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THE BLUE BOOK

FOURTH EDITION

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Manual of Childhood Infections

Fourth edition

Chief Editor

Mike Sharland

Professor of Paediatric Infectious Diseases,
St George's Hospital, London, UK

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Foreword to the fourth edition

We are very pleased to write a foreword for the fourth edition of the Blue Book on Childhood infections. The last edition was around five years ago and this new edition has again been re-written and updated. The book provides a clinical evidence-based handbook approach to the management of both common and unusual infections in children. The Editorial Board has nearly 200 authors writing the 120 chapters of this new edition. The book has been written by paediatricians, microbiologists, and a wide range of international experts in paediatric infectious disease. The book is aimed at both trainee and practising hospital- and community-based paediatricians, nursing, and other medical staff caring for children in the United Kingdom, Europe, and internationally. It aims to provide an up-to-date reference guide including common differential diagnoses, medical management, and information on over 100 medicines.

The aim of the book is to improve the evidence-based management to a child's infection. This new edition has short abstracts, key references, and key learning points which are now fully updated. Recent immunisation campaigns have substantially reduced rates of serious bacterial infection in children yet new and emerging infections remain a very serious concern. Rates of hospital-acquired infection are now a serious threat to children and much remains to be done to reduce nosocomial infection. Antimicrobial resistance has been flagged by the World Health Organization as one of the three greatest threats to human health. New chapters on antimicrobial stewardship demonstrate the way forward for reducing the inappropriate antibiotic prescribing that drives this very serious problem.

The development of an eBook format now provides a bedside approach to the practical management of common infections. All paediatricians should be encouraged to manage a child's infection using this practical, simple evidence-based approach.

The European Society for Paediatric Infectious Diseases is very pleased to be working in partnership with the Royal College of Paediatrics and Child Health. This edition has an ever-increasing international focus. There is still considerable variation of practice and management of children's infection. Much of this reflects cultural differences and child care practice across Europe. There is still some variation in practice that cannot necessarily be explained just by altered prevalence of infections and resistance pattern. Although evidence-based guidelines will vary across European countries, the manual is an attempt to be a synthesis of published evidence of systematic reviews providing the core basic evidence. The Blue Book has been produced as a teaching tool for trainees internationally and for practising paediatricians. It can be used as a source to look up, check, or think about management plans, differential diagnosis, or recent epidemiology. In most chapters, sections define what is new and what is coming. The Blue Book also acts to identify future research priorities and aims to encourage collaboration across Europe.

The Blue Book also recognizes that antimicrobial dosing varies considerably across Europe. For this new edition an evidenced approach to the formulary has been produced and for the first time will provide information about grading the level of evidence for antimicrobials. The Blue Book again does not aim to replace national or local formularies but provides a pragmatic and reasonable summary of the evidence base for each drug.

Professor Neena Modi (RCPCH)
Professor Adam Finn (ESPID)

Contents

Section 2 Specific infections

Section editors

Karina Butler
Department of Infectious Diseases & Immunology, Our Lady's Children's Hospital Crumlin and UCD School of Medicine and Medical Sciences, Dublin, Ireland

Andrew Cant
Department of Paediatric Immunology, Allergy and Infectious Diseases, Great North Children's Hospital, Newcastle, UK

Ron Dagan
Pediatric Infectious Disease Unit, Soroka University Medical Center, and Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel

Graham Davies
Great Ormond Street Hospital, London, UK

David Elliman
Whittington Health, Haringey Children Community Health Services, St Ann's Hospital, London, UK

Susanna Esposito
Paediatric Highly Intensive Care Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy

Adam Finn
School of Clinical Sciences, University of Bristol, Bristol, UK

Manolis Galanakis
Paediatric Infectious Diseases Unit, Heraklion University Hospital, Crete, Greece

Carlo Giaquinto
Department of Women and Child Health, University of Padova, Italy

Jim Gray
Department of Microbiology, Birmingham Children's Hospital, Birmingham, UK

Ronald de Groot
Department of Paediatrics, Radboudumc Amalia Children's Hospital, Nijmegen, The Netherlands

Paul Heath
Paediatric Infectious Diseases Research Group, Institute of Infection and Immunity, St George's, University of London, London, UK

Terho Heikkinen
Department of Paediatrics, University of Turku, Turku, Finland

Ulrich Heininger
Paediatric Infectious Diseases and Vaccinology, University Children's Hospital Basel, Switzerland

Philipp Henneke
Center for Chronic Immunodeficiency (CCI) and Center for Pediatrics, Medical Center, University of Freiburg, Germany

Shamez Ladhani
Public Health England, London, UK; Paediatric Infectious Diseases Research Group, Institute of Infection and Immunity, St George's, University of London, London, UK

Irja Lutsar
Institute of Medical Microbiology, University of Tartu, Tartu, Estonia

Hermione Lyall
Department of Paediatrics, St Mary's Hospital, London, UK

Federico Martinon Torres
Translational Pediatrics and Infectious Diseases, Hospital Clínico Universitario de Santiago de Compostela, Santiago, Spain

Andrew Pollard
Department of Paediatrics, University of Oxford, Oxford, UK

Mary Ramsay
Immunisation, Hepatitis and Blood Safety Department, Public Health England, London, UK

Andrew Riordan
Alder Hey Children's NHS Foundation Trust, Liverpool, UK

Fernanda Rodrigues
Infectious Diseases Unit & Emergency Service, Coimbra Children's Hospital, Coimbra, Portugal

Emmanuel Roilides
3rd Department of Paediatrics, Medical Faculty, Aristotle University School of Health Sciences, Hippokration Hospital, Thessaloniki, Greece

Pablo Rojo
Pediatric Infectious Disease Unit, Department of Pediatrics, Hospital 12 de Octubre, Madrid, Spain

Mike Sharland
Department of Paediatrics, St George's University Hospital, London, UK

Delane Shingadia
Department of Infectious Diseases, Great Ormond Street Hospital, London, UK

Steve Tomlin
Children's Medicine Service, Evelina London, Guy's and St Thomas' NHS Foundation Trust, London, UK

Maria Tsolia
Faculty of Medicine, National and Kapodistrian University of Athens, Greece

Contributors

Lei Ang
Department of Microbiology, Royal University Hospital, Saskatoon, Saskatchewan, Canada

Charalampos Antachopoulos
3rd Department of Paediatrics, Medical Faculty, Aristotle University School of Health Sciences, Hippokration Hospital, Thessaloniki, Greece

Alasdair Bamford
Paediatric Infectious Disease, Great Ormond Street Hospital, London, UK

Shalom Ben-Shimol
Pediatric Infectious Disease Unit, Soroka University Medical Center and The Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel

Jolanta Bernatoniene
Paediatric Infectious Disease & Immunology Department, Bristol Royal Hospital for Children, Bristol, UK

Maria Bitsori
Department of Paediatrics, Heraklion University Hospital, Crete, Greece

Jan Bonhoeffer
Paediatric Infectious Diseases and Vaccinology, University Children's Hospital Basel, Switzerland

Paul Brogan
UCL Institute of Child Health, and Great Ormond Street Hospital NHS Trust, London, UK

Tim Brown
Rare and Imported Pathogens Laboratory, Public Health England, UK

Penelope Bryant
Infectious Diseases Unit, Department of General Medicine, The Royal Children's Hospital, Melbourne and Murdoch Children's Research Institute, Department of Paediatrics, University of Melbourne, Australia

Jim Buttery
Infection and Immunity, Monash Children's Hospital, Murdoch Children's Research Institute, Department of Paediatrics, Monash University, Melbourne, Australia

Hsin Chi
Division of Infectious Diseases, Department of Paediatrics, MacKay Children's Hospital, Tapei, Taiwan

Nan-Chang Chiu
Department of Paediatrics, MacKay Children's Hospital, Taipei, Taiwan

Georgl Christov
Great Ormond Street Hospital, London, UK

Theresa Cole
Royal Children's Hospital, Melbourne, Australia

Richard Cooke
University of Liverpool, Merseyside, UK

Robert Cunney
Clinical Microbiology, The Children's University Hospital and The Health Protection Surveillance Center, Dublin, Ireland

Ron Dagan
Pediatric Infectious Disease Unit, Soroka University Medical Center, and Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel

Patrizia D'argenio
Cardiac Pediatric Surgery Department, Bambino Gesù Hospital, Rome, Italy

Graham Davies
Great Ormond Street Hospital, London, UK

Suzanne Davison
Paediatric Hepatology, Leeds Teaching Hospitals NHS Trust, Leeds, UK

Garth Dixon
Great Ormond Street Hospital, London, UK

Kirsty le Doare
Division of Infectious Diseases, Imperial College Healthcare NHS Trust, London, UK

Katja Doerholt
Paediatric Infectious Diseases, St Georges NHS Trust, London, UK

Rogier van Doorn
Centre for Tropical Medicine, Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam

Simon Drysdale
Imperial College Healthcare NHS Trust, London, UK

Veronika Dvorakova
Dermatology Department, Our Lady's Children's Hospital Crumlin, Dublin, Ireland

Geoffrey Edwards
Molecular and Clinical Pharmacology, Institute of Translational Medicine, The University of Liverpool, Liverpool, UK

Despina Eleftheriou
Department of Rheumatology, UCL Institute of Child Health and Great Ormond Street Hospital, London, UK

Alyson Elliman
Croydon Health Services NHS Trust, Croydon, UK

David Elliman
Whittington Health, Haringey Children Community Health Services, St Ann's Hospital, London, UK

Matthew Ellis
Academic Centre for Child & Adolescent Health, Bristol, UK

Marieke Emonts
Paediatric Infectious Diseases and Immunology, Newcastle upon Tyne Hospitals NHS Foundation Trust, Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK

Susanna Esposito
Paediatric Highly Intensive Care Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy

Saul Faust
Paediatric Immunology and Infectious Diseases, University of Southampton, and NIHR, Wellcome Trust Clinical Research Facility, University Hospital Southampton NHS Foundation Trust, Southampton, UK

Adam Finn
School of Clinical Sciences, University of Bristol, Bristol, UK

Michiel van der Flier
Department of Paediatrics, Radboudumc Amalia Children's Hospital, Nijmegen, The Netherlands

Laura Folgori
Unit of Vascular and Interventional Radiology, Bambino Gesù Hospital, Rome, Italy

Livia Gargiullo
Unit of Vascular and Interventional Radiology, Bambino Gesù Hospital, Rome, Italy

Patrick Gavin
Department of Infectious Diseases & Immunology, Our Lady's Children's Hospital Crumlin and The Children's University Hospital, Dublin, Ireland

Carlo Giaquinto
Department of Women and Child Health, University of Padova, Italy

Maria Isabel Gonzalez-Tome
Pediatric Infectious Disease Unit, Department of Pediatrics, Hospital 12 de Octubre, Madrid, Spain

Herman Goossens
Research Centre for Control of Antibiotic Resistance, University of Copenhagen, Copenhagen, Denmark

Jim Gray
Department of Microbiology, Birmingham Children's Hospital, Birmingham, UK

Alfredo Guarino
Public Health England, Centre for Infections Services, London, UK

Scott Hackett
Immunodeficiency Centre, Birmingham Heartlands Hospital, UK

Jennifer Handforth
Evelina Children's Hospital, London, UK

Paul Heath
Paediatric Infectious Diseases Research Group, Institute of Infection and Immunity, St George's, University of London, London, UK

Rowan Heath
Kingston Hospital NHS Trust, Kingston, UK

Terho Heikkinen
Department of Paediatrics, University of Turku, Turku, Finland

Ulrich Heininger
Paediatric Infectious Diseases and Vaccinology, University Children's Hospital Basel, Switzerland

Jethro Herberg
Section of Paediatrics, Imperial College, London, UK

Philipp Henneke
Center for Chronic Immunodeficiency (CCI) and Center for Pediatrics, Medical Center, University of Freiburg, Germany

David Hill
Institute for Global Public Health, School of Medicine Quinnipiac University, Hamden, USA

Peter J Hotez
Texas Children's Hospital Endowed Professor of Tropical Paediatrics, National School of Tropical Medicine, Baylor College of Medicine, Houston, Texas, USA

Samreen Ijaz
Public Health England, London, UK

Wai-Tim Jim
Paediatric ICU, Department of Paediatrics, Tamsui Branch, MacKay Memorial Hospital, Taipei, Taiwan

Piia Jõgi
Children's Clinic of Tartu University Hospital, Tartu, Estonia

Nicole van der Kar
Radboudumc-Amalia Children's Hospital, Nijmegen, The Netherlands

Aspasia Katragkou
3rd Department of Paediatrics, Medical Faculty, Aristotle University School of Health Sciences, Hippokration Hospital, Thessaloniki, Greece, and Transplantation-Oncology Infectious Disease Program, Weill Cornell Medical College, New York, NY, USA

Julia M Kenney
Institute of Child Health, University College London, UK

Alison Kent
Murdoch Children's Research Institute, Parkville, VIC, Australia

Nigel Klein
Great Ormond Street Hospital for Children, London, UK

Herwig Kollaritsch
Institute for Specific Prophylaxis and Tropical Medicine, University of Vienna, Vienna, Austria

Shamez Ladhani
Public Health England, London, UK; Paediatric Infectious Diseases Research Group, Institute of Infection and Immunity, St George's, University of London, London, UK

Beatriz Larru
The Children's Hospital of Philadelphia, Pennsylvania, USA

T Ronan Leahy
Department of Infectious Diseases & Immunology, Our Lady's Children's Hospital Crumlin and The Children's University Hospital, Dublin, Ireland

Dominique Legros
World Health Organization, Geneva, Switzerland

Thomas Lehrnbecher
Division of Paediatric Haematology and Oncology, Hospital for Children and Adolescents of the University of Frankfurt, Frankfurt, Germany

Sue Liebeschuetz
Barts Health NHS Trust, Department of Infection, London

Susanna Liviadiotti
Clinical Trials Centre, Bambino Gesù Hospital, Rome, Italy

Suzanne Luck
Department of Paediatrics, Kingston Hospital, NHS Foundation Trust, UK

Irja Lutsar
Institute of Medical Microbiology, University of Tartu, Tartu, Estonia

Hermione Lyall
Department of Paediatrics, St Mary's Hospital, London, UK

Janet McCulloch
Specialist Nurse and Workforce Development Lead, Public Health England, UK

Ian Maconochie
St Mary's Hospital, Imperial College, London, UK

Rick Malley
Boston Children's Hospital, Boston, USA

Cilian O Maoldomhnaigh
Department of Infectious Diseases & Immunology, Our Lady's Children's Hospital Crumlin, Dublin, Ireland

Nuria Martinez-Alier
Paediatric Infectious Diseases, Immunology and General Paediatrics, Evelina Children's Hospital, St Thomas' Hospital, London, UK

Patrick Meyer Sauteur
Department of Pediatrics Division of Infectious Diseases and Immunology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands

Michael Millar
Barts Health NHS Trust, Department of Infection, London, UK

Anita Modi
Acute Paediatric Services, Luton and Dunstable Hospital, Luton, UK

Karyn Moshal
Department of Infectious Diseases, Great Ormond Street Hospital, London, UK

Eleni Nastouli
Department of Clinical Microbiology and Virology, University College London Hospital, UK

Siew Lin Ngui
Blood Borne Viruses Unit, Microbiology Services Colindale, London, UK

Vas Novelli
Great Ormond Street Hospital for Children, London, UK

Miguel O'Ryan
Microbiology and Mycology Program, Institute of Biomedical Sciences, Faculty of Medicine, University of Chile, Chile

Marta Palusinka Szysz
Maria Curie-Sklodowska University, Lublin, Poland

Anna Papa
Centre for Tropical Medicine, Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam

Vana Papaevangelou
Maria Curie-Sklodowska University, Lublin, Poland

Christopher Parry
Liverpool School of Tropical Medicine, Liverpool, UK

Mitul Patel
Department of Microbiology Birmingham Children's Hospital, UK

Ville Peltola
Department of Paediatrics, Turku University Hospital, Turku, Finland

Stanley Plotkin
University of Pennsylvania, Principal, Vaxconsult, USA

Andrew Pollard
Department of Paediatrics, University of Oxford, Oxford, UK

Nicola Principi
Paediatric Highly Intensive Care Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy

Athimalaipet Ramanan
School of Clincial Sciences, University of Bristol, Bristol, UK

Mary Ramsay
Hepatitis and Blood Safety Department, Public Health England, London, UK

Muhammed Raza
Microbiology, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK

Andrew Riordan
Alder Hey Children's NHS Foundation Trust, Liverpool, UK

Marion Roderick
Department of Paediatrics, University Hospital Bristol, Bristol, UK

Claire Rohan
Whittington Health, Haringey Children Community Health Services, St Ann's Hospital, London, UK

Emmanuel Roilides
3rd Department of Paediatrics, Medical Faculty, Aristotle University School of Health Sciences, Hippokration Hospital, Thessaloniki, Greece

Lorenza Romani
Unit of Vascular and Interventional Radiology, Bambino Gesù Hospital, Rome, Italