for 1 day. In most respects, valacyclovir is appropriate when oral acyclovir is used and may be a potential substitute for IV acyclovir. However, the exact situations in which oral valacyclovir may be safely substituted for IV acyclovir, especially in the immunosuppressed patient, remain to be defined.

Pharmacokinetics

Valacyclovir is readily absorbed from the GI tract after oral intake and is almost completely converted to acyclovir and L-valine via first-pass intestinal and/or hepatic metabolism. Acyclovir is primarily excreted in the urine.

Major toxicities

The major toxicities are similar to those of acyclovir.

Drug interactions

There are no known clinically significant drug–drug interactions. Probenecid coadministration does result in an increase of the acyclovir Cmax and area under the curve but are of doubtful clinical relevance.

VALGANCICLOVIR

Valganciclovir hydrochloride is a nucleoside analog and is the prodrug of ganciclovir. After oral administration, valganciclovir is rapidly converted to ganciclovir by hepatic and intestinal esterases. The active metabolite, ganciclovir triphosphate, is formed by phosphorylation by both viral and cellular kinases. Ganciclovir triphosphate is virustatic, by inhibiting viral DNA synthesis.

Valganciclovir is indicated for the treatment of AIDS-related CMV retinitis and for the prevention of CMV disease in high-risk recipients of kidney, heart, and kidney–pancreas transplants. It is commonly used for the prevention of CMV disease in HIV-1-infected patients who are felt to be at high risk for CMV disease because of a severely impaired immune system (most often determined by a very low CD4 lymphocyte count). It has significant advantages over ganciclovir, as it is administered orally thereby avoiding the need for indwelling catheters. For treatment of active CMV retinitis, it is recommended to induce the patient with 900 mg twice daily for 21 days, followed by maintenance with 900 mg daily. Valganciclovir should be dosed with food. To prevent CMV disease in patients who have received a kidney, heart, or kidney–pancreas transplant, valganciclovir, 900 mg, should be dosed daily (with food) within 10 days of transplant until 100 days post-transplantation.

Pharmacokinetics

Valganciclovir is well absorbed from the GI tract and is rapidly hydrolyzed to ganciclovir in the intestinal wall and in the liver. The major route of elimination is by renal excretion through glomerular filtration and active tubular secretion. The terminal half-life following oral administration of valganciclovir is 4.08 hours in healthy or HIV/CMV-positive patients. The terminal half-life in transplant patients is 6.48 hours. Dose adjustment is necessary in patients with renal impairment.

Major toxicities

As for ganciclovir, the major toxicity of valganciclovir is hematologic, often causing anemia, neutropenia, and thrombocytopenia. Additional adverse effects associated with its use include GI upset, fever, headache, peripheral neuropathy, paresthesias, tremors, renal insufficiency, and infections. Valganciclovir may be teratogenic or embryotoxic in humans.

Drug interactions/precautions

The clinician should avoid coadministering other drugs with the potential to suppress the bone marrow. Caution should also be exercised when considering the coadministration of other agents with nephrotoxic potential. Probenecid causes increased levels of valganciclovir. An increased incidence of seizures has been noted with the concomitant use of imipenem and cisplatin.

VIDARABINE

Vidarabine (Ara-A, adenine arabinoside) is a purine analog made from *Streptomyces antibioticus* that inhibits viral DNA polymerases. It has been

supplanted by acyclovir because of the greater efficacy and lower toxicity of acyclovir in HSV and VZV infections. It was the first agent used against HSV encephalitis but has been made almost obsolete by acyclovir. Acyclovir-resistant strains of HSV and VZV are currently treated with foscarnet. Vidarabine is currently only used as an ointment for the treatment of herpetic keratitis caused by HSV-1 and HSV-2.

ZANAMIVIR

Zanamivir is a neuraminidase inhibitor that is indicated for the treatment of influenza A and influenza B in patients aged ≥7 years who have been symptomatic for no longer than 2 days. It is also indicated for the prophylaxis of influenza in patients who are at least 5 years old. It is not recommended for patients with underlying airway disease such as COPD or asthma. It is administered to the respiratory tract by oral inhalation. It has been proposed that the mechanism of action of zanamivir is through inhibition of influenza virus neuroaminidase with possible alteration of viral particle aggregation and release.

Zanamivir is dosed as two inhalations every 12 hours for 5 days for the treatment of influenza.

Pharmacokinetics

Between 4% and 17% of oral inhaled zanamivir is systemically absorbed. It is renally excreted unchanged. Unabsorbed drug is excreted fecally. The serum half-life is between 2.5 and 5.1 hours.

Common toxicities

The use of zanamivir can precipitate bronchospasm and decline in pulmonary function. Many of these cases have occurred in patients with underlying airway disease, such as asthma or COPD. Other common adverse events associated with its use are GI upset, sinusitis, dizziness, headache, bronchitis, cough, and allergic reactions (including oropharyngeal edema and rash).

Drug interactions

There are no clinically relevant known pharmacokinetic drug interactions.

SUGGESTED READING

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209. Probiotics

Varsha Gupta and Ritu Garg

Probiotics recently are defined as "live microorganisms which when administered in adequate amount confer a health benefit on the host" by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO).

MECHANISM OF ACTION OF PROBIOTICS

- *Competitive exclusion of pathogenic bacteria*. Probiotics may compete with pathogenic bacteria for epithelial binding sites and thus prevent gut colonization by bacterial species such as *Clostridium difficile*, *Salmonella choleraesuis*, *Staphylococcus aureus*, and others.
- *Induction of defensin production*. Cytoprotective and antimicrobial substances are produced by the intestinal epithelium to control the microenvironment of the gut. Defensins are antimicrobial peptides synthesized by Paneth cells located in the crypts to counteract bacterial adherence and invasion.
- *Production of antibacterial substances*. Many lactic acid-producing bacteria (LAB) produce antibacterial peptides called bacteriocins, such as lactacin B from *Lactobacillus acidophilus*, having a narrow activity spectrum acting only against closely related bacteria.
- *Improved intestinal barrier function*. Recent data indicate that probiotics may initiate repair of the barrier function after damage.
- *Modulation of host immune functions*. Probiotic bacteria may act through the stimulation of Toll-like receptors (TLRs) and it appears that certain effects exerted by some probiotic strains or preparations are mediated through interactions with distinct TLRs. It can be assumed that probiotic bacteria stimulate dendritic cells which in turn produce anti-inflammatory cytokines.

An ideal probiotic preparation should harbor the characteristics mentioned in Table 209.1. For an adequate amount of health benefits, a dose of 5 billion colony-forming units (CFU) a day (5×10^9 CFU/day), for at least 5 days, has been recommended. Bacteria and yeasts may be used as probiotics either in the form of a single strain or combination of microorganisms or mixed with prebiotics (Table 209.2).

Table 209.1 The characteristics of an ideal probiotic preparation

- It should have high cell viability, thus should be resistant to low pH and acids
- It should have the ability to persist in the intestine, even if the probiotic strain cannot colonize the gut
- It should be adhesive to the gut epithelium, so that it can cancel the flushing effects of peristalsis
- It should be able to interact or send signals to the immune cells associated with the gut and influence local metabolic activity
- It should be of human origin
- It should be nonpathogenic, nontoxic, free of serious side effects
- It should be resistant to processing and be present in the product in an adequate number of viable cells to confer the health benefit

Table 209.2 List of microbes being used in probiotic preparation

Genus	Species
Lactobacillus	*L. acidophilus, L. casei, L. fermentum, L. gasseri, L. johnsonii, L. lactis, L. paracasei, L. plantarum, L. reuteri, L. rhamnosus GG, L. salivarius, L. bulgaricus, L. sporogenes, L. delbrueckii, L. brevis, L. cellobiosus, L. helveticus, L. crispatus, L. delbrueckii* subsp. *lactis, L. salivarius* subsp. *salicinius*
Bifidobacterium	*B. bifidum, B. breve, B. lactis, B. longum, B. infantis, B. thermophilum, B. animalis, B. adolescentis*
Streptococcus	*S. thermophilus, S. salivarius, S. lactis, S. cremoris, S. intermedius*
Saccharomyces	*S. boulardii, S. cerevisiae*
Other	*Bacillus cereus, Escherichia coli, Enterococcus faecalis, Enterococcus faecium, Propionibacterium, Leuconostoc, Pediococcus, Aspergillus niger, Aspergillus oryzae, Candida pintolopesii*

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APPLICATIONS OF PROBIOTICS FOR HUMAN USE

Evidences of probiotic effectiveness in necrotizing enterocolitis (NE)

NE is one devastating intestinal disorder that a preterm infant may face in a neonatal intensive care unit (NICU). Low-birth-weight preterm infants delivered by cesarean section often require intensive care and are breastfed only after several days. The normal process by which microorganisms, such as lactobacilli, are ingested via vaginal birth and propagated by the mother's milk does not take place in these infants. A human trial with 2.5×10^8 CFU of live *Lactobacillus acidophilus* and 2.5×10^8 CFU of live *Bifidobacterium infantis* given to 1237 newborns in Columbia resulted in 60% reduction in NE and overall mortality.

Diarrhea

Probiotics can prevent or ameliorate diarrhea through their effects on the immune system. Moreover, probiotics might prevent infection because they compete with pathogenic viruses or bacteria for binding sites on epithelial cells. Probiotics might also inhibit the growth of pathogenic bacteria by producing bacteriocins. A Cochrane review on the efficacy of probiotics for treating infectious diarrhoea, including both adults and children, evaluated 63 studies with a total of 8014 participants. No adverse events were attributed to probiotic intervention. The use of probiotics reduced the duration of diarrhoea, although the size of the effect varied considerably between studies. Probiotics have preventive as well as curative effects on several types of diarrhea of different etiologies.

There is ample evidence that probiotics reduce the duration and severity of rotavirus diarrhea.

At least two systematic reviews suggest that probiotics, including various bacterial species and the yeast *Saccharomyces boulardii*, effectively reduce the incidence of diarrhea in patients who are taking antibiotics (antibiotic-associated diarrhea [AAD]). While research using probiotics has extended to a vast array of diseases, the most investigated field continues to remain infectious diarrhea.

Helicobacter pylori infection

H. pylori is a major cause of chronic gastritis and peptic ulcer and a risk factor for gastric malignancies. Antibiotics directed towards *H. pylori* eradication are 90% effective. However, these treatments are expensive and can cause side effects, along with antibiotic resistance. Probiotic treatment can also reduce the side effects associated with *H. pylori* therapy.

Constipation

In adults, data suggest a favorable effect of treatment with *Bifidobacterium lactis* DN-173 010, *Lactobacillus casei* Shirota, and *Escherichia coli* Nissle 1917 on the frequency of defecation and stool consistency.

Role in lactose intolerance

This condition results from an insufficient activity of the lactose-cleaving enzyme lactase (β-galactosidase) in the small intestine. The health effect associated with the consumption of fermented milk products is the enhancement of lactose digestion and avoidance of intolerance symptoms in lactose malabsorbers. Yoghurt commonly made from *Lactobacillus bulgaricus* and *Streptococcus salivarius* subsp. *thermophilus* is usually effective.

Inflammatory bowel disease (IBD)

Inflammatory bowel disease classically includes ulcerative colitis, Crohn's disease, and chronic pouchitis, representing different patterns of chronic inflammation of the gastrointestinal tract. Recent clinical and experimental observation implicates an imbalance in the intestinal mucosa with relative predominance of aggressive bacteria and relative paucity of protective bacteria and an increase in fungal and a decrease in methanogen diversity; also there is stimulation of proinflammatory immunologic mechanisms, based on the activation of the pattern recognition receptors in the gastrointestinal tract of IBD patients.

Various preliminary studies suggest a positive response to probiotics in patients with IBD and pouchitis.

Role in urogenital tract infections (UTIs)

The dominant presence of lactobacilli in the urogenital microbiota of healthy women and the obliteration of lactobacilli in patients who develop UTIs and many other genital infections has led to a focus on these bacteria. The concept of treating and preventing urogenital infections by instilling probiotic organisms has great appeal to

patients and caregivers. Hence, the administration of *Lactobacillus rhamnosus* GR-1 and *Lactobacillus fermentum* RC-14 as a therapy to restore and maintain urogenital health is a major step for prevention and treatment of urogenital infections.

Bacterial vaginosis (BV)

A growing body of evidence suggests that vaginal H_2O_2-producing lactobacilli may have a protective effect against urogenital infections, including UTI. It is hypothesized that lactobacilli prevent uropathogen colonization of the vagina, a necessary step in ascending infection of the bladder. BV can lead to complications in pregnancies, causing premature rupture of membranes, premature death, or the death of the fetus or newborn. Certain *Lactobacillus* strains, including *Lactobacillus crispatus* CTV05, *L. rhamnosus* GR-1, and *L. fermentum* RC-14, are able to remain in the vagina for several months after insertion.

Candidal vaginitis

The studies have shown a significant reduction in vaginal colonization with *Candida* after the oral administration of *L. acidophilus* and there was clinical improvement with a 7-day course of vaginal suppositories of *Lactobacillus rhamnosus* GG (LGG) in women with recurrent vaginitis.

Cancers

In intestinal tumors, prevention or delay of tumor development by lactobacilli is due to the binding to mutagenic compounds in the intestine and also suppressing the growth of bacteria which convert procarcinogens into carcinogens.

Respiratory infections

A meta-analysis that included ten randomized controlled trials (RCTs) comparing probiotics with placebo to prevent acute upper respiratory tract infections showed that probiotics were more effective than the placebo in reducing the number of participants experiencing episodes of acute upper respiratory tract infections, reducing the rate ratio of episodes of acute upper respiratory tract infections, and reducing antibiotic use.

A meta-analysis of five RCTs showed that the administration of probiotics is associated with lower incidence of ventilator-associated pneumonia compared with placebo.

Role in mucosal immunity

The gastrointestinal mucosa is the primary interface between the external environment and the immune system. In the complete absence of intestinal microbiota antigen transport is increased, indicating that the normal gut flora maintains gut defenses. Secretory immunoglobulin A (IgA) plays an important role in mucosal immunity, acting as a barrier against pathogenic bacteria and viruses. An increased IgA immune response has been noticed in children with Crohn's disease treated with LGG.

Role in allergy

The composition of the vaginal microbiota has been shown to influence the ultimate asthmatic condition of children. According to a double-blind, randomized, placebo-controlled trial LGG given to pregnant women for 4 weeks prior to delivery and then to newborn children at high risk of allergy for 6 months caused a significant reduction in early atopic disease. Other clinical studies showed that LGG and *B. lactis* BB-12 have been useful in infants allergic to cow's milk. There are studies to suggest probiotics might have a role in atopic rhinitis by reducing symptom severity and medication use.

Role in autoimmunity

Lactobacillus casei strain Shirota (LcS) induced recovery of host immune responses that were decreased by treatment with carcinogens and augmented the natural killer activity and T-cell functions of host immune cells. After LcS ingestion by the host, it is incorporated into M cells in Peyer's patches and digested to form active components. The results suggest that some probiotic bacteria have the potential to augment or modify the host immune function through the regulation of host immune cells.

Role of probiotics in lowering of serum cholesterol

Large dietary intake of yoghurt was found to lower dietary cholesterolemia, and the findings suggested that yoghurt contains a factor that inhibits the synthesis of cholesterol from acetate.

Improvement of hypertension

Probiotics have antihypertensive roles via the improvement and treatment of lipid profiles, modulation of insulin resistance and sensitivities,

the modulation of renin levels, and also the conversion of bioactive phytoestrogens as an alternative replacement of sexual hormones such as estrogen and progesterone.

Diabetes

It has been suggested that the consumption of probiotics can lower the onset of insulin resistance and consequently reduce the incidence of hypertensive conditions that are closely related to diabetes.

Obesity

One emerging finding has suggested that the gut microbiota has a role in the regulation of energy balance and weight. Future studies are needed to better understand the causal relationship between gut microbiota of varied composition and the propensity to be obese or lean and to assess whether modulating the gut microbiota could help reduce obesity.

Oral medicine and dentistry

Particular species of *Lactobacillus* and *Bifidobacterium* may exert beneficial effects in the oral cavity by inhibiting carcinogenic streptococci and *Candida* spp. *Lactobacillus reuteri* was efficacious in reducing both gingivitis and plaque in patients with moderate to severe gingivitis.

Antibacterial effects

In vitro studies suggest multiple specific activities of different probiotic agents against several pathogens, including *Listeria monocytogenes, Salmonella typhimurium, E. coli*, and *H. pylori* among others. Therefore, probiotic agents may provide prototypic antimicrobial substances that will be useful for pharmaceutical companies in the development of new antibiotics. Another field of interest for the researchers is to decrease antibiotic consumption and fight the negative effects of antibiotic use.

Probiotics in critical illness

Some studies propose that probiotics have an important emerging role in managing critical illnesses originating in the gastrointestinal tract, such as acute pancreatitis. In cirrhotic patients, probiotics have shown to decrease the incidence of encephalopathy. Reduction of post liver transplant infective complications using probiotics has also been reported.

Surgical infections

Before the advent of antiseptics and antibiotics, fermented milk was used for healing wounds and to fight infections. Recent studies show some success in the application of probiotics for treating and preventing surgical infections.

Effect on bones

Several studies in humans have shown positive effects of nondigestible oligosaccharides (NDO) on mineral absorption and metabolism, and bone composition and architecture. Synbiotics, i.e., a combination of probiotics and prebiotics, can induce additional effects. Proposed future applications include the treatment of rheumatoid arthritis, prevention of ethanol-induced liver disease, and prevention or treatment of graft-versus-host disease.

SAFETY ISSUES

Generally recognized as safe (GRAS) status is defined by the US Food and Drug Administration for food adjuncts that may not meet the usual requirements for safety assessment but have been used extensively without demonstrable harm. Probiotics are claimed to be GRAS as they comprise organisms identical to those in human gut and vaginal flora, although strain dependence needs to be considered and GRAS is only granted to one specific probiotic preparation used in one specific food product. Various studies conducted on *Lactobacillus* and *Bifidobacterium* species showed no adverse effects. In immunocompromised individuals, however, this might be different, especially in patients with severe underlying comorbidities.

The use of safety becomes more complicated if one considers organisms such as *Enterococcus* spp., *S. boulardii*, and *E. coli* as probiotics.

In order to establish safety guidelines for probiotic organisms, the FAO and the WHO recommended that probiotic strains should be characterized at a minimum with a series of tests, including antibiotic resistance patterns, metabolic activities, toxin production, hemolytic activity, infectivity in immunocompromised animal models, and side effects and adverse incidents in consumers.

CONCLUSION

In conclusion, studies done in humans suggest that probiotics have a considerable role to play for preventive or therapeutic applications in various diseases mainly related to the gastrointestinal tract, allergic disorders, and to some extent in the urogenital tract of humans. However, it is worth mentioning that many probiotic health claims have not yet been substantiated by thoroughly conducted experimental studies. We still need well-designed, placebo-controlled, sufficiently powered studies that will reflect the actual role of probiotics.

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210. Hypersensitivity to antibiotics

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Adverse drug reactions (ADRs) are usefully separated into type A reactions (predictable from known pharmacologic properties and largely dose related) and type B reactions (unpredictable and restricted to a vulnerable subpopulation). Type B reactions comprise 10% to 15% of all ADRs and include *immunologic drug reactions, drug intolerance* (e.g., tinnitus after single aspirin tablet), and *idiosyncratic reactions*, some of which are pseudoallergic (e.g., aspirin-induced reactions).

Immune mechanisms are thought to be involved in 6% to 10% of all ADRs. Allergenic drugs can induce the entire spectrum of immunopathologic reactions, which are clinically indistinguishable from reactions elicited by foreign macromolecules (Table 210.1). Gell and Coombs' type I reactions are caused by drug/antigen-specific immunoglobulin E (IgE) that binds to high-affinity Fc-IgE receptors on mast cells and basophils. Cross-linking of these receptors leads to the release of vasoactive mediators such as histamine and cysteinyl leukotrienes. Typical syndromes include urticaria, anaphylaxis, rhinitis, and bronchoconstriction, which can occur immediately in a previously sensitized individual. Type II cytolytic reactions are generally confined to rapidly haptenating drugs such as penicillins and are based on immunoglobulin G (IgG)-mediated cytotoxic mechanisms, resulting mainly in blood cell cytopenias. Type III reactions are immune complex mediated and may involve complement activation and stimulation of Fc-α receptor-activated inflammatory cells. Drug-specific immune complexes result from high-dose, prolonged therapy and may produce drug fever, a classic serum sickness syndrome, and various forms of cutaneous vasculitis. Type IV reactions are mediated by T lymphocytes and cause "delayed hypersensitivity reactions," the most typical examples being delayed maculopapular exanthem and contact dermatitis from topically applied drugs. Many drug-induced hypersensitivity reactions such as bullous, pustular, and some morbilliform skin eruptions that are presumed to have an immune etiology did not seem to fit into the older Gell and Coombs classification. Recent studies of T-cell subsets and functions in the pathogenesis of delayed-onset immune reactions have suggested subcategories of type IV reactions as shown in Table 210.1.

However, some drug reactions resemble allergic syndromes but are not immunologic in origin. These nonimmune hypersensitivity reactions are also known as "pseudoallergic reactions." Most pseudoallergic reactions mimic type 1 IgE-mediated reactions such as urticaria, angioedema, bronchospasm, and anaphylaxis. In such cases basophils and mast cells are activated by nonimmune mechanisms, and vasoactive mediators are released.

In this chapter, we review type B ADRs to antibiotics with a focus on current concepts in the diagnosis and management of allergies to β-lactam antibiotics, the prototype of immunologic drug allergies. We also address the management of multiple antibiotic sensitivity syndromes.

EPIDEMIOLOGY OF ANTIBIOTIC ALLERGY

β-Lactams and sulfonamides are the most prevalent causes of antibiotic hypersensitivity. In a cross-sectional survey of a general population from Porto, Portugal, history of hypersensitivity to penicillin and other β-lactam antibiotics was found in 4.5% of adults. In the United States, in recent large healthcare insurance database studies, history of hypersensitivity to penicillin was recorded in about 10% of patients. Data from developing countries are limited, but

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Table 210.1 Features of immunopathologic reactions to antibiotics and management strategies

Reaction category	Clinical manifestation	Common examples for antibiotics	Timing for sensitization with the first use of the drug	Onset after re-exposure to the drug	Skin tests	In vitro tests	Readministration of the drug (DPT/ desensitization)
Type I (IgE)	Urticaria, angioedema, rhinitis, bronchospasm, anaphylaxis	β-lactam antibiotics Sulfamethoxazole	Required: 1–2 wk	Usually within 1 h (rarely after hours)	Immediate (wheal/ flare)[a] Intradermal tests	RAST (serum IgE) Serum mast cell tryptase level Basophil activation	Desensitization if skin test +
Type II (IgG and complement)	Hemolytic anemia, drug-induced nephritis, thrombocytopenia, neutropenia	Penicillins Cephalosporins Sulfonamides	Required: 1–2 wk	Many days or weeks	None	Complete blood count Coombs tests	Cautious DPT
Type III (IgG immune complexes)	Serum sickness, fever, vasculitis	Penicillins Cephalosporins Sulfonamides Streptomycin	Required: 10–21 d	Usually days to weeks	None	ESR CRP Immune complex Serum complement levels	Cautious DPT
Type IVa (Th1 lymphocytes)	Allergic contact dermatitis	Penicillins Neomycin Bactrim	Required: 1–3 wk	8–120 h	Patch tests Intradermal tests (delayed response at 48–72 h)	Lymphocyte transformation tests	Likely contraindicated
Type IVb (Th2 lymphocytes)	Maculopapular eruptions	Penicillins, especially diaminopenicillins like amoxicillin and ampicillin Sulfonamides	Required: 4–14 d		Patch tests Intradermal tests (delayed response at 48–72 h)	Lymphocyte transformation tests[b]	DPT useful
Type IVc cytotoxic lymph. (perforin/ granzyme B)	Contact dermatitis, maculopapular and bullous exanthema, hepatitis, SJS, TEN	Sulfonamides Penicillins Macrolides	Required: 1–2 wk		Patch tests Intradermal tests (delayed response at 48–72 h)	Lymphocyte transformation tests[b]	Contraindicated (for bullous exanthem and SJS/TEN)
Nonimmunologic	Urticaria, angioedema, rhinitis, erythema bronchospasm	Vancomycin (red man syndrome)	Not required Reaction may occur with first dose	Within minutes, infusion rate dependent	None	None	Slow infusion Use premedication

Abbrevations: DPT = drug provocation tests; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; RAST = radioallergosorbent test; IgE = immunoglobulin E; IgG = immunoglobulin G; SJS = Stevens–Johnson syndrome; TEN = toxic epidermal necrolysis.

[a] Only validated for penicillin skin testing, which has high negative predictive value. Positivity may be helpful with certain antibiotics; however, negative skin tests do not exclude the diagnosis for many immediate reactions to antibiotics.

[b] Clinically false positivity may occur.

According to Gell and Coombs, as modified.

Table 210.2 Relative risks of immunologic reactions to commonly used antibiotics

Risk of inducing an immunologic reaction[a]	Antibiotic (or its class)
Common (>2%)	Penicillins Antimicrobial sulfonamides Nitrofurantoin
Intermediate (0.1%–2%)	Bacitracin Cephalosporins Penems Itraconazole Quinolones Minocycline
Rare (0.1%)	Monobactam (aztreonam) Aminoglycosides Amphotericin B Chloramphenicol Clindamycin Fluconazole Griseofulvin Ketoconazole Macrolide antibiotics Vancomycin Tetracyclines Polymyxin Metronidazole

[a] Among patients receiving multiple courses of therapy.

suggest that penicillin allergy is the most commonly reported antibiotic allergy. History of hypersensitivity to sulfonamides has been reported to occur in 2% to 4% of populations, but is increased among acquired immunodeficiency syndrome (AIDS) patients to 40% to 80%. Immunologic reactions to the newer classes of antibiotics are often rare and poorly documented. The perceived relative risk of immunologic drug reactions with commonly used antibiotics is given in Table 210.2.

BURDEN OF ANTIBIOTIC ALLERGY

β-Lactams are among the most commonly prescribed antibiotics for treatment of many types of bacterial infections. However, recent data show a significant decrease in β-lactam prescriptions, in part due to a rising prevalence of histories of allergy, which can exceed 30% in intensive care environments. Emergence of bacterial resistance as well as introduction of newer antibiotics have also contributed to this trend. Prescriptions of quinolones and macrolides as alternative antibiotics for common infections have been increasing as has the use of vancomycin in patients with histories of penicillin allergy, yet only 10% to 15% of the subjects with a history of penicillin reactions have positive type I skin tests. Unevaluated histories of antibiotic allergies may lead to the substitution of often less effective or more toxic, and more expensive, alternative drugs, which can result in high medical and economic burdens on health care. In a retrospective study of hospital practice, penicillin-allergic patients had higher antibiotic costs and were more likely to receive a broader-spectrum antibiotic such as cephalosporins, macrolides, and quinolones. At the Mayo Clinic, prophylactic vancomycin use in patients with a history of penicillin or cephalosporin allergy undergoing elective orthopedic surgery was substantially reduced by targeted allergy consultation and penicillin allergy skin testing. Similar benefits are likely to occur in patients with histories of other antibiotic allergies who are appropriately evaluated before alternative antibiotics are selected.

CLINICAL FEATURES

The presentation of antibiotic allergies is similar to known hypersensitivity reactions, and the clinical features are variable depending on the type and severity of the reaction and the organ systems affected (Table 210.1). Many factors such as the immunologic profile of the antibiotic; treatment factors, including dosage, administration route, and frequency; host factors such as immune status and comorbidities; and the inflammatory milieu in which antibiotics are used can influence the frequency and characteristics of hypersensitivity reactions.

The skin is the most common organ involved in antibiotic reactions. Maculopapular eruptions (MPEs), urticaria, and pruritus are the most common presentations that typically occur after hours, days, or even weeks of antibiotic exposure but can also be part of an acute allergic reaction. Immunologic drug reactions require a sensitization period, whereas a nonimmunologic mast cell release can occur on first exposure in susceptible patients. Antibiotics can also cause severe but rare exfoliative skin syndromes such as toxic epidermal necrolysis (TEN) and Stevens–Johnson syndrome (SJS). Other targeted organ manifestations such as interstitial pneumonitis and immune cytopenias are rare. Life-threatening reactions such as anaphylaxis are also rare. Although β-lactams are the most

Table 210.3 Clinical features of hypersensitivity reactions

Antibiotic	Common	Less common/rare
β-lactams	Urticaria, MPE	Exfoliative dermatitis, TEN, SJS, serum sickness syndrome, vasculitis, cytopenias, anaphylaxis, nephritis
Sulfonamide	Fixed drug eruption HIV(+): delayed MPE+fever, urticaria, angioedema	Erythema multiforme, SJS, TEN Anaphylactic reactions
Quinolones	Urticaria, FDE, photoallergic reactions	Acute interstitial nephritis, acute hepatitis, serum sickness, SJS, TEN, MPE, acute pancreatitis, anemia; thrombocytopenia
Macrolides	Urticaria, angioedema, FDE, and MPE	TEN, vasculitis
Vancomycin	"Red man syndrome," lineary IgA bullous dermatosis	MPE, FDE, vasculitis, thrombocytopenia, erythema multiforme, and urticaria anaphylaxis

Abbrevations: FDE = fixed drug eruptions; MPE = maculopapular eruption; TEN = toxic epidermal necrolysis; SJS = Stevens–Johnson syndrome; IgA = immunoglobulin A; HIV = human immunodeficiency virus.

common antibiotic class inducing anaphylaxis, IgE antibody responses have also been documented for sulfonamides; those now in use are given in Table 210.3.

CLINICAL ASSESSMENT

Drug allergy syndromes are recognized by the constellation of signs and symptoms identified with a particular mechanism of immunopathology (Table 210.1). Appropriate diagnosis of these cases depends largely on careful history taking, with attention to prior drug experience and the chronology of the reaction, supplemented by compatible physical and laboratory findings, and knowledge of drug allergenicity profiles. For atypical or discordant reactions, skepticism is appropriate to avoid labeling the patient as "drug allergic" incorrectly.

Step 1: initial evaluation

HISTORY TAKING

A detailed history is essential for the initial evaluation of patients with suspected drug allergies. The history guides a decision about performing further diagnostic testing and other evaluation strategies. It is also possible to make a reasonable decision about risks of reintroduction of the suspected drug by using historical detail. Medical records that describe previous reactions and treatment can be very helpful, especially in patients with vague histories or altered mental status. Occasionally, information provided by a relative or friend who witnessed the event can also be very helpful in differential diagnosis.

The clinical history of suspected drug allergy should be focused on both medication-related and patient-related factors. The medication(s) implicated, clinical features of the reaction(s), and the previous exposure and reaction to each drug and related compounds as well as comorbid disorders of the patients should be recorded. For example, patients with chronic urticaria often attribute cutaneous reactions to drugs and foods. Similarly symptoms of chest tightness or pain, dyspnea, and tachycardia after use of a drug can be a sign of underlying cardiovascular disease. Other patient comorbidities include the high frequency of amoxicillin-induced morbilliform rashes in patients with mononucleosis, and frequent trimethoprim–sulfamethoxazole reactions in AIDS patients. Another example is that patients with cystic fibrosis have a higher risk for immune reactions to antibiotics, probably because of frequent re-exposure.

History taking provides information helpful in assessing the likelihood of immune mediation. Immunologic reactions require a sensitization period, so putatively allergic patients should have a history of prior use of either the drug itself or a structurally related compound. For first drug exposure, an immunologic reaction may be seen after 3 to 10 days, which can be sufficient for primary sensitization. Nonimmunologic reactions do not require sensitization, and reactions may be seen even after the first dose. Pseudoallergic reactions can often be distinguished from IgE-mediated reactions with similar clinical manifestations by reliable histories of previous drug use. Based on clinical features and the chronology of the reaction, conclusions can often be drawn

about whether a reaction is immunologically mediated (Table 210.1).

PHYSICAL EXAMINATION

Direct observation of patients undergoing presumed drug reactions can be useful for both differential diagnosis and objective assessment of severity, which can often be exaggerated in retrospective patient accounts. A complete physical examination is desirable as many organ systems have the potential for involvement. For skin reactions occurring with drug use, a detailed dermatologic examination is often helpful. Viral exanthems are easily confused with maculopapular drug eruptions. Fever and coryza or pharyngitis can help to identify the former.

Step 2: decision about application of further diagnostic testing

History alone is often not sufficient for establishing current drug sensitivity. Only 10% to 15% of subjects with a convincing history of IgE-dependent penicillin allergy will be positive by validated skin testing, indicating a very low diagnostic accuracy of history alone for current sensitivity. Data with other drugs are similar, suggesting that sensitivity may wane with time. Drug provocation tests that are the gold standard for the diagnosis of current drug allergy have a similarly low positivity rate in patients with history of drug allergy. These data indicate that diagnosis of current sensitivity based on history alone is often not advisable. Further diagnostic tests for definite diagnosis may be needed.

Unfortunately, many in vivo and in vitro diagnostic tests for allergy have shown limited value in the diagnosis of allergy to haptenic (small molecular weight) drugs.

Although skin testing provides valuable information for the diagnosis of immediate reactions to penicillins and in some cases to other β-lactams, the validity of skin tests with other antibiotics is limited as the antigenic determinants are not adequately known. In vitro tests for drug-specific IgE to antibiotics are of limited value because they are less sensitive than intradermal tests. A positive result, however, is usually reliable and corresponds to skin test results. If there is no contraindication, drug provocation testing with the offending drug is the most reliable test for diagnosis of current antibiotic hypersensitivity for many haptenic drug allergies. Because such testing carries some risk for the patient, its use is usually restricted to cases where alternative antibiotics are unacceptable or there are multiple antibiotic sensitivities. A stepwise approach to the diagnosis of antibiotic allergy is given in Figure 210.1. Diagnostic testing can be pursued based on likely immunopathology as given in Table 210.1.

EVALUATION OF IMMEDIATE-TYPE SENSITIVITIES

Skin testing for β-lactam antibiotics

Intradermal skin testing with a 15- to 20-minute readout of wheal and flare has been validated for detecting drug-specific IgE antibodies to penicillins and other β-lactam antibiotics. A major determinant analog (*penicilloyl-polylysine*) and minor determinants (*benzylpenicilloate*, *benzylpenilloate*, and *benzylpenicillin* isomers of penicillin) are used for skin test evaluation for IgE-dependent penicillin allergy. IgE antibodies to minor determinants are clinically associated with anaphylactic reactions and can predict the risk of more severe reactions. IgE antibodies to the major penicilloyl determinant correlate loosely with risk for urticarial reactions.

Testing is undertaken with two or more reagents, usually penicilloyl–polylysine (PrePen) antigen and either penicillin alone (10 000 IU/mL) or a mixture of minor antigens, including at least benzylpenicillin and benzylpenicilloate (10 mM each). Of these minor determinants, only benzylpenicillin is available commercially in the United States. Skin prick testing with full-strength reagents is done first, and if these tests are negative at 15 minutes, they are followed by intracutaneous testing, raising an initial bleb of 2 to 3 mm. A wheal diameter of least 3 mm greater than negative control is considered positive. In some centers, elective testing is followed by the administration of one to three doses of oral penicillin and a period of observation to confirm that the drug is tolerated. For hospitalized patients with serious infection, a rapid dose escalation of the intravenous antibiotic of choice is judiciously employed.

Falsely negative penicillin skin testing is rare, and all reports are of mild, self-limited, and/or transient reactions. About 85% to 90% of history-positive patients will have negative penicillin

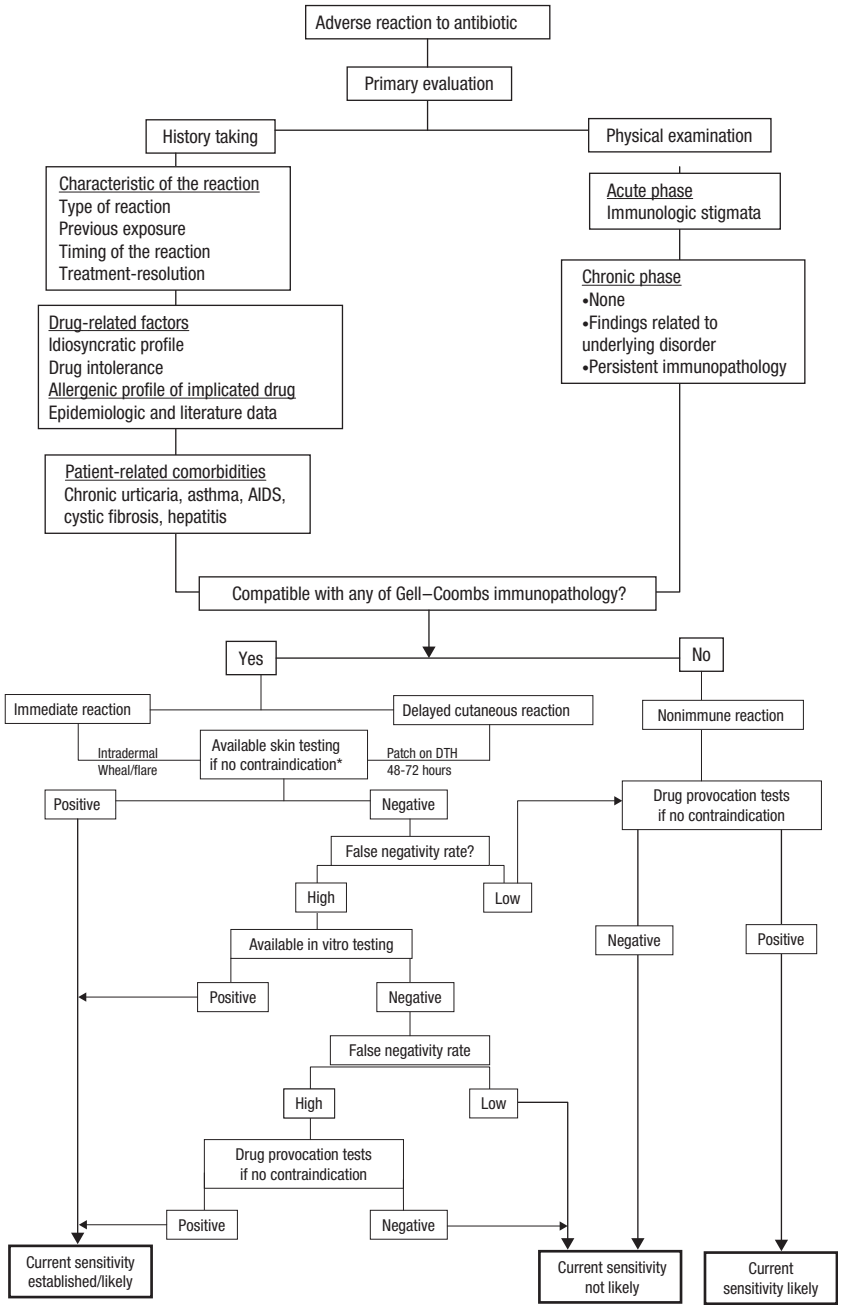

Figure 210.1
A diagnostic algorithm for evaluation of putative immunologic reactions to antibiotics. *Contraindications for skin immunoglobulin E testing are extensive skin lesion, recent antihistamine use, and history of serious immediate systemic reaction with allergen exposure. AIDS = acquired immunodeficiency syndrome; DTH = delayed-type hypersensitivity.

testing, allowing a large majority of such patients to be retreated safely. Despite this substantial diagnostic power, it has been difficult to maintain persistent commercial sources for these reagents in the United States and Europe. Some academic centers have produced the reagents for their own use, but concerns persist about access to these orphan drug products.

Recent studies show promising results with cephalosporin skin tests. Concentrations of 2 to 3 mg/mL of a parenteral cephalosporin preparation are reported to be usually nonirritating, but each cephalosporin requires concurrent evaluation for its irritant potential in nonallergic subjects. Although a positive cephalosporin skin test implies the presence of drug-specific

IgE antibodies, a negative test does not exclude immediate hypersensitivity.

Commercial cephalosporin skin test reagents are not currently available in the United States. Positive intradermal skin tests have been reported for imipenem and other β-lactams, but validated skin testing protocols have not been developed.

In vitro tests

Specific IgE tests have been established for a wide variety of immediate-type drug allergies. Only with penicillin allergy have in vitro test results been systematically compared with skin tests. The consistent finding has been diagnostic sensitivity for penicilloyl–IgE by radioallergosorbent test (RAST) of 65% to 85% compared with penicilloyl–polylysine skin tests and 32% to 50% compared with a combination of skin testing and challenge. Minor determinant penicillin IgE antibodies are not reliably detected by available immunoassays. In recent years, flow cytometry has been increasingly used in the diagnosis of allergy. Assessment of basophil activation by means of increase in surface markers such as CD63 has been investigated in penicillin allergy. In one study from Europe, sensitivity was $\leq$30% compared with a diagnosis confirmed by skin testing. As with unvalidated skin tests, a clearly positive result is of greater clinical value than a negative result, thus in vitro basophil activation tests remain investigational.

EVALUATION OF NONIMMEDIATE REACTIONS

Skin testing

European studies suggest that both patch tests and intradermal tests with delayed cutaneous readouts (at 48 and 72 hours) are useful in evaluating nonimmediate reactions to aminopenicillins and certain β-lactams and that both can reliably predict the results of rechallenge. Additional studies are required to confirm and extend these results to other drug allergies and to define more precisely the clinical correlation and predictive value for retreatment.

Other tests

Drug-specific T lymphocytes, which are involved in some cutaneous hypersensitivity reactions, may be detected with the use of in vitro lymphocyte transformation tests, which are utilized in Europe but not approved for diagnostic use in the United States. However, sensitization may be found after recent treatment even in the absence of any clinical reactivity, and positive test results have been demonstrated after both immediate and delayed antibiotic-induced reactions caused by β-lactam antibiotics, sulfonamides, and quinolones. Cytokine detection assays are also available to evaluate delayed-type hypersensitivity drug reactions, but are still investigational.

USE OF DRUG PROVOCATION TESTS

Definitive diagnosis of drug allergy involves provocation testing as the last step, during which gradually increasing doses of the offending drug are given. Provocation testing may be necessary to accurately identify the responsible agent when multiple drugs are given simultaneously and a reaction occurs. It is particularly important not to incorrectly label a patient allergic to an antibiotic because it may severely restrict antibiotic choices for life.

Studies indicate that only a small minority of history-positive subjects have positive drug challenges. Drug provocation tests should be considered only after evaluating the risk–benefit ratio for an individual patient, and should be performed by experienced personnel in an appropriate environment. Informed consent of the patient should be obtained prior to the procedure.

MANAGEMENT OF ANTIBIOTIC ALLERGY

Alternatives for drug-allergic patients

Three alternative approaches are available to provide acceptable pharmacotherapy for infection in antibiotic-allergic patients (Figure 210.2). The physician may choose to use an unrelated antibiotic, or potentially cross-reactive alternative, or to readminister the implicated antibiotic after an induction of drug tolerance procedure, also commonly known as drug desensitization. A structurally unrelated antibiotic is usually chosen if the trade-offs of safety, efficacy, and cost are acceptable. This often occurs in the treatment of uncomplicated outpatient infections. If there is no acceptable alternative to the offending drug class, a potentially cross-reacting member of the same antibiotic family

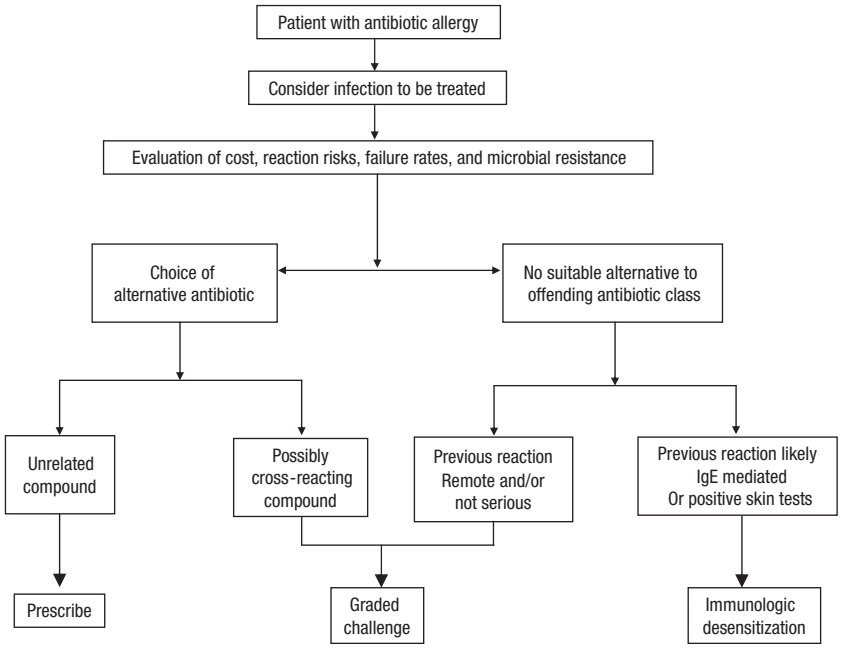

Figure 210.2 An approach to treating patients with antibiotic allergy.

may be administered using rapid dose escalation under careful observation. If a reaction occurs during graded challenge, then an induction of drug tolerance protocol is warranted. Classical induction of drug tolerance is applied only for IgE-dependent allergy in patients with demonstrable or presumed IgE antibody responses. Induction of drug challenge protocols have been used for non-IgE-mediated reactions; however, neither the effectiveness of the procedure nor a clear mechanism of action has been demonstrated. The procedure aims to induce a temporary state of drug tolerance.

Induction of drug tolerance procedures usually start at 1/10 000 of the full dose with a 2- to 2.5-fold dose increment every 30 to 60 minutes. The procedure entails risk of acute allergic reactions, which occur in mild form in 30% to 80% of penicillin-allergic patients undergoing desensitization. Reactions are generally confined to local and mild systemic reactions during the procedure and, occasionally, late-occurring reactions during therapy, including urticaria or serum sickness and hemolytic anemia if prolonged high-dose therapy is used. The protocol should usually be performed in a hospital setting where experienced personnel and emergency treatment are available. Induction of drug tolerance is an active and reversible process dependent on the continuous presence of the drug. After drug discontinuation, the tolerized state dissipates over days to weeks, and the induction of tolerance procedure would need to be repeated for subsequent treatment courses. Both oral and parenteral routes can be used to initiate drug tolerance, and both appear equally effective in inducing clinical tolerance. The oral approach is arguably safer, although not always feasible.

A variety of protocols have been used for reintroducing β-lactams, trimethoprim–sulfamethoxazole, vancomycin, and other antimicrobials. Tables 210.4 and 210.5 show illustrative published protocols for penicillin.

Management of β-lactam allergy

β-Lactam antibiotics are the most commonly prescribed class of antibiotics and the most frequent cause of antibiotic allergy. It is the only group of antibiotics for which skin tests have been validated. This group includes penicillins, cephalosporins, carbapenems, and monobactams, all of which share a β-lactam ring but otherwise vary in nuclear structure and side chains.

Table 210.4 Oral densensitization protocol

Step[a]	Phenoxymethyl penicillin (U/mL)	Amount (mL)	Dose (U)	Cumulative dosage (U)
1	1 000	0.1	100	100
2	1 000	0.2	200	300
3	1 000	0.4	400	700
4	1 000	0.8	800	1 500
5	1 000	1.6	1 600	3 100
6	1 000	3.2	3 200	6 300
7	1 000	6.4	6 400	12 700
8	10 000	1.2	12 000	24 700
9	10 000	2.4	24 000	48 700
10	10 000	4.8	48 000	96 700
11	80 000	1.0	80 000	176 000
12	80 000	2.0	160 000	336 700
13	80 000	4.0	320 000	656 700
14	80 000	8.0	640 000	1 296 700
Observe patient for 30 minutes Changes to benzylpenicillin G IV (slow IV drip over 15 minutes)				
15	500 000	0.25	125 000	
16	500 000	0.50	250 000	
17	500 000	1.00	500 000	
18	500 000	2.25	1 125 000	

[a] 15-minute interval between steps.

Abbreviation: IV = intravenous.

Adapted from Sullivan TJ. Penicillin allergy. In: Lichtenstein LM, Fauci AS, eds. *Current Therapy in Allergy, Immunology, and Rheumatology*. Toronto: BC Decker; 1985:57.

Table 210.5 Parenteral desensitization protocol

Infection number	Benzylpenicillin concentration (U/mL)	Volume/route (mL)
1	100	0.1 ID
2	100	0.2 SC
3	100	0.4 SC
4	100	0.8 SC
5	1 000	0.1 ID
6	1 000	0.3 SC
7	1 000	0.6 SC
8	10 000	0.1 ID
9	10 000	0.2 SC
10	10 000	0.4 SC
11	10 000	0.8 SC
12	100 000	0.1 ID
13	100 000	0.3 SC
14	100 000	0.6 SC
15	1 000 000	0.1 ID
16	1 000 000	0.2 SC
17	1 000 000	0.2 IM
18	1 000 000	0.4 IM
19	Continuous IV infusion (1 000 000 U/h)	

Doses are administered at 20-minute intervals. Observe skin wheal and flare response to intradermal doses.

Abbreviations: ID = intradermal; SC = subcutaneous; IM = intramuscular; IV = intravenous.

Adapted from Wesis ME, Adkinson NF. Immediate hypersensitivity reactions to penicillin and related antibiotics. *Clinical Allergy*. 1988;18:515–540.

If skin testing reagents are available, then therapy may be dispensed according to the result of skin tests. When reagents or consultants are not available, an approach is outlined in Figure 210.3. Patients with histories of a reaction to a β-lactam class other than penicillin should first be skin tested with the benzylpenicillin reagents and, if negative, with the diluted β-lactam chosen for use.

Cross-reactivity among β-lactam antibiotics

Cross-reactivity within the penicillin class is virtually complete. A patient who is allergic to any penicillin is likely to react to all penicillins. However, some data suggest that there are patients that are selectively allergic to amoxicillin or ampicillin while tolerating other penicillins. Immunologic cross-reactivity between cephalosporins and penicillins is readily demonstrated in vitro and by skin testing, yet multiple studies have shown that most patients with penicillin IgE responses can be safely treated with cephalosporins, especially those of third and fourth generation. Still, penicillin allergy conveys an odds ratio of 4.8 for acute reactions to first-generation cephalosporin in a recent meta-analysis, and in one series a majority of cases of fatal anaphylactic reactions to cephalosporins involved penicillin-allergic patients. Because of this, administration of cephalosporins to penicillin-allergic patients should be undertaken cautiously, especially for patients with previous life-threatening reactions to β-lactam antibiotics of any class.

Penicillin-allergic patients can be given the monobactam aztreonam with little risk because

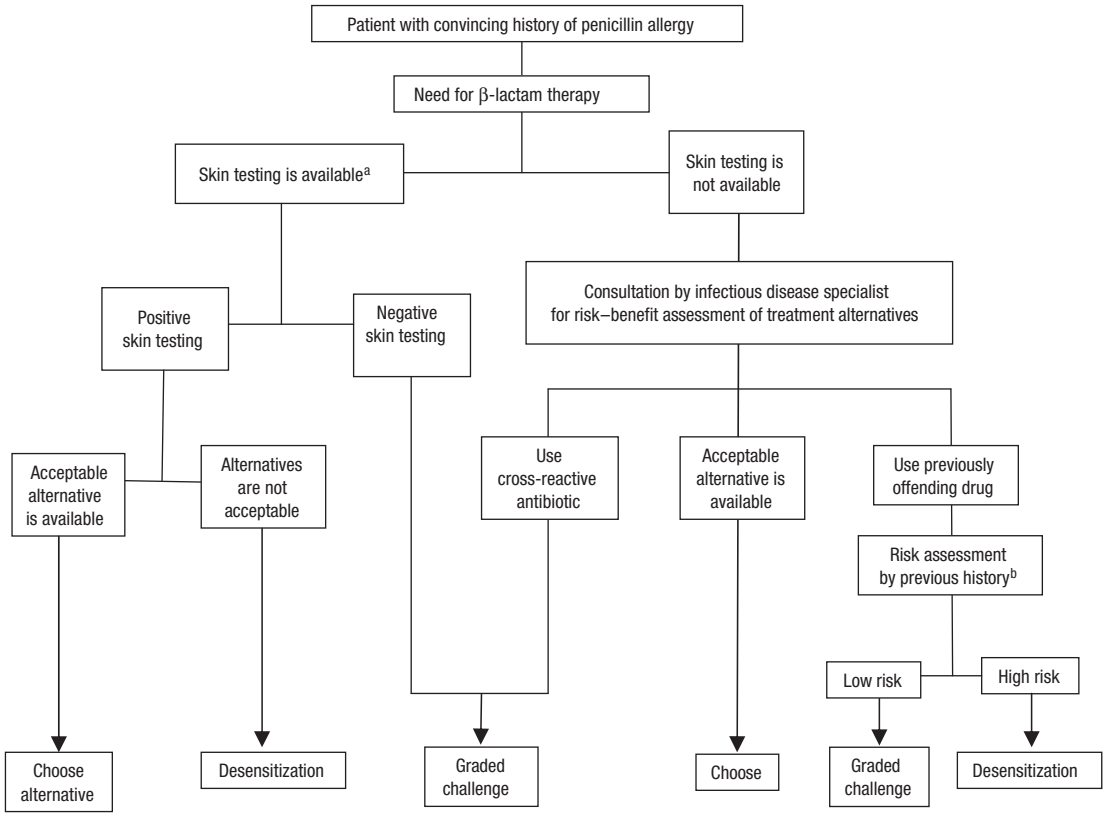

Figure 210.3 Diagnostic evaluation of patients with histories of penicillin allergy.
[a] Intradermal skin tests should include penicilloyl–polylysine (Pre-Pen) as a major determinant analog, plus one or more minor determinants (especially benzylpenicillin, benzylpenicilloate); the previously offending antibiotic if known and/or the currently desired antibiotic choice may be usefully included, especially in evaluating non-penicillin β-lactams.
[b] Risk assessment by previous history: High risk: Histories of bronchospasm, angioedema, hypotension, shock that occurred within 30 minutes of penicillin administration in the last year. Low risk: History of isolated urticaria or maculopapular rash occurring after days of treatment remotely >5 years in the past.

clinically significant cross-reactivity between penicillin and monobactams has not been demonstrated. In contrast, cross-reactions between aztreonam and ceftazidime have been reported, presumably due to identical side chains. The carbapenem antibiotics (imipenem, meropenem, and ertapenem) will induce positive skin tests in about half of penicillin-allergic patients. However, a clinical report from Europe found that 100% of 110 patients with positive penicillin skin tests tolerated imipenem. A more recent study found a cross-reactivity rate of 0.8% between penicillin and imipenem in 124 children. These data suggest that cautious cross-treatment may be reasonably attempted.

Sulfonamide antimicrobials (sulfamethoxazole, sulfadiazine, sulfisoxazole, and sulfacetamide) are extensively cross-reactive and also cross-react with dapsone. Sulfonamide antimicrobial agents differ from other sulfonamide-containing medications by having an aromatic amine group at the N4 position and a substituted ring at the N1 position that are not found in nonantibiotic sulfonamide-containing drugs. Patients allergic to sulfonamide antibiotics generally tolerate thiazide diuretics, oral hypoglycemic agents, and other SO_2-containing drugs and vice versa.

Other antibiotics

Immunologic reactions to quinolones and macrolides are very rare. These antibiotics mostly evoke maculopapular eruptions and

occasionally urticaria and angioedema (Table 210.3). As there are no validated skin or in vitro tests, drug provocation tests are the only available diagnostic methods for these classes of antibiotics.

Vancomycin is associated with two main types of hypersensitivity reactions, namely a nonallergic hypersensitivity reaction known as "red man syndrome" and anaphylaxis. Skin testing with vancomycin at $\leq$100 μg/mL is diagnostic for the presence of IgE antibodies that can be elicted by multiple courses of therapy.

Topical antibiotics such as bacitracin and neomycin usually cause delayed-type skin reactions. Although immediate-type reactions are rarely reported, repeated usage of bacitracin has been associated with near fatal anaphylaxis in a few cases. Hypersensitivity reactions to metronidazole are infrequently reported. Fixed drug eruptions and delayed-type skin reactions are the most common clinical presentations.

The general approach to antibiotic allergy as depicted in Figure 210.1 is also useful for management of adverse reactions to non-β-lactam antibiotics.

Multiple antibiotic allergy syndromes

Some patients show a marked propensity to react to several chemically unrelated antibiotics and sometimes nonantibiotic drugs. This condition has been termed the multiple drug allergy syndrome (MDAS). In most cases, MDAS presents clinically as acute urticaria +/− angioedema after ingestion of multiple doses of offending drugs. However, other variants including non-urticarial rashes, including SJS, anaphylaxis, serum sickness-like reactions, and immune cytopenias, have also been described. Mechanisms underlying multiple drug reactivity are still unclear. Published studies have suggested a high propensity to MDAS among patients with a history of allergy to β-lactams or any other antimicrobial drug. Whether MDAS results from a facilitated ability to make immune responses to drug haptens or an increased vulnerability to drug-induced immunopathology has yet to be determined. Some cases of MDAS are "pseudoallergic" and reflect classically conditioned responses that can readily be misinterpreted as anaphylaxis.

Clinical management of MDAS is similar to that of patients with single antibiotic allergy. Avoidance of unnecessary use of drugs should be the first step. Preferential use of low-risk antibiotics such as macrolides and quinolones may be helpful. If validated skin or in vitro tests are available, they can be helpful in permitting readministration of previously implicated drugs, especially β-lactams.

CONCLUSION

Patients relating a history of immune or nonimmune reactions to antibiotics are not rare in medical practice. As history alone has low diagnostic value, it is desirable that the history-positive patients should be evaluated by diagnostic tests when validated or by drug provocation tests when the index of suspicion is low. Although alternative antimicrobials can often be identified, they can have higher costs and treatment failures or greater toxicity. For the truly drug-allergic patient, management approaches include cautious administration of cross-reactive antimicrobials from the same class or drug desensitization. When approached systematically, almost all antibiotic-sensitive patients can be safely and effectively treated.

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211. Antimicrobial agent tables

Jomy George and Rosalie Pepe

INTRODUCTION

The following tables of antimicrobial agents are organized as follows:

Table 211.1: Antibacterial Agents
Table 211.2: Antimycobacterial Agents
Table 211.3: Antifungal Agents
Table 211.4: Antiviral Agents
Table 211.5: Antiparasitic Agents

The listings are alphabetical by generic name, with the corresponding brand name provided; available data are included for dosage, cost, change in absorption with food, pregnancy class, dosage adjustment for renal failure and dialysis, and major toxicities.

Some agents no longer available in the United States are available elsewhere and are listed in generic form only.

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Table 211.1 Antibacterial agents

Name		Usual dose		Cost (AWP unit price)[a]	Change in absorption with food
Generic	**Brand**	**Adult**	**Child**		
Amikacin[c]	Amikin	15 mg/kg/d; divide q8–12h IV 10–40 mg IT q24h	15 mg/kg/d; divide q8–12h	250 mg/mL injection; 4 mL vial = $4.05	n.a.
Amoxicillin	Amoxil	0.25–0.5 g PO q8h or 875 mg PO q12h or 1000 mg PO q12h (*Helicobacter pylori*)	6.6–13.3 mg/kg PO q8h (neonate: 0–7 d, 25 mg/kg q12h; 1–4 wk 25 mg/kg q8h)	250 mg capsule: $0.25 500 mg capsule: $0.44 875 mg tablet: $0.87 400 mg/5 mL (50 mL) oral susp: $4.85	Decreased
Amoxicillin–clavulanate	Augmentin	0.25–0.5 g PO q8h 875 mg PO q12h 2000 mg PO q12h XR tablets	6.6–13.3 mg/kg PO q8h	250/150 mg tablet: $4.11 500/125 mg tablet: $3.78 875/125 mg tablet: $5.05 XR 1000/62.5 mg tablet: $3.87 400 mg/5 mL (50 mL) oral susp: $68.93	Decreased
Ampicillin	Ampen, Omnipen	0.5–1 g PO q8h; 1–2 g IV q4–6h	12.5–25 mg/kg PO q8h 6.25–25 mg/kg IV q8h	250 mg capsule: $0.22 500 mg capsule: $0.40 250 mg IV vial: $3.98 1000 mg IV vial: $8.20	Decreased
Ampicillin–sulbactam	Unasyn	1.5–3 g IV q6h	25–50 mg/kg IV q6h	1.5 g IV vial: $7.73 3 g IV vial: $14.60	n.a.
Azithromycin	Zithromax	5 g day 1; 0.25 g days 2–5 PO	–[b]	250 mg tablet: $7.78 500 mg tablet: $21.21 500 mg IV vial: $7.20 100 mg/5 mL (15 mL) oral susp: $32.93	Decreased
Azlocillin		2–4 g IV q4–6h	75 mg/kg IV q6h	Data not available	n.a.
Aztreonam	Azactam	1–2 g IV q6–8h	30–50 mg/kg q6–12h (n.a.)	1 g IV vial: $39.50 2 g vial: $80.34	n.a.
Bacampicillin		0.4–0.8 g PO q12h	12.5–25 mg/kg PO q12h	Data not available	None
Carbenicillin indanyl sodium		1–2 0.382-g tabs PO q6h	7.5–12.5 mg/kg PO q6h	Data not available	Increased
Cefaclor	Ceclor	0.25–0.5 PO q8h	20–40 mg/kg/d; divide q8h PO	250 mg capsule: $1.98 500 mg capsule: $3.89	Decreased
Cefadroxil	Duricef	0.5–1 g PO q12–24h	30 mg/kg/d; divide q12h PO	500 mg capsule: $3.72	Decreased
Cefamandole		0.5–2 g IV q4–8h	50–150 mg/kg/d; divide q4–8h IV	Data not available	n.a.
Cefazolin	Ancef, Kefzol	0.5–2 g IV q8h	25–100 mg/kg/d; divide q6–8h IV	500 mg IV vial: $1.30 1 g IV vial: $2.61	n.a.

Pregnancy class[a]	Dose interval adjustment for reduced CrCl			Supplemental dose in dialysis		Major toxicity
	>50	10–50	≤10	HD	PD	
D	q8–12h	q12–48h	>48h	2.5–3.75 mg/kg pHD	2.5 mg/kg/d IV or 3–4 mg/2 L dialysate removed	Renal toxicity, vestibular or auditory toxicity, CNS reactions, neuromuscular blockade (rare)
B	q8h	q8–12h	q16–24h	0.25–0.5 g	0.25 g q12h	Allergic reactions (rare: anaphylactic), rash, diarrhea, nausea, vomiting
B	q8h	q12h	q12–24h	0.25 g PO	–[b]	Allergic reactions (rare: anaphylactic), diarrhea, nausea, vomiting, cholestatic hepatitis
B	q4–6h	q8h	q12–24h	0.5–2 g	0.25 g PO q12h or 1–4 g IV q24h	Allergic reactions (rare: anaphylactic), diarrhea, nausea, vomiting
B	q6–8h	q8–12h	q24h	2 g ampicillin pHD	–[b]	Allergic reactions (rare: anaphylactic), diarrhea, nausea, vomiting
B	Usual	Usual	Usual	–[b]	–[b]	GI disturbance, headache
B	q4–6h	q8h	q12h	3 g pHD	–[b]	Allergic reactions (rare: anaphylactic), diarrhea, nausea, vomiting
B	q6–8h	q12–18h	q24h	18 first dose (60–250 mg) pHD	Usual dose (1–2 g) then usual dose at usual intervals	Rash, diarrhea, nausea, vomiting, elevated AST/ALT
B	q12h	q12h	–[b]	–[b]	–[b]	Allergic reactions (rare: anaphylactic), diarrhea, nausea, vomiting
B	–[b]	–[b]	–[b]	–[b]	–[b]	Allergic reactions (rare: anaphylactic), diarrhea, nausea, vomiting
B	q8h	q8h	q8h	0.25–0.5 g	–[b]	Allergic reactions, GI disturbance, arthritis, serum sickness
B	q12–24h	0.5 g q12–24h	0.5 g q36h	0.5–1 g	–[b]	Allergic reactions, GI disturbance
B	q4–8h	q8h	0.5–1 g q12h	0.5–1 g	–[b]	Thrombophlebitis with IV infusion, allergic reactions, GI disturbance
B	q8h	0.5–1 g q8–12h	0.5–1 g q24h	0.25–0.5 g	–[b]	Allergic reactions, GI disturbance, diarrhea

Table 211.1 *(continued)*

Name		Usual dose		Cost (AWP unit price)[a]	Change in absorption with food
Generic	**Brand**	**Adult**	**Child**		
Cefdinir	Omnicef	300 mg PO q12h	14 mg/kg/d PO qd divide q12–24h	300 mg capsule: $5.10 250 mg/5 mL (60 mL): $51.01	Minimal decrease
Cefditoren	Spectracef	400 mg PO BID	400 mg PO BID	400 mg capsule: $14.74	Increased
Cefepime	Maxipime	0.5–2 g IV q12h	50 mg/kg IV q8h (n.a.)	1 g IV vial: $6.96 2 g IV vial: 11.86	n.a.
Cefixime	Suprax	0.4 g PO q24h	8 mg/kg/d; divide PO q24h	400 mg tablet: $20.16	Decreased
Cefmetazole		2 g IV q6–12h	–[b]	Data not available	n.a.
Cefonicid		0.5–2 g IV q24h	–[b]	Data not available	n.a.
Cefoperazone		1–2 g IV q6–12h	25–100 mg/kg IV q12h (n.a.)	Data not available	n.a.
Cefotaxime	Claforan	0.5–2 g IV q8–12h; 3 g q6h for CNS	50–200 mg/kg/d; divide IV q4–8h (neonate: 0–7 d, 50 mg/kg q12h; 1–4 wk: 50 mg/kg q6–8h)	500 mg IV vial: $3.65 1 g IV vial: $4.36 2 g IV vial: $8.54	n.a.
Cefotetan	Cefotan	1–2 g IV q12h	40–60 mg/kg/d; divide IV q12h (n.a.)	1 g IV vial: $17.58 2 g IV vial: $25.14	n.a.
Cefoxitin	Mefoxin	1–2 g IV q6–8h	80–160 mg/kg/d; divide IV q4–8h	1 g IV vial: $11.22 2 g IV vial: $22.50	n.a.
Cefpodoxime	Vantin	0.1–0.4 g PO q12h	5 mg/kg PO q12h	100 mg tablet: $6.73 200 mg tablet: $8.45	Increased
Cefprozil	Cefzil	0.25–0.5 g PO q12–24h	15 mg/kg PO q12h	250 mg tablet: $4.37 500 mg tablet: $9.04	No effect
Ceftaroline	Teflaro	600 mg IV q12h	–[b]	600 mg IV: $59.98	n.a.
Ceftazidime	Fortaz, Tazicef, Tazidime	1–2 g IV q8–12h	25–50 mg/kg IV q8h	1 g IV vial: $12.90 2 g IV vial: $18.59	n.a.
Ceftibuten	Cedax	400 mg PO q12h	3–6 mg/kg PO q8h	400 mg capsule: $19.19	Increased
Ceftizoxime	Cefizox	1–3 g IV q6–8h	33–50 mg/kg IV q6–8h	No data available	n.a.
Ceftriaxone	Rocephin	0.5–2 g IV q12–24h (neonate: 0–7 d, 50 mg/kg q24h; 1–4 wk, 50–75 mg/kg q24h)	50–100 mg/kg/d; divide IV q12–24h	250 mg IV vial: $1.50 500 mg IV vial: $1.50 1 g IV vial: $2.64 2 g IV vial: $5.28	n.a.

Pregnancy class[a]	Dose interval adjustment for reduced CrCl			Supplemental dose in dialysis		Major toxicity
	>50	10–50	≤10	HD	PD	
B	Usual	300 mg q24h	300 mg q24h	Not defined	Not defined	Anaphylaxis, TEN, erythema multiforme, neutropenia
B	400 mg PO BID	200 mg PO BID	200 mg PO qd	None	–[b]	Anaphylaxis, leukopenia, neutropenia, thrombocytopenia
B	0.5–2 g IV q12h	q24h	0.25–0.5 g q24h	Dose pHD	0.5–2 g q48h	Nausea, diarrhea, vomiting, rash, phlebitis
B	q24h	0.3 g q24h	q48h	None	–[b]	Thrombophlebitis, allergic reactions, GI disturbance
B	q6–12h	q16–24h	q48h	–[b]	–[b]	Thrombophlebitis, allergic reactions, GI disturbance
B	q24h	4–15 mg/kg q24–48h	3–15 mg/kg q3–5 days	None	–[b]	Allergic reactions, GI disturbance, hypoprothrombinemia or hemorrhage
B	q6–12h	q6–12h	q6–12h	Dose after HD	–[b]	Thrombophlebitis, allergic reactions, GI disturbance
B	q8–12h	q12–24h	0.5 g q24–48h	0.5–2 g	–[b]	Thrombophlebitis, allergic reactions, GI disturbance
B	q12h	q24h	q48h	25% dose nonHD days, 50% HD	–[b]	Thrombophlebitis, allergic reactions, GI disturbance, hypoprothrombinemia, hemorrhage
B	q6–8h	q12–24h	0.5–1 g q12–24h	1–2 g	–[b]	Thrombophlebitis, allergic reactions, GI disturbance
B	q12h	q24h	q24h	Dose 3 × wk	–[b]	Allergic reactions, GI disturbance
B	q12–24h	50% dose q12–24h	50% dose q12–24h	–[b]	–[b]	Allergic reactions, GI disturbance
B	q12h	300-400 mg q12h	200 mg q12h	None	–[b]	Allergic reactions, diarrhea, nausea, direct Coombs seroconversion
B	q8–12h	q12–24h	q24–48h	1 g load then 1 g pHD	0.5 g IV q24h or 250 mg/2 L dialysate	Thrombophlebitis, allergic reactions, GI disturbance
B	for CrCl 30: 400 mg q12–24h PO 12; for CrCl 5: 29–200 mg PO qd	for CrCl 30: 400 mg q24h PO 12; for CrCl 5: 29–200 mg PO qd	100 mg q24h	400 mg pHD		Seizures, anaphylaxis, TEN, Stevens–Johnson syndrome, erythema multiforme
B	q6–8h	0.25–1 g q12h	0.5 g q24h	Dose pHD	3 g q48h	Thrombophlebitis, allergic reactions, GI disturbance
B	q12–24h	q12–24h	q12–24h	None	–[b]	Thrombophlebitis, allergic reactions, GI disturbance, cholelithiasis

Table 211.1 *(continued)*

Name		Usual dose		Cost (AWP unit price)*	Change in absorption with food
Generic	**Brand**	**Adult**	**Child**		
Cefuroxime	Zinacef, Kefurox	0.75–1.5 g IV q8h	50–100 mg/kg/d divide IV q6–8h	750 mg IV vial: $3.67 1.5 g IV vial: $13.12	n.a.
Cefuroxime axetil	Ceftin	0.125–0.5 g PO q12h	0.125–0.25 g PO q12h	250 mg tablet: $4.39 500 mg tablet: $8.01	Decreased
Cephalexin	Keflex, Biocef, Keftab	0.25–1 g PO q6h	25–100 mg/kg/d; divide PO q6h	250 mg capsule: $0.69 500 mg capsule: $1.37 750 mg capsule: $7.69	Unchanged
Cephalothin		0.5–2 g IV q4–6h	80–160 mg/kg/d; divide IV q6h	Data not available	n.a.
Cephapirin		0.5–2 g IV q4–6h	40–80 mg/kg/d divide IV q6h	Data not available	n.a.
Cephradine		0.25–1 g PO q6h 0.5–2 g IV q4–6h	25–100 mg/kg/d; divide PO q6–12h 50–100 mg/kg divide IV q6h	Data not available	Decreased
Chloramphenicol	Chloromycetin	0.25–0.75 g PO q6h 0.25–1 g IV q6h	50–100 mg/kg/d; divide q6h PO, IV	PO: data not available 1 g IV vial: $17.00	Vitamins may increase absorption
Cinoxacin		0.25 g q6h, 0.5 g PO q12h	N.R.	Data not available	Delayed absorption and lower mean peak serum levels
Ciprofloxacin	Cipro	0.25–0.75 g PO q12h 0.2–0.4 g IV q12h	N.R.	250 mg tablet: $0.31 500 mg tablet: $0.36 750 mg tablet: $0.40	Decreased
Clarithromycin	Biaxin	0.25–0.5 g PO q12h	7.5 mg/kg q12h (n.a.)	250 mg tablet: $4.50 500 mg tablet: $4.52	Increased or unchanged
Clindamycin	Cleocin	0.15–0.3 g PO q6h 0.3–0.9 g IV q6–8h	8–25 mg/kg/d; divide PO q6–8h 15–40 mg/kg/d; divide IV q6–8h (newborn: 0–7 d, 15 mg/kg/d q6–8h; 1–4 wk, 15–20 mg/kg/d q6–8h)	150 mg capsule: $1.19 300 mg IV bag: $0.11 600 mg IV bag: $0.16 900 mg IV bag: $0.19	Unchanged
Cloxacillin		0.5–1 g PO q6h	12.5–25 mg/kg PO q6h	Data not available	Decreased
Colistin		5–15 mg/kg/d PO q8h 2.5–5 mg/kg/d IV q6–12h	5–15 mg/kg/d; divide PO q8h 2.5–5 mg/kg/d; divide IV q6–12h	150 mg IV vial: $57.00	Not significantly absorbed orally
Dapsone		0.05–0.1 g PO q24h	1–2 mg/kg/d; divide q24h	25 mg tablet: $1.06 100 mg tablet: $1.30	No effect
Daptomycin	Cubicin	4–6 mg/kg IV q24h	Not defined	500 mg IV vial: $382.44	n.a.
Dicloxacillin	Dynapen	0.25–0.5 g PO q6h	3.125–6.25 mg/kg PO q6h	250 mg capsule: $0.66 500 mg capsule: $1.12	Decreased

Pregnancy class[a]	Dose interval adjustment for reduced CrCl			Supplemental dose in dialysis		Major toxicity
	>50	10–50	≤10	HD	PD	
B	q8h	q8–12h	0.75 g q24h	0.75 g pHD	15 mg/kg pPD	Thrombophlebitis, allergic reactions, GI disturbance
B	q12h	q12h	0.25 g q24h	–[b]	–[b]	Allergic reactions, GI disturbance
B	q6h	q8–12h	q24–48h	0.25–1 g	–[b]	Allergic reactions, GI disturbance
B	q4–6h	1–1.5 g q6h	0.5 g q8h	0.5–2 g	Add up to 6 mg/kg to dialysate	Thrombophlebitis with IV infusion, allergic reactions, GI disturbance
B	q4–6h	q8h	q12h	7.5–15 mg/kg pHD then q12h	–[b]	Thrombophlebitis, allergic reactions, GI disturbance
B	q6h	0.5 g q6h	0.25 g q12h	0.25 g before HD, then 12, 36, and 48 h pHD	0.5 g q6h	Allergic reactions, GI disturbance
C	Usual	Usual	Usual	Dose pHD	Usual	Blood dyscrasias, gray baby syndrome, GI disturbance
C	q6h	0.25 g q12–24h	N.R.	–[b]	–[b]	Nausea, vomiting, dizziness, headache, tremors, confusion
C	q12h	0.25–0.5 g PO q12h, IV q12–24h	0.25–0.5 g PO q18h, IV q18–24h	0.25–0.5 g q24h, pHD on HD days	0.25–0.5 g q24h	Nausea, vomiting, dizziness, headache, tremors, confusion
B	q12h	q12–24h	q24h	–[b]	–[b]	GI disturbance, abnormal taste, headache
B	Usual	Usual	Usual	Usual	Usual	Diarrhea, including pseudomembranous colitis, allergic reactions
B	q6h	q6h	q6h	Usual	Usual	Allergic reactions (rare: anaphylactic), diarrhea, nausea, vomiting
Not established	q6–12h	2.5 mg/kg/d q12–24h	1.5 mg/kg q36h	–[b]	–[b]	Nephrotoxicity, CNS side effects including confusion, coma, seizures
C	q24h	q24h	q24h	–[b]	–[b]	Rash, headache, GI irritation, infectious mono-like syndrome
B	4–6 mg/kg q24h	4–6 mg/kg q48h	4–6 mg/kg q48h	4–6 mg/kg q48h. Administer after dialysis session on dialysis days	4–6 mg/kg q48h	Arrhythmias, hypersensitivity rxn, anaphlyaxis, thrombocytopenia, myopathy
Not established	q6h	q6h	q6h	Usual	Usual	Allergic reactions (rare: anaphylactic), diarrhea, nausea, vomiting

Table 211.1 *(continued)*

Name		Usual dose		Cost (AWP unit price)[a]	Change in absorption with food
Generic	**Brand**	**Adult**	**Child**		
Doripenem	Doribax	500 mg IV q8h	—[b]	250 mg IV vial: $25.30 500 mg IV vial: $45.99	n.a.
Doxycycline	Vibramycin	0.1 g PO, IV q12h	2.2 mg/kg PO, IV q12–24h	100 mg tablet: $4.06 100 mg IV vial: $18.02	Decreased with milk, antacids
Enoxacin		0.4 g PO, IV q12h	N.R.	Data not available	Decreased
Ertapenem	Invanz	1 g IM/IV qd	30 mg/kg/d IM/IV BID	1 g vial: $84.89	n.a.
Erythromycin base		0.25–0.5 g PO q6h	30–50 mg/kg/d; divide q6h	Data not available	Decreased
Erythromycin estolate		0.25–0.5 g PO q6h	3–50 mg/kg/d; divide q6h	Data not available	Decreased
Erythromycin ethyl succinate	EES, EryPed	0.4 g PO q8h	30–50 mg/kg/d divide PO q8h	400 mg tablet: $3.26	Increased
Erythromycin lactobionate		0.5–1 g IV q6h	15–20 mg/kg/d; divide IV q6h	Data not available	n.a.
Fidaxomicin	Dificid	200 PO BID	—[b]	200 mg tablet: $177.46	None
Gatifloxacin		400 mg daily PO or IV	—[b]		None
Gentamicin[c]	Garamycin	3–5 mg/kg/d; divide IV q8h 4–8 mg/d IT	3–7.5 mg/kg/d; divide IV q8h (newborn: 0–7 d, 2.5 mg/kg q12h; 1–4 wk, 7.5 mg/kg/d q8h)	100 mg/100 mL IV bag: $0.04	n.a.
Grepafloxacin		400 mg or 600 mg daily	—[b]	Data not available	No change
Imipenem	Primaxin	0.5–1 g IV q6h	15–25 mg/kg IV q6h (n.a.) (neonate: 0–7 d, 25 mg/kg q12h; 1–4 wk, 25 mg/kg q8h)	250 mg IV vial: $11.76 500 mg IV vial: $23.52	n.a.
Kanamycin[c]	Kantrex	15 mg/kg/d; divide IV q8–12h	15 mg/kg/d; divide IV q8–12h (newborn: 0–7 d, 15–20 mg/kg/d q12h; 1–4 wk, 15 mg/kg/d q8–12h)	1 g vial: $19.32	n.a.
Levofloxacin	Levaquin	0.25–0.75 g/d PO or IV	N.R.	250 mg tablet: $16.81 500 mg tablet: $19.26 750 mg tablet: $36.07 250 mg IV bag: $0.15 500 mg IV bag: $0.12	Unchanged
Lincomycin	Lincocin	0.5 g PO q6–8h 0.6–1 g IV q8–12h	30–60 mg/kg/d; divide PO q6–8h 10–20 mg/kg/d; divide IV q6h	PO: data not available 300 mg/mL (10 mL) vial: $9.48	Decreased

Pregnancy class[a]	Dose interval adjustment for reduced CrCl			Supplemental dose in dialysis		Major toxicity
	>50	10–50	≤10	HD	PD	
B	q8h	250 mg q8h	250 mg q12h	–[b]	–[b]	Anaphylaxis, hypersensitivity, GI disturbance
D	q12h	q12h	q12h	Usual	Usual	GI disturbance, photosensitivity reactions, hepatic toxicity, esophageal ulcers
C	q12h	0.1–0.2 g q12h	0.1–0.2 g q12h	–[b]	–[b]	Nausea, vomiting, dizziness, headache, tremors, confusion
B	1 g IM/IV qd	CrCl ≤30: 500 mg qd	CrCl ≤30: 500 mg qd	30% of daily dose should be supplemented pHD	–[b]	Thrombocytopenia, increased LFTs, diarrhea, allergic reactions
B	q6h	q6h	q6h	Usual	Usual	GI disturbance; rare: allergic reactions, hepatic dysfunction, hearing loss
B	Usual	Usual	Usual	No change	No change	Cholestatic hepatitis, hearing loss or tinnitus, GI disturbance, hypersensitivity reactions
B	Usual	Usual	Usual	Usual	Usual	GI disturbance; rare: allergic reactions, hepatic dysfunction
B	Usual	Usual	Usual	Usual	Usual	GI disturbance; rare: allergic reactions, hepatic dysfunction, hearing loss
B	Usual dose	Usual dose	Usual dose	None	None	Nausea, vomiting, hypersensitivity reaction
	Usual dose	400 mg ×1 then 50% q24h	–[b]	–[b]	–[b]	Hyperglycemia, hypoglycemia, QT prolongation, tendon rupture
C	q8–12h	q12–48h	>48 h	1–1.7 mg/kg pHD	1 mg/2 L dialysate removed	Renal toxicity, vestibular and auditory toxicity, CNS reactions, neuromuscular blockade (rare)
	–[b]	–[b]	–[b]	–[b]	–[b]	Phototoxicity, QT prolongation, tendon rupture
C	q6h	0.5 g q8–12h	0.25–0.5 g q12h	0.25–0.5 pHD then q12h	–[b]	Fever, rash, nausea, vomiting, diarrhea, seizures (rare)
D	q8–12h	q12–48h	>48 h	4–5 mg/kg pHD	3.75 mg/kg/d	Cranial nerve VIII and renal damage
C	Usual	0.25 g q24–48h	0.25 g q48h	0.25 g q48h	0.25 g q48h	Diarrhea, nausea, headache
Not established	Usual	Usual	Usual	–[b]	–[b]	Diarrhea, including pseudomembranous colitis, allergic reactions

Table 211.1 *(continued)*

Name		Usual dose		Cost (AWP unit price)[a]	Change in absorption with food
Generic	**Brand**	**Adult**	**Child**		
Linezolid	Zyvox	600 mg PO/IV q12h	>12 y: 600 mg PO q12 0–11: 30 mg/kg PO/IV q8h	600 mg tablet: $140.37 600 mg IV bag: $144.40	Unchanged
Lomefloxacin		0.4 g PO q24h	N.R.	Data not available	Decrease
Loracarbef		0.2–0.4 g PO q12–24h	15–30 mg/kg/d; q12h	Data not available	Decreased
Meropenem	Merrem	0.5–1 g IV q8h	20–40 mg/kg IV q8h	500 mg IV vial: $9.24 1 g IV vial: $18.48	n.a.
Metronidazole	Flagyl	0.25–0.5 g PO q6–12h 0.5 g IV q6–8h	15 mg/kg/d; divide TID (n.a.)	250 mg tablet: $0.32 500 mg tablet: $0.59 500 mg IV bag: $2.50	Unchanged
Mezlocillin		3–4 g IV q4–6h	50 mg/kg IV q4–6h	Data not available	n.a.
Minocycline	Minocin, Dynacin	0.1 g PO, IV q12h	2 mg/kg PO, IV q12h	100 mg capsule: $0.67 100 mg IV: $65.30	Decreased with milk, antacids
Moxifloxacin	Avelox	400 mg PO/IV q24h	N.R.	400 mg tablet: $27.52 400 mg IV: $46.08	Absorption delayed
Nafcillin	Nallpen, Unipen	0.5–2 g IV q4–6h	150 mg/kg/d; divide IV q4–6h (neonate: 0–7 d, 25 mg/kg q8–12h; 1–4 wk, 25 mg/kg q6–8h)	2 g IV bag: $24.95	Decreased (PO)
Neomycin	Neo-tabs	50 mg/kg/d; divide PO q6h	–-	500 mg tablet: $1.36	Neomycin not significantly absorbed PO
Netilmicin[c]		4–6.5 mg/kg/d; divide IV q8–12h	3–7.5 mg/kg/d; divide IV q8–12h (newborn: 0–4 wk, 4–6.5 mg/kg/d q12h)	Data not available	n.a.
Nitrofurantoin	Macrodantin, Macrobid	0.05–0.1 g PO q6h	5–7 mg/kg/d; divide q6h	100 mg capsule (Macrobid): $17.11 100 mg capsule (Macrodantin): $3.91	Increased
Norfloxacin	Noroxin	0.4 g PO q12h	N.R.	400 mg tablet: $4.84	Decreased
Ofloxacin	Floxin	0.2–0.4 g PO, IV q12h	N.R.	200 mg tablet: $4.78 400 mg tablet: $6.00 IV: data not available	Decreased
Oxacillin	Bactocil	0.5–1 g IV q4–6h	37.5–50 mg/kg IV q6h (neonate: 0–7 d, 25 mg/kg q8–12h; 1–4 wk, 25 mg/kg q6–8h)	1 g IV vial: $14.60	Decreased
Penicillin V	Pen–VeeK, Pen–V	0.25–0.5 g PO q6h	6.25–12.5 mg/kg PO q6h	250 mg tablet: $0.46 500 mg tablet: $0.74	Decreased

Pregnancy class[a]	Dose interval adjustment for reduced CrCl			Supplemental dose in dialysis		Major toxicity
	>50	10–50	≤10	HD	PD	
C	Usual	Usual	Usual	200 mg	–[b]	Leukopenia, pancytopenia, lactic acidosis, peripheral neuropathy, optic neuropathy
C	q24h	0.2 g q24h	0.2 g q24h	0.4 g load, then 0.2 g q24h	–[b]	Nausea, vomiting, dizziness, headache, tremors, confusion, photosensitivity
B	q12–24h	q24–48h	q3–5d	Dose pHD	–[b]	Allergic reactions, GI disturbance
B	0.5–1 g IV q8h	q12h	0.25–0.5 q24h	–[b]	–[b]	Nausea, diarrhea, vomiting, rash
B	Usual	Usual	Usual	Usual	Usual	Nausea, headache, metallic taste
B	q4–6h	q8h	q8h	2–3 g then 3–4 g q12h	3 g q12h	Allergic reactions (rare: anaphylactic), diarrhea, nausea, vomiting
D	q12h	q12h	q12h	Usual	Usual	GI disturbance, photosensitivity, hepatic toxicity, esophageal ulcers, vestibular toxicity; tooth discoloration
C	Usual	Usual	Usual	No change	No change	Anaphylaxis, phototoxicity, increased ICP, toxic psychosis
B	q4–6h	q4–6h	q4–6h	Usual	Usual	Allergic reactions (rare: anaphylactic), diarrhea, nausea, vomiting; platelet dysfunction with high doses
Not established	–[b]	–[b]	–[b]	–[b]	–[b]	Cranial nerve VIII and renal damage
D	q8–12h	q12–48h	>48 h	2 mg/kg pHD	–[b]	Renal toxicity, vestibular and auditory toxicity, CNS reactions, neuromuscular blockade (rare)
B	Usual	Avoid	Avoid	Avoid	Avoid	Rash, nausea/vomiting, pancreatitis, anemia, leukopenia, LFT elevation, neuropathy, urine discoloration
C	q12h	q24h	q24h	–[b]	–[b]	Nausea, vomiting, dizziness, headache, tremors, confusion
C	q12h	q24h	0.1–0.2 g q24h	0.2 g load; then 0.1 g q24h	–[b]	Nausea, vomiting, dizziness, headache, tremors, confusion
B	q4–6h	q4–6h	q4–6h	Usual	Usual	Allergic reactions (rare: anaphylactic), diarrhea, nausea, vomiting
B	q6h	q6h	q6h	250 mg	–[b]	Allergic reactions (rare: anaphylactic), diarrhea, nausea, vomiting

Table 211.1 *(continued)*

Name		Usual dose		Cost (AWP unit price)[a]	Change in absorption with food
Generic	**Brand**	**Adult**	**Child**		
Penicillin G benzathine	Bicillin L-A	600 000–2 400 000 U IM ×1	600 000 U IM ×1 (neonate: 1–4 wk, 50 000 U/kg IM ×1)	600 000 units/mL (4 mL) IM injection: $37.51	n.a.
Penicillin G		0.5–1 g PO q6h 1–4 million U IV q4–6h	25 000–90 000 U/kg/d; divide q4–8h PO 25 000–400 000 U/kg/d; divide IV q4–6h (neonate: 0–7 d, 50 000–150 000 U/kg/d q8–12h; 1–4 wk, 75 000–200 000 U/kg/d q6–8h)	Data not available PO 2 million units/50 mL IV bag: $10.55 3 million units/50 mL IV bag: $10.95	Decreased
Piperacillin		3–4 g IV q4–6h	50 mg/kg IV q4–6h (n.a.)	Data not available	n.a.
Piperacillin–tazobactam	Zosyn	3.375 g IV q6–8h	90–112.5 mg/kg IV q8h	3.375 g IV vial: $21.46	n.a.
Polymyxin B	Aerosporin, Neosporin	15 000–25 000 U/kg/d IV q12h	15 000–25 000 U/kg/d IV q12h	500 000 units vial: $12.00	n.a.
Procaine penicillin G	Wycillin	0.6–1.2 million U IM q12h	25 000–50 000 U/kg IM q12–24h	600 000 units/mL (2 mL) IM injection: $16.92	n.a.
Quinupristin–dalfopristin	Synercid	7.5 mg/kg IV q8h	–[b]	350 mg IV vial: $247.46	n.a.
Rifaximin	Xifaxan	200 mg PO TID	–[b]	200 mg tablet: $16.04 550 mg tablet: $26.43	Unchanged
Sparfloxacin		0.4 g PO ×1 d then 0.2 g/d	–[b]	No data available	Unchanged
Spectinomycin		2 g IM qd	–[b]	Data not available	n.a.
Streptomycin		0.5–1 g IV or IM q12h	20–40 mg/kg/d; divide IV or IM q6–12h	1 g IM injection: $22.50	n.a.
Sulfadiazine	Microsulfon	2–4 g/d; PO q4–8h	120–150 mg/kg/d; divide PO q4–6h	500 mg tablet: $4.28	Decreased
Sulfamethoxazole		1 g PO q8–12h	50–60 mg/kg/d; divide PO q12h	Data not available	Decreased
Sulfisoxazole		0.5–1 g PO q6h 25 mg/kg IV q6h	120–150 mg/kg/d; divide PO q4–6h	Data not available	Decreased
Teichoplanin		0.2–0.4 g IV q24h	10 mg/kg IV q24h	Data not available	n.a.
Telavancin	Vibativ	10 mg IV q24h	–[b]	750 mg IV vial: $358.00	n.a.

Pregnancy class[a]	Dose interval adjustment for reduced CrCl			Supplemental dose in dialysis		Major toxicity
	>50	10–50	≤10	HD	PD	
B	Usual	Usual	Usual	Usual	Usual	Allergic reactions (rare: anaphylactic), diarrhea, nausea, vomiting
B	q4–6h	q4–6h	25%–50% of standard dose q4–6h	500 000 U	–[b]	Allergic reactions (rare: anaphylactic), diarrhea, nausea, vomiting
B	q4–6h	q6–8h	q8–12h	1 g pHD, then 2 g IV q8h	–[b]	Allergic reactions (rare: anaphylactic), diarrhea, nausea, vomiting; platelet dysfunction with high doses
B	q6–8h	2.25 g q6h	2.25 g q8h	–[b]	–[b]	Allergic reactions (rare: anaphylactic), diarrhea, nausea, vomiting
Not established	q12h	q12h	2250–3750 U/kg/d; divide q12h	–[b]	–[b]	Nephrotoxicity, flushing; CNS effects: confusion, seizures; allergic reactions
B	q12h	q12h	q12h	–[b]	–[b]	Allergic reactions (rare: anaphylactic), diarrhea, nausea, vomiting
–[b]	Usual	Usual	Usual	–[b]	–[b]	Pain at infusion site, thrombophlebitis, arthralgia, myalgia
C	–[b]	–[b]	–[b]	–[b]	–[b]	Headache, constipation, vomiting
C	Usual	0.2 g q48h	0.2 g q48h	–[b]	–[b]	Photosensitivity, diarrhea, nausea, headaches, cardiac arrhythmias in patients taking antiarrhythmic drugs
B	q24h	q24h	q24h	–[b]	–[b]	Pain at injection site, nausea, allergic reactions
D	q12h	7.5 mg/kg q24h	7.5 mg/kg q72–96h	0.5 g pHD	–[b]	Cranial nerve VIII damage, paresthesias, rash, fever, renal toxicity, neuromuscular blockade, optic neuritis
C	–[b]	–[b]	–[b]	–[b]	–[b]	Rash, photosensitivity, drug fever
C	–[b]	–[b]	–[b]	–[b]	–[b]	Rash, photosensitivity, drug fever
C	q6h	q8–12h	q12–24h	–[b]	–[b]	Rash, photosensitivity, drug fever
Not established	q24h	q48h	q72h	–[b]	–[b]	Ototoxicity
C	q24h	q48h	–[b]	–[b]	–[b]	Nephrotoxicity, nausea, QT prolongation

Table 211.1 *(continued)*

Name		Usual dose		Cost (AWP unit price)*	Change in absorption with food
Generic	**Brand**	**Adult**	**Child**		
Telithromycin	Ketek	800 mg PO qd	–[b]	400 mg tablet: $17.27	Unchanged
Tetracycline	Achromycin	0.25–0.5 g PO q6h	25–50 mg/kg/d; divide q6–12h	250 mg capsule: $0.05 500 mg capsule: $0.07	Decreased with milk, antacids
Ticarcillin		3 g q4–6h	50 mg/kg q4–6h (neonate: 0–7 d, 75 mg/kg q8–12h; 1–4 wk, 75 mg/kg q8h if <2 kg; 100 mg/kg q8h if >2 kg)	Data not available	n.a.
Ticarcillin–clavulanate	Timentin	3.1 IV q4–8h	50 mg/kg IV q4–6h	3.1 g IV vial: $16.00	n.a.
Tigecycline	Tygacil	100 mg IV ×1 then 50 mg IV q12h	–[b]	50 mg IV vial: $104.38	n.a.
Tinidazole	Tindamax	1-2 g PO q24h	–[b]	250 mg tablet: $7.92 500 mg tablet: $15.86	Unchanged
Tobramycin[c]	Nebcin	3–5 mg/kg/d; divide IV q8h 4–8 IT mg/d	3–6 mg/kg/d; divide IV q8h (newborn: 0–7 d, ≤4 mg/kg/d q12h; 1–4 wk, 3–5 mg/kg/d q8h)	40 mg/mL (2 mL) IV vial: $1.18	n.a.
Trimethoprim–sulfamethoxazole	Bactrim, Septra	0.16–0.8 g PO q12–24h 3–5 mg/kg IV q6–8h trimethoprim	6–12 mg/kg/d; divide q6–12h PO/IV	80/400 mg tablet: $1.72 160/800 mg tablet: $3.12	Decreased
Trimethoprim	Proloprim	0.1 g PO q12h	4 mg/kg/d; divide PO q12h	100 mg tablet: $0.69	Decreased
Trovafloxacin		0.2–0.2 g/d PO 0.2–0.3 g/d IV	–[b]	Data not available	Unchanged
Vancomycin	Vancocin	0.5–2 g PO q6–8h 1 g IV q12h 5–10 mg IT: q48–72h	40 mg/kg/d; divide PO q6–8h 40 mg/kg/d; divide IV q6–12h (newborn: 0–7 d, 15 mg/kg load, then 10 mg/kg q12h; 1–4 wk, 10 mg/kg q8h)	500 mg IV vial: $3.81 1 g vial: $4.73 125 mg capsule: $30.08 250 mg capsule: $55.46	Not absorbed

Abbreviations: CrCl = creatinine clearance (mL/min); HD = hemodialysis; PD = peritoneal dialysis; CNS = central nervous system; GI = gastrointestinal; TEN = toxic epidermal necrolysis; rxn = reaction; ICP = intracranial pressure; P = post; LFTs = liver function tests.

[a] Food and Drug Administration pregnancy categories: A = adequate studies in pregnant women, no risk; B = animal studies no risk, human studies inadequate, benefit may outweigh risk; X = fetal abnormalities in humans, risk exceeds benefit.

[b] Insufficient information available to make a recommendation.

[c] Aminoglycoside dosing may be modified after obtaining serum levels. The generally desired peak and trough concentrations are as follows: for gentamicin and trough ≤5–10 μg/mL. With once-daily administration of aminoglycosides, doses are 5–7 mg/kg q24h for gentamicin and tobramycin, 6.5 mg/kg for netilmicin trough ≤1 μg/mL; for netilmicin, peak 22–30 μg/mL, trough ≤1 μg/mL; for amikacin, kanamycin and streptomycin, peak 56–64 μg/mL, trough ≤1 μg/mL.

* 2013 Red Book Online ®; AWP = average wholesale price; unit price = per dose.

Pregnancy class[a]	Dose interval adjustment for reduced CrCl			Supplemental dose in dialysis		Major toxicity
	>50	10–50	≤10	HD	PD	
C	Usual	Usual	600 mg PO qd	Dose pHD	–[b]	QT prolongation, arrhythmias, hepatotoxicity, visual disturbances
D	q6h	Use doxycycline	Use doxycycline	500 mg pHD	–[b]	GI disturbance, photosensitivity, hepatic toxicity, esophageal ulcers
B	q4–6h	q6–8h	2 g q12h	3 g pHD; then 2 g q12h	3 g q12h	Allergic reactions (rare: anaphylactic), diarrhea, nausea, vomiting
B	q4–6h	q6–8h	2 g IV q12h	3.1 g	3.1 g q12h	Allergic reactions (rare: anaphylactic), diarrhea, nausea, vomiting
D	Usual	Usual	Usual	Usual	–[b]	Tooth discoloration, pancreatitis, photosensitivity
c	Usual	Usual	Usual	50% dose pHD	–[b]	Taste disturbance
D	q8–12h	q12–48h	>48 h	1 mg/kg pHD	1 mg/2 L dialysate removed	Renal toxicity, vestibular and auditory toxicity, CNS reactions, neuromuscular blockade (rare)
C	q6–12h	q24h	Avoid	4–5 mg/kg pHD	0.16–0.8 g q48h	Rash, nausea, vomiting
C	q12h	q18–24h	Avoid	–[b]	–[b]	Nausea, vomiting
C	Usual	Usual	Usual	–[b]	–[b]	Hepatotoxicity, including severe liver failure, dizziness, nausea, headache
B	Levels vary; use serum assays and manufacturer's nomogram to guide dosage	Levels vary; use serum assays and manufacturer's nomogram to guide dosage	Levels vary; use serum assays and manufacturer's nomogram to guide dosage	None needed	None needed	Thrombophlebitis, fever, chills, rash, cranial nerve VIII toxicity

pHD = posthemodialysis; n.a. = not approved; AST = aspartate aminotransferase; ALT = alanine aminotransferase; N.R. = not recommended; IT = intrathecal;

or animal toxicity, human studies no risk; C = animal studies show toxicity, human studies inadequate but benefit may exceed risk; D = evidence of human risk,

tobramycin, peak 6–12 μg/mL and trough ≤2 μg/mL; for netilmicin, peak 6–10 μg/mL, trough ≤2 μg/mL; for amikacin and kanamycin, peak 15–30 μg/mL, and 15 mg/kg q24h for amikacin, kanamycin, and streptomycin, and desired serum levels are as follows: for gentamicin and tobramycin, peak 16–24 μg/mL, The dose is infused over 60 minutes to avoid neuromuscular blockade.

Table 211.2 Antimycobacterial agents

Name		Usual dose		Cost (AWP unit price)*	Change in absorption with food
Generic	**Brand**	**Adult**	**Child**		
Bediquiline	Sirturo	400 mg q24h × 2 weeks then 200 mg 3×/wk	–[b]	100 mg tablet: $191.48	Increased
Capreomycin	Capastat	1 g IM q24h	10–20 mg/kg q24h (n.a.)	1 g injection: $143.92	Unknown
Clofazimine		0.1 g PO q24h	–[b]	Data not available	Increased
Cycloserine	Seromycin	0.25–0.5 g PO q12h	10–20 mg/kg q12h (n.a.)	250 mg capsule: $9.00	Decreased
Ethambutol	Myambutol	15–25 mg/kg PO q24h	10–15 mg/kg q24h (N.R.)	100 mg tablet: $0.50 400 mg tablet: $1.50	Unchanged
Ethionamide	Trecator	0.25–0.5 g PO q12h	15–20 mg/kg q24h (n.a.)	250 mg tablet: $4.22	No data
INH + RIF + PZA	Rifater	6 tabs/d	–[b]	1 tablet: $4.17	Decreased
INH + RIF	Rifamate	2 caps/d	–[b]	1 capsule: $5.64	Decreased
Isoniazid		0.3 g PO, IM q24h	10–20 mg/kg/d; divide PO, IM q12–24h	300 mg tablet: $0.25 100 mg/mL (10 mL) IM injection: $35.20	Decreased
Para-amino salicylic acid		150 mg/kg q6–12h	150–360 mg/kg/d; divide q6–8h	Data not available	Decreased but advised
Pyrazinamide	15–30 mg/kg PO q24h	30 mg/kg/d; divide q12–24h (n.a.)		500 mg tablet: $1.20	No data
Rifabutin (ansamycin)	Mycobutin	0.3 g PO q24h	–[b]	150 mg capsule: $18.17	Unchanged
Rifampin	Rifadin, Rimactane	0.6 g PO, IV q24h	10–20 mg/kg/d; divide PO, IV q12–24h	150 mg capsule: $1.50 300 mg capsule: $2.13 600 mg IV: $78.00	Decreased
Rifapentine	Priftin	4 tabs 2×/wk	–[b]	150 mg tablet: $4.55	Increased
Streptomycin		1 g IM q24h	20–40 mg/kg IM q24h	1 g IM injection: $22.50	n/a

Abbreviations: CrCl = creatinine clearance mL/min; HD = hemodialysis; PD = peritoneal dialysis; CNS = central nervous system; GI = gastrointestinal; peritoneal dialysis.

[a] Food and Drug Administration pregnancy categories: A = adequate studies in pregnant women, no risk; B = animal studies no risk, human studies D = evidence of human risk, benefit may outweigh risk; X = fetal abnormalities in humans, risk exceeds benefit.

[b] Insufficient information available to make a recommendation.

* 2013 Red Book Online ®; AWP = average wholesale price; unit price = per dose.

Pregnancy class[a]	Dose interval adjustment for reduced CrCl			Supplemental dose in dialysis		Major toxicity
	>50	10–50	≤10	HD	PD	
B	Usual	Usual	Use with caution	–[b]	–[b]	QT prolongation, hepatotoxicity
C	q24h	7.5 mg/kg q24–48h	7.5 mg/kg 2×/wk	–[b]	–[b]	Renal and cranial nerve VIII toxicity, hypokalemia, sterile abscesses at injection site
C	q24h	q24h	q24h	–[b]	–[b]	Hyperpigmentation, ichthyosis, dry eyes, GI disturbance
C	q12h	q24h	0.25 g q24h	–[b]	–[b]	Anxiety, depression, confusion, hallucinations, headache, peripheral neuropathy
B	q24h	q24–36h	q48h	15 mg/kg/d pHD	15 mg/kg/d	Optic neuritis, allergic reactions, GI disturbance, acute gout
C	q12h	q12h	5 mg/kg q24h	–[b]	–[b]	GI disturbance, liver toxicity, CNS disturbance
As with individual drugs	q24h	q24h	Avoid	–[b]	–[b]	As with individual drugs
As with individual drugs	q24h	q24h	Avoid	–[b]	–[b]	As with individual drugs
C	q24h	q24h	½ dose in slow acetylators	5 mg/kg pHD	Daily dose pPD	Peripheral neuropathy, liver toxicity (possibly fatal), glossitis, GI disturbance, fever
C	–[b]	–[b]	–[b]	–[b]	–[b]	GI disturbance
C	q24h	q24h	12–20 mg/kg q24h	–[b]	–[b]	Arthralgia, hyperuricemia, liver toxicity, GI disturbance, rash
C	–[b]	–[b]	–[b]	–[b]	–[b]	Uveitis, orange discoloration of urine, sweat, tears; liver toxicity, GI disturbance
B	q24h	q24h	q24h	–[b]	–[b]	Orange discoloration of urine, sweat, tears; liver toxicity, GI disturbance, flu-like syndrome
C	–[b]	–[b]	–[b]	–[b]	–[b]	Similar to rifampin
D	q24h	q24–72h	q72–96h	0.5 g pHD	–[b]	Vestibular nerve damage, paresthesias, rash, fever, pruritus, renal toxicity

pHD = posthemodialysis; n.a. = not approved; N.R. = not recommended; IT = intrathecal; INH = isoniazid; PZA = pyrazinamide; RIF = rifampin; pPD = post

inadequate, or animal toxicity, human studies no risk; C = animal studies show toxicity, human studies inadequate but benefit may exceed risk;

Table 211.3 Antifungal agents

Name		Usual dose			
Generic	**Brand**	**Adult**	**Child**	**Cost (AWP unit price)***	**Change in absorption with food**
Amphotericin B	Fungizone	0.25–1 mg/kg IV q24h	0.25–1 mg/kg IV q24–48h	50 mg IV vial: $45.60	n/a
Amphotericin B lipid complex	Abelcet	5 mg/kg IV q24h	5 mg/kg IV q24h	100 mg IV vial: $12.00	n/a
Amphotericin B liposomal	AmBisome	3–5 mg/kg IV q24h	3–5 mg/kg IV q24h	50 mg IV vial: $188.40	n/a
Amphotericin B cholesteryl sulfate complex		3–4 mg/kg q24h	3–4 mg/kg q24h	Data not available	n/a
Anidulafungin	Eraxis	100 mg IV q24h	No data	100 mg IV vial: $216.00	n/a
Caspofungin	Cancidas	50 mg IV q12h	No data	50 mg IV vial: $405.25	n/a
Clotrimazole	Mycelex	10 mg PO 5×/d	–[b]	10 mg lozenge: $1.61	Not absorbed
Fluconazole	Diflucan	0.05–0.4 g PO, IV q24h	3–6 mg/kg qd (n.a.)	100 mg tablet: $8.75 150 mg tablet: $13.93 200 mg tablet: $14.13 400 mg IV: $8.82	Unchanged
Flucytosine	Ancobon	50–150 mg/kg/d; divide PO q6h	50–150 mg/kg/d; divide PO q6h	250 mg capsule: $24.12 500 mg capsule: $46.69	Decreased
Griseofulvin	Grisactin, Grifulvin, Fulvicin	0.5–1 g PO q24h	15 mg/kg/d PO q24h	125 mg/5 mL (120 mL) bottle: $61.96	Increased
Itraconazole	Sporanox	0.2–0.4 g PO q24h 0.2 g PO q12h	–[b]	100 mg capsule: $15.72 10 mg/mL (150 mL) oral solution: $274.91	Increased
Ketoconazole	Nizoral	0.2–0.4 g PO q12–24h	5–10 mg/kg/d; divide PO q12–24h	200 mg tablet: $3.16	Increased
Micafungin	Mycamine	50 mg IV qd	No data	50 mg IV: $112.20	n/a
Miconazole		0.4–1.2 g IV q8h	20–40 mg/kg/d; divide IV q8h	Data not available (IV)	n/a
Nystatin	Mycostatin	400 000–1 000 000 U PO q8h	400 000–600 000 U PO q6h	100 000 units/mL (60 mL): $16.94	Not absorbed
Posaconazole	Noxafil	200 mg PO TID	200 mg PO TID	40 mg/mL (105 mL) bottle: $1085.11	Increased
Voriconazole	Vfend	4 mg/kg IV q12h	4 mg/kg IV q12h 200 mg PO q12h	200 mg tablet: $68.37 200 mg IV vial: $162.76	n/a (IV) Decreased (PO)

Abbreviations: CrCl = creatinine clearance mL/min; HD = hemodialysis; PD = peritoneal dialysis; GI = gastrointestinal; pHD = posthemodialysis;
[a] Food and Drug Administration pregnancy categories: A = adequate studies in pregnant women, no risk; B = animal studies no risk, human studies D = evidence of human risk, benefit may outweigh risk; X = fetal abnormalities in humans, risk exceeds benefit.
[b] Insufficient information available to make a recommendation.
* 2013 Red Book Online ®; AWP = average wholesale price; unit price = per dose

Pregnancy class[a]	Dose interval adjustment for reduced CrCl			Supplemental dose in dialysis		Major toxicity
	>50	10–50	≤10	HD	PD	
B	q24h	q24h	q24h	Usual	Usual	Fever, chills, nausea with infusion; renal insufficiency, anemia
B	Usual	–[b]	–[b]	–[b]	–[b]	Fever, chills, renal insufficiency (less than non-liposomal amphotericin)
B	Usual	–[b]	–[b]	–[b]	–[b]	Fever, chills, renal insufficiency (less than non-liposomal amphotericin)
B	Usual	–[b]	–[b]	–[b]	–[b]	Fever, chills, renal insufficiency (less than nonliposomal amphotericin)
C	Usual	Usual	Usual	–[b]	–[b]	Diarrhea, infusion site reaction, hypokalemia
C	Usual	Usual	Usual	Usual	Usual	Infusion site reaction, headache, nausea
C	Usual	Usual	Usual	Usual	Usual	Elevated liver enzymes, nausea, taste disturbance
C	q24h	50% dose q24h	25% dose q24h	–[b]	–[b]	Nausea, vomiting, rash, elevated liver enzymes
C	q6h	q12–24h	15–25 mg/kg q24h	20–37.5 mg/kg pHD	–[b]	Leukopenia
C	q24h	q24h	q24h	–[b]	–[b]	GI disturbance, allergic and photosensitivity reactions, blood dyscrasias, liver toxicity, exacerbation of SLE and leprosy
C	q12–24h	Usual	Usual	Usual	Usual	Nausea, rash, headache, edema, hypokalemia, hepatotoxicity
C	q12–24h	Usual	Usual	Usual	Usual	Nausea, vomiting, gynecomastia, decreased testosterone synthesis, rash, hepatotoxicity, adrenal insufficiency
C	q24h	No adjustment	No adjustment	–[b]	–[b]	Thrombophlebitis, rash, headache, leukopenia
C	q8h	q8h	q8h	–[b]	–[b]	Phlebitis, thrombocytosis, pruritus, rash, blurred vision, anaphylaxis (rare)
C	q8h	q8h	q8h	–[b]	–[b]	GI disturbance, allergic reactions
C	TID	No adjustment	No adjustment	–[b]	–[b]	Fever, nausea, vomiting, diarrhea, QT prolongation, hyperbilirubinemia (rare)
D	q12h	IV: avoid use PO: no adjustment	IV: avoid use PO: no adjustment	–[b]	–[b]	Abnormal vision, rash, torsades de pointes (rare)

n.a. = not approved; SLE = systemic lupus erythematosus.

inadequate, or animal toxicity, human studies no risk; C = animal studies show toxicity, human studies inadequate but benefit may exceed risk;

Table 211.4 Antiviral agents

Name		Usual dose			
Generic	**Brand**	**Adult**	**Child**	**Cost (AWP unit price)[a]**	**Change in absorption with food**
Abacavir	Ziagen	0.3 g PO q12h	8 mg/kg PO q12h	300 mg tablet: $10.05 20 mg/mL (240 mL) bottle oral solution: $176.23	Unchanged
Abacavir/ lamivudine	Epzicom	1 daily	–[b]	600 mg/300 mg tablet: $41.31	Unchanged
Acyclovir	Zovirax	0.2–0.8 g PO 2–5×/d 5–12 mg/kg IV q8h	0.2 g 5×/d (HSV) PO 20 mg/kg PO q6h, max 800 mg q6h (VZV) 25–50 mg/kg/d IV q8h	200 mg capsule: $0.97 400 mg capsule: $2.17 800 mg capsule: $ 4.21 200 mg/5mL (473 mL) bottle oral solution: $137.77 500 mg IV: $22.82 1000 mg IV: $42.59	Unchanged
Amantadine	Symmetrel	0.1 g PO q12h	2.2–4.4 mg/kg PO q12h	100 mg capsule: $2.01	No data
Amprenavir		1.2 g PO q12h	–[b]	Data not available	Decreased with high-fat meal
Atazanavir	Reyataz	300–400 mg PO qd	–[b]	200 mg capsule: $21.97 300 mg capsule: $43.54	Increased
Boceprevir	Victrelis	800 mg PO TID	–[b]	200 mg capsule: $21.73	Increased
Cidofovir	Vistide	5 mg/kg IV qwk ×2 wk, then 5 mg/kg q2wk	–[b]	375 mg IV vial: $799.20	n/a
Darunavir	Prezista	600 mg PO BID with 100 mg PO ritonavir	–[b]	600 mg tablet: $21.82 800 mg tablet: $43.63	Increased
Didanosine	Videx	0.167–0.2 g PO q12h	0.143–0.248 mg/m^2 divided PO q12h	125 mg capsule: $3.86 250 mg capsule: $7.87 400 mg capsule: $6.18 10 mg/mL (100 mL) bottle oral solution: $66.50	Decreased
Efavirenz	Sustiva	0.6 g PO qhs	–[b]	600 mg tablet: $26.19	Unchanged
Emtricitabine	Emtriva	200 mg PO qd	6 mg/kg PO sol qd (3 mo–17 yr)	200 mg capsule: $19.14 10 mg/mL (170 mL) bottle oral solution: $135.58	Unchanged
Enfuvirtide	Fuzeon	90 mg SC BID	2 mg/kg SC BID	90 mg subcutaneous injection: $55.76	n/a
Entecavir	Baraclude	0.5–1 mg PO qd	>16 yr, 0.5–1 mg PO qd	0.5 mg tablet: $41.59 1 mg tablet: $41.59 0.05 mg/mL (210 mL) bottle oral solution: $873.31	Decreased
Etravirine	Intelence	200 mg PO BID	>6 yr, based on weight	200 mg tablet: $17.35	Increased
Famciclovir	Famvir	0.125 g PO q12h (HSV) 0.5 g PO q8h (VZV)	–[b]	125 mg tablet: $8.57 250 mg tablet: $9.32	Unchanged

Pregnancy class[a]	Dose interval adjustment for reduced CrCl			Supplemental dose in dialysis		Major toxicity
	>50	10–50	≤10	HD	PD	
C	Usual	Usual	–[b]	–[b]	–[b]	Nausea, hypersensitivity reaction with myalgias, fever, rash; anaphylaxis
C	Usual	–[b]	N.R.	N.R.	N.R.	See individual drugs
C	2–5×/d PO IV q8h	2–5×/d PO IV q12–24h	0.2–0.8 g PO q24h 2.5–6 mg/kg IV q24h	0.5 g PO pHD	2–5 mg/kg/d	Headache, rash, renal toxicity, CNS symptoms (rare)
C	q12h	0.1–0.2 g 2–3×/wk	0.1–0.2 g qwk	–[b]	–[b]	Livedo reticularis, edema, insomnia, dizziness, lethargy
–[b]	Usual	Usual	Usual	No supplement	No supplement	Nausea, diarrhea, rash
B	Usual	Usual	Usual	No supplement	No supplement	Hyperbilirubinemia, rash
B	Usual	Usual	Usual	No supplement	No supplement	Anemia, neutropenia, hypersensitivity reactions, nausea, dysgeusia
C	Check prescribing information	Check prescribing information	Check prescribing information	–[b]	–[b]	Proteinuria, renal insufficiency, neutropenia
B	Usual	Usual	Usual	No supplement	No supplement	Erythema multiforme, neutropenia
B	q12h	q12–24h	100 mg PO q24h	Dose pHD	–[b]	Diarrhea, nausea, vomiting, pancreatitis, peripheral neuropathy
D	Usual	Usual	Usual	Usual	Usual	Drowsiness, CNS side effects, rash
B	Usual	q48–72h	q96h	Give dose after dialysis session on HD days	–[b]	Lactic acidosis, hepatotoxicity, neutropenia
B	Usual	Usual	–[b]	–[b]	–[b]	Injection site reactions, hypersensitivity rxn
C	Usual	0.25 mg–0.15 mg PO qd	0.05 mg PO qd	0.05 mg pHD	0.05 mg P capd	Lactic acidosis, elevated transaminases
B	Usual	Usual	Usual	No supplement	No supplement	Skin, hypersensitivity reactions
B	0.5 g q8h; 0.125 g q12h	0.5 g q12–24h; 0.125 g q12–24h	0.25 g q48h; 0.125 g q48h	Dose pHD	–[b]	Headache, nausea

Table 211.4 *(continued)*

Name		Usual dose			
Generic	**Brand**	**Adult**	**Child**	**Cost (AWP unit price)[a]**	**Change in absorption with food**
Fosamprenavir	Lexiva	700–1400 mg PO BID	–[b]	700 mg tablet: $17.40	Unchanged
Foscarnet	Foscavir	60 mg/kg IV q8h ×14–21 d; then 90 mg/kg/d	–[b]	6000 mg (24 mg/mL) 250 mL IV bottle: $283.08	n/a
Ganciclovir	Cytovene	5 mg/kg IV q12h ×14–21 d; then 5 mg/kg/d	5 mg/kg IV q12h	500 mg IV: $104.99	IV: n/a
Indinavir	Crixivan	800 mg PO q8h	–[b]	$16.50	Decreased
Lamivudine	Epivir	150 mg PO q12h	4 mg/kg PO q12h	200 mg capsule: $1.53 400 mg capsule: $3.05	Unchanged
Lopinavir/ritonavir	Kaletra	400/100 mg PO BID	12 mg/3 mg/kg PO BID 6 mo–12 yr	100 mg/25 mg tablet: $3.85 200 mg/50 mg tablet: $7.69 80 mg/mL-20 mg/mL (160 mL) bottle oral solution: $461.38	Increased
Maraviroc	Selzentry	150–600 mg PO BID	–[b]	150 mg tablet: $21.63 300 mg tablet: $21.63	Unchanged
Nelfinavir	Viracept	0.75 g PO TID or 1.25 g PO q12h	0.2–0.3 mg/kg q8h	250 mg tablet: $3.37 625 mg tablet: $8.45	Increased
Nevirapine	Viramune	200 mg PO q24h ×14 d, then 200 mg PO q12h	–[b]	200 mg tablet: $12.78	Unchanged
Oseltamivir	Tamiflu	75 mg PO BID ×5 d	>1 yr, weight based. See prescribing information	75 mg capsule: $13.28 6 mg/mL (60 mL) bottle oral solution: $132.77	Unchanged
Raltegravir	Isentress	400 mg PO BID	>2 yr, weight based. See prescribing information	400 mg tablet: $21.48	Unchanged
Ribavirin	Copegus, Rebetol, Virazole	12–18 h/d ×3 d via aerosol, 0.4–0.6 g PO q12h, IV investigational	12–22 h/d × 6 d via aerosol	200 mg capsule: $9.52 6 g inhalation powder: $6471.22 (Virazole)	–[b]
Rimantadine	Flumadine	0.1 g PO q12h	–[b]	100 mg tablet: $1.83	Unchanged
Ripilvirine	Edurant	25 mg PO daily	–[b]	25 mg tablet: $28.53	Increased
Ritonavir	Norvir	600 mg PO q12h	–[b]	100 mg tablet: $10.29	Unchanged
Saquinavir hard gel	Invirase	1.0 g PO q12h with 0.2 g PO ritonavir		200 mg capsule: $4.06 500 mg tablet: $9.34	Increased
Saquinavir soft gel		1.2 g PO TID		Data not available	Increased
Stavudine	Zerit	0.04 g PO q12h	–[b]	40 mg capsule: $6.08	Unchanged
Telaprevir	Incivek	750 mg PO TID	–[b]	375 mg tablet: $157.51	Increased
Telbivudine	Tyzeka	600 mg PO qd	>16 yr 600 mg PO qd	600 mg tablet: $35.47	Unchanged
Tenofovir	Viread	300 mg PO qd	–[b]	300 mg tablet: $33.29	Increased

Pregnancy class[a]	Dose interval adjustment for reduced CrCl			Supplemental dose in dialysis		Major toxicity
	>50	10–50	≤10	HD	PD	
C	–[b]	–[b]	–[b]	–[b]	–[b]	Diarrhea, rash, nausea, hemolytic anemia (rare)
C	63–90 mg/kg/d maintenance	78–63 mg/kg/d maintenance	–[b]	–[b]	–[b]	Renal dysfunction, anemia, nausea, disturbances of calcium, magnesium, phosphorus, potassium metabolism
C	q12h	2.5 mg/kg q24h	1.25 mg/kg q24h	1.25 mg/kg pHD	–[b]	Neutropenia, thrombocytopenia
C	–[b]	–[b]	–[b]	–[b]	–[b]	Nephrolithiasis, nausea, headache
C	150 mg PO q12h	100–150 g PO qd	25–50 mg PO qd	–[b]	–[b]	Headache, nausea, neutropenia, increased AST, and ALT
C	–[b]	–[b]	–[b]	–[b]	–[b]	Diarrhea, dyslipidemia, LFT elevation
B	Usual	Usual	–[b]	–[b]	–[b]	Skin, hypersensitivity reactions, hepatotoxicity
B	Usual	Usual	Usual	Usual	Usual	Diarrhea, nausea
B	–[b]	–[b]	–[b]	–[b]	–[b]	Rash, including Stevens–Johnson syndrome; hepatotoxicity
C	Usual	qd CrCl 10–30	–[b]	–[b]	–[b]	Nausea, vomiting, headache
C	Usual	Usual	Usual	Usual	Usual	Insomnia, nausea, headache, fatigue
X	–[b]	–[b]	–[b]	–[b]	–[b]	Anemia, headache, hyperbilirubinemia, bronchospasm
C	q12h	q12h	q12h	–[b]	–[b]	Fewer CNS side effects than amantadine
B	Usual	Usual	Use caution	Usual	Usual	Depressive disorders, elevated transaminases
B	Usual	Usual	Usual	Usual	Usual	Nausea, vomiting, diarrhea
B	Usual	Usual	Usual	Usual	Usual	Diarrhea, nausea
B	Usual	Usual	Usual	Usual	Usual	Diarrhea, nausea, headache
C	–[b]	–[b]	–[b]	–[b]	–[b]	Peripheral neuropathy, liver toxicity
B	Usual	Usual	–[b]	–[b]	–[b]	Skin reactions, hypersensitivity, anemia, nausea
B	Usual	q48h	q72h	q96h: give after the end of the dialysis session on dialysis days	–[b]	Lactic acidosis, myopathy, elevated CPK, elevated LFTs
B	Usual	q48h	Twice weekly	–[b]	pHD q7d	Lactic acidosis, nephrotoxicity

Table 211.4 *(continued)*

Name		Usual dose			
Generic	**Brand**	**Adult**	**Child**	**Cost (AWP unit price)***	**Change in absorption with food**
Tenofovir/ emtricitabine	Truvada	1 daily	–[b]	300 mg/200 mg tablet: $48.93	Increased
Tenofovoir/ emtricitabine/ efavirenz	Atripla	1 daily	–[b]	300 mg/200 mg/600 mg tablet: $75.13	Increased
Tenofovir/ emtricitabine/ elvitegravir/ cobicistat	Stribild	1 daily	–[b]	300 mg/200 mg/150 mg/ 150 mg tablet: $93.70	Increased
Tenofovir/ emtricitabine/ ripilverine	Complera	1 daily	–[b]	300 mg/200 mg/25 mg tablet: $77.46	Increased
Tipranavir	Aptivus	500 mg PO BID with 200 mg PO ritonavir	–[b]	250 mg soft gel capsule: $11.79	Unchanged
Valacyclovir	Valtrex	1 g PO TID (VZV); 0.5 g PO BID (HSV)	Unchanged	500 mg tablet: $8.04 1 g tablet: $14.07	No effect
Valganciclovir	Valcyte	900 mg PO q12h × 21 d, then 900 mg PO q24h	–[b]	450 mg tablet: $70.90	Increased
Vidarabine		10–15 mg/kg/d IV over 12 h	10–15 mg/kg/d IV over 12 h	Data not available	n/a
Zalcitabine		0.375–0.75 g PO q8h	0.75 g PO q8h (children >13 yr)	Data not available	Decreased
Zanamivir	Relenza	10 mg BID by inhaler × 5d	5 mg BID by inhaler × 5 d, > 6 yr	5 mg/actuation inhalation discus: $3.54	No change
Zidovudine	Retrovir	0.1 g PO q4h or 0.2 g PO q8h 1–2 mg/kg IV q4h	180 mg/m^2 PO q6h	100 mg capsule: $2.02 300 mg tablet: $6.02 50 mg/5 mL (240 mL) bottle oral solution: $56.42	Decreased

Abbreviations: CrCl = creatinine clearance mL/min; HD = hemodialysis; PD = peritoneal dialysis; CNS = central nervous system; GI = gastrointestinal; simplex virus; VZV = varicella-zoster virus; LFT = liver function test; rxn = reaction; P = post; capd = continuous ambulatory peritoneal dialysis;

[a] Food and Drug Administration pregnancy categories: A = adequate studies in pregnant women, no risk; B = animal studies no risk, human studies inadequate, benefit may outweigh risk; X = fetal abnormalities in humans, risk exceeds benefit.

[b] Insufficient information available to make a recommendation.

* 2013 Red Book Online ®; AWP = average wholesale price; unit price = per dose.

Pregnancy class[a]	Dose interval adjustment for reduced CrCl			Supplemental dose in dialysis		Major toxicity
	>50	10–50	≤10	HD	PD	
B	Usual	N.R.	N.R.	N.R.	N.R.	See individual drugs
D	Usual	N.R.	N.R.	N.R.	N.R.	See individual drugs
B	Usual	N.R.	N.R.	N.R.	N.R.	Renal insufficiency, do not initiate if CrCl <70. Lactic acidosis
B	Usual	N.R.	N.R.	N.R.	N.R.	See individual drugs
C	Usual	Usual	Usual	Usual	–[b]	Diarrhea, hepatotoxicity, hyperlipidemia, bleeding
B	Usual	q12–24h	0.5 g q24h	0.5 g q24h	0.5 g q24h	Nausea, headache; thrombotic thrombocytopenic purpura in immunocompromised patients
C	Usual	0.45 g q12–48h	N.R.	N.R.	N.R.	Neutropenia, thrombocytopenia
Not established	Usual	Usual	10 mg/kg/d over 12 h	Usual dose pHD	–[b]	GI disturbance, nausea, vomiting, thrombophlebitis
C	q8h	q12h	q24h	–[b]	–[b]	Peripheral neuropathy, stomatitis, esophageal ulcers, pancreatitis
C	Usual	Usual	Usual	Usual	Usual	Bronchospasm, nasal and throat discomfort
C	q4h	q6h	q6–12h	100 mg pHD	100 mg q6–12h	Anemia, granulocytopenia, headache, nausea, insomnia, nail pigment changes

pHD = posthemodialysis; n.a. = not approved; AST = aspartate aminotransferase; ALT = alanine aminotransferase; N.R. = not recommended; HSV = herpes
CPK = creatine phosphokinase.
or animal toxicity, human studies no risk; C = animal studies show toxicity, human studies inadequate but benefit may exceed risk; D = evidence of human risk,

Table 211.5 Antiparasitic agents

Name		Usual dose			
Generic	**Brand**	**Adult**	**Child**	**Cost (AWP unit price)***	**Change in absorption with food**
Albendazole	Albenza	15 mg/kg/d PO	–[b]	200 mg tablet: $59.70	Increased
Artemether–lumefantrine	Coartem	400 mg PO, repeat in 8 h then twice daily for 48 h	Weight based, see full prescribing information	$84 (3-day course)	Increased
Artemisinin[c]		10 mg/kg/d ×5 d	Same as adult	Data not available	–[b]
Atovoquone	Mepron	750 mg PO BID	–[b]	750 mg/5 mL oral suspension packet: $6.32 750 mg/5 mL (210 mL) bottle oral suspension: $1393.67	Increased
Benznidazole[c]		5 mg/kg PO BID 1–4 mo	–[b]	Data not available	–[b]
Bithionol[d]	Bitin	30–50 mg/kg on alternate days ×10–15 d	Same as adult	Data not available	–[b]
Chloroquine HCl	Aralen HCl	300 mg PO qwk (prophylaxis) 600 mg PO, then 300 mg after 6, 24, 48 h 200 mg IM q6h (treatment)	5 mg/kg qwk PO (for prophylaxis) 10 mg/kg, then 5 mg/kg, same intervals as adult (treatment) IM treatment not recommended	Data not available	Increased
Chloroquine phosphate	Aralen phosphate	500 mg PO qwk (prophylaxis) 1 g, then 500 mg after 6, 24, 48 h (treatment)	8.3 mg/kg qwk PO (prophylaxis)	500 mg tablet: $5.64	Increased
Dehydroemetine[d]		1–1.5 mg/kg/d IM (maximum dose 90 mg)	1–1.5 mg/kg IM qd, divided in 2 doses	Data not available	–[b]
Diethyl carbamazine[d]	Hetrazan	Day 1: 50 mg PO Day 2: 50 mg TID Day 3: 50 mg TID Days 4–21: 6 mg/kg/d divided TID	Day 1: 1 mg/kg PO Day 2: 1 mg/kg TID Day 3: 1–2 mg/kg TID Days 4–21: 6 mg/kg/d divided TID	Available from manufacturer without charge for compassionate use only	–[b]
Diloxanide furoate[c]	Furamide	500 mg TID × 10 d	20 mg/kg/d divided TID × 10 d	Data not available	–[b]
Eflornithine[c]	Ornidyl	400 mg/kg/d IV divided QID × 14 d, then 300 mg/kg/d PO ×3–4 wk	–[b]	Data not available	–[b]
Furazolidone	Furoxone	100 mg PO q6h	25–50 mg PO q6h	Data not available	–[b]
Halofantrine	Halfan	500 mg PO q6h ×3, repeat in 1 wk	8 mg/kg PO q6h ×3 (patient ≤40 kg), repeat in 1 wk	Data not available	Increased
Hydroxy-chloroquine	Plaquenil	400 mg PO qwk (prophylaxis) 800 mg, then 400 mg after 6, 24, 48 h (treatment)	5 mg/kg PO qwk (prophylaxis) 10 mg/kg, then 5 mg/kg at same intervals as adult (treatment)	200 mg tablet: $0.24 200 mg tablet (Plaquenil): $4.48	–[b]

Pregnancy class[a]	Dose interval adjustment for reduced CrCl			Supplemental dose in dialysis		Major toxicity
	>50	10–50	≤10	HD	PD	
Not established	Usual	–[b]	–[b]	–[b]	–[b]	Diarrhea, abdominal discomfort, elevated AST, ALT and bone marrow suppression, alopecia with high dose
Not established	Usual	Usual	–[b]	–[b]	–[b]	Headache, anorexia, fever, QT prolongation
Not established	Usual	–[b]	–[b]	–[b]	–[b]	Transient heart block, elevated AST and ALT, neutropenia, decreased reticulocyte count, abdominal pain, diarrhea, fever
C	Usual	–[b]	–[b]	–[b]	–[b]	Rash, GI disturbance, fever, headache
Not established	–[b]	–[b]	–[b]	–[b]	–[b]	Peripheral neuropathy, rash, bone marrow suppression
Not established	–[b]	–[b]	–[b]	–[b]	–[b]	Hypotension, wheezing, angioedema, rash, hyperthermia, diarrhea, anorexia, nausea, vomiting, dizziness, headache
C	–[b]	–[b]	–[b]	–[b]	–[b]	Blurred vision (retinopathy with prolonged use), GI effects, pruritus, hemolysis in patients with G6PD deficiency
C	Usual	–[b]	–[b]	–[b]	–[b]	Blurred vision (retinopathy with prolonged use), GI effects, pruritus, hemolysis in patients with G6PD deficiency
Not established	Usual	–[b]	–[b]	–[b]	–[b]	Diarrhea, nausea, vomiting, cardiac arrhythmias, tachycardia
Not established	usual	–[b]	–[b]	–[b]	–[b]	Headache, malaise, arthralgia, nausea, vomiting, anorexia, pruritus, fever, hypotension, lymphadenitis, encephalopathy
Not established	Usual	–[b]	–[b]	–[b]	–[b]	Flatulence
Not established	Usual	–[b]	–[b]	–[b]	–[b]	Anemia, thrombocytopenia, leukopenia, nausea, vomiting, diarrhea, transient hearing loss
Not established	Usual	–[b]	–[b]	–[b]	–[b]	Nausea, vomiting, rash, fever, headache, hemolysis in patients with G6PD deficiency
Not established	Usual	–[b]	–[b]	–[b]	–[b]	Abdominal pain, vomiting, diarrhea, headache, pruritus, rash
C	Usual	–[b]	–[b]	–[b]	–[b]	Blurred vision, GI effects, pruritus; rare: cardiomyopathy

Table 211.5 *(continued)*

Name		Usual dose			
Generic	**Brand**	**Adult**	**Child**	**Cost (AWP unit price)***	**Change in absorption with food**
Iodoquinol	Yodoxin, Diquinol	650 mg PO TID	30–40 mg/kg/d; divide PO TID	650 mg tablet: $1.47	Minimally absorbed
Ivermectin	Stromectol	200 μg/kg	–[b]	3 mg tablet: $5.58	Decreased
Mebendazole	Vermox	100 mg PO BID depending on infection being treated	Same as adults	Data not available	Minimally absorbed
Mefloquine	Lariam	250 mg/wk (prophylaxis) 1250 mg ×1 (treatment)	25 mg/kg PO qwk (prophylaxis)	250 mg tablet: $10.59	Increased
Meglumine antimonate[c]	Glucantine	20 mg/kg IV ×2 d (850 mg/d limit)	–[b]	Data not available	n/a
Melarsoprol B[d]	Mel B, Arsobal	1.2 mg/kg IV TID × 3 d; repeat qwk ×2 wk	–[b]	Data not available	n/a
Niclosamide	Niclocide	2 g PO qd	0.5–1.5 g/d PO	Data not available	Not absorbed
Nifurtimox[d]	Lampit	3 mg/kg PO TID ×3 mo	–[b]	Data not available	–[b]
Niridazole[c]	Ambilhar	–[b]	–[b]	Data not available	–[b]
Oxamniquine[c]	Vansil	12–60 mg/kg qd or divide BID	20–60 mg/kg divided BID	Data not available	Decreased
Paromomycin	Humatin	25–35 mg/kg PO divided TID 2–3 g qd divided QID in AIDS	–[b]	250 mg capsule: $5.67	Not absorbed
Pentamidine	Pentam, Nebupent	3–4 mg/kg/d IV 300 mg aerosolized qmo	3–4 mg/kg/d IV	300 mg IV: $118.50 300 mg inhalation: $118.50	n/a
Piperazine citrate[c]	Antepar	2–3.5 g/d PO	65–75 mg/kg PO qd	Data not available	–[b]
Praziquantel	Biltricide	5–25 mg/kg ×1 (intestinal cestodiasis) 50–75 mg/kg/d, divided TID (other infections)	Not shown to be safe for children <4 yr	600 mg tablet: $17.27	Increased
Primaquine phosphate		26.3 mg/d PO ×14 d 29 mg PO qwk × 8 wk	0.5 mg/kg/d PO 1.5 mg/kg PO qwk	26.3 mg tablet: $1.78	–[b]
Proguanil HCl and atovaquone	Malarone	400/1000 mg PO qd (treatment) 100/250 mg PO daily 1–2 d before entering endemic area, during stay, and for 7 d after return (prophylaxis)	50/125–1000/400 mg PO qd (depending on weight) (treatment) 25/62.5–100/250 mg PO qd (depending on weight) (prophylaxis)	100 mg/250 mg tablet: $8.24 25 mg/62.5 mg tablet: $2.99	Increased
Pyrantel pamoate	Antiminth, Pin-X	11 mg/kg (max 1 g/d) PO	11 mg/kg/d PO; not recommended for children ≤2 yr	Data not available	–[b]
Pyrimethamine	Daraprim	25–75 mg/d PO	0.5–2 mg/kg PO, divide BID Contraindicated for children ≤2 yr	25 mg tablet: $14.14	–[b]

Pregnancy class[a]	Dose interval adjustment for reduced CrCl			Supplemental dose in dialysis		Major toxicity
	>50	10–50	≤10	HD	PD	
Not established	Usual	–[b]	–[b]	–[b]	–[b]	Optic neuritis, peripheral neuropathy, anorexia, nausea, vomiting, diarrhea, skin reactions
Not established	Usual	–[b]	–[b]	–[b]	–[b]	Fever, pruritus, headache, edema
B	Usual	–[b]	–[b]	–[b]	–[b]	Diarrhea, nausea, vomiting, abdominal pain, fever, headache, neutropenia, thrombocytopenia
C	Usual	–[b]	–[b]	–[b]	–[b]	Nausea, dizziness, seizures, bradycardia, rash
Not established	Usual	–[b]	–[b]	–[b]	–[b]	Bradycardia, hypotension, rashes, facial edema, injection site pain, pancreatitis, leukopenia, nephrotoxicity
Not established	Usual	–[b]	–[b]	–[b]	–[b]	Fever, hypertension, abdominal pain, vomiting, arthralgia, encephalopathy, rash, hemolysis in patients with G6PD deficiency
B	Usual	–[b]	–[b]	–[b]	–[b]	Nausea, abdominal discomfort, diarrhea, drowsiness, dizziness, headache
Not established	Usual	–[b]	–[b]	–[b]	–[b]	Nausea, vomiting, abdominal pain, anorexia, weight loss, restlessness, insomnia, paresthesias, seizures, rash, neutropenia
Not established	Usual	–[b]	–[b]	–[b]	–[b]	Seizures, hallucinations
Not established	Usual	–[b]	–[b]	–[b]	–[b]	Dizziness, drowsiness, headache, nausea, vomiting, abdominal pain, orange-red discoloration of urine
Not established	Usual	Usual	Usual	–[b]	–[b]	Anorexia, nausea, vomiting, abdominal pain, diarrhea, malabsorption
C	Usual	–[b]	–[b]	–[b]	–[b]	Nephrotoxicity, hypotension, sterile abscess with IM injection, hypoglycemia or hyperglycemia, nausea, vomiting, abdominal pain, pancreatitis, hypocalcemia, cough and bronchospasm with inhalation
Not established	Usual	–[b]	–[b]	–[b]	–[b]	Nausea, vomiting, diarrhea, abdominal cramps, headache, dizziness, rash, hemolytic anemia, ataxia
B	Usual dose	N.R.	N.R.	–[b]	–[b]	Transient dizziness, headache, drowiness, fatigue, seizures, CSF reaction syndrome with treatment of neurocysticercosis, abdominal pain, nausea, rash
Not established	Usual	–[b]	–[b]	–[b]	–[b]	Hemolytic anemia in patients with G6PD deficiency, nausea, vomiting, abdominal cramps, headache, pruritus
C	Usual	N.R. in patients with CrCl ≤30 mL/min	N.R. in patients with CrCl ≤30 mL/min	N.R. in patients with CrCl ≤30 mL/min	N.R. in patients with CrCl ≤30 mL/min	Rare hematologic toxicity
C	Usual	–[b]	–[b]	–[b]	–[b]	Nausea, vomiting, cramps, dizziness, drowsiness, headache
C	Usual	–[b]	–[b]	–[b]	–[b]	Bone marrow suppression with high doses, pulmonary eosinophilia, photosensitivity

Table 211.5 *(continued)*

Name		Usual dose			
Generic	**Brand**	**Adult**	**Child**	**Cost (AWP unit price)***	**Change in absorption with food**
Pyrimethamine + sulfadiazine	Fansidar	1 tab PO qwk (prophylaxis) 3 tabs PO ×1 (treatment)	½ tab PO 5–10 kg 1 tab 10–20 kg 1½ tab 21–30 kg 2 tabs 31–40 kg For children >2 yr	Data not available	–[b]
Quinacrine HCl[c]	Atabrine	100 mg TID PC ×5 d	6 mg/kg TID PC ×5 d (≤50 kg)	Data not available	–[b]
Quinidine gluconate		10 mg/kg load over 1–2 h, then 0.02 mg/kg/min ×72 h	Same as adult	800 mg (80 mg/mL) 10 mL IV: $21.56	Increased
Quinine sulfate	Legatrin Quinamm	325–650 g PO BID–TID	25–30 mg/kg/d PO; divide TID	325 mg capsule: $0.90	–[b]
Spiramycin[c]	Rovamycine	3 g/d PO	50–100 mg/kg once or 2× daily (depending on infection being treated)	Data not available	No effect
Stibogluconate	Pentostam	20 mg/kg IV qd × 20 d (not to exceed 850 mg)	–[b]	Data not available	n/a
Suramin[d]	Germanin	1 g IV qwk ×5 wk (100-mg test dose)	–[b]	Data not available	n/a
Thiabendazole	Mintezol	25 mg/kg PO BID (maximum 3 g/d)	22 mg/kg PO BID	Data not available	–[b]
Trimetrexate	Neutrexin	45 mg/m^2/d with leucovorin 20 mg/m^2 q6h; continue leucovorin at least 72 h after last dose	–[b]	Data not available	n/a

Abbreviations: CrCl = creatinine clearance mL/min; HD = hemodialysis; PD = peritoneal dialysis; AST = aspartate aminotransferase; N.R. = not recommended; PC = after meals; CSF = cerebrospinal fluid; n.a. = not approved; LFT = liver function test.

[a] Food and Drug Administration pregnancy categories: A = adequate studies in pregnant women, no risk; B = animal studies no risk, human studies D = evidence of human risk, benefit may outweigh risk; X = fetal abnormalities in humans, risk exceeds benefit.

[b] Insufficient information available to make a recommendation.

[c] Not available in the United States.

[d] Available from the Centers for Disease Control and Prevention drug service.

* 2013 Red Book Online ®; AWP = average wholesale price; unit price = per dose.

Pregnancy class[a]	Dose interval adjustment for reduced CrCl			Supplemental dose in dialysis		Major toxicity
	>50	10–50	≤10	HD	PD	
C	Usual	–[b]	–[b]	–[b]	–[b]	Leukopenia, hemolysis in patients with G6PD deficiency, rash and hypersensitivity reactions including Stevens–Johnson syndrome, hepatitis, pulmonary hypersensitivity reactions
C	Usual	–[b]	–[b]	–[b]	–[b]	Nausea, vomiting, headache, dizziness, yellow discoloration of skin and urine, rash, fever, psychosis
C	Usual	–[b]	–[b]	–[b]	–[b]	Diarrhea, abdominal pain, hypersensitivity reactions, systemic lupus erythematosus-like syndrome, elevated AST, elevated ALT, jaundice, cardiac arrhythmias
X	Usual	–[b]	–[b]	–[b]	–[b]	Flushing, pruritus, rash, fever, tinnitus, headache, nausea, thrombocytopenia, hemolysis in patients with G6PD deficiency, hypoglycemia
C	Usual	–[b]	–[b]	–[b]	–[b]	QT interval prolongation, vasculitis, rash, diarrhea, increased LFTs
Not established	Usual	–[b]	–[b]	–[b]	–[b]	Abdominal pain, nausea, vomiting, malaise, headache, elevated AST and ALT, nephrotoxicity, myalgia, arthralgia, fever, rash, cough
Not established	Usual	–[b]	–[b]	–[b]	–[b]	Nausea, vomiting, shock, loss of consciousness, death during administration; fever, rash, exfoliative dermatitis, paresthesia, photophobia, renal insufficiency, diarrhea
C	Usual	–[b]	–[b]	–[b]	–[b]	Anorexia, nausea, vomiting, dizziness
D	Usual	–[b]	–[b]	–[b]	–[b]	Neutropenia (must be given with leucovorin); rash; elevated AST and ALT; reversible peripheral neuropathy

ALT = alanine aminotransferase; GI = gastrointestinal; G6PD = glucose-6-phosphate dehydrogenase; AIDS = acquired immunodeficiency syndrome;

inadequate, or animal toxicity, human studies no risk; C = animal studies show toxicity, human studies inadequate but benefit may exceed risk;

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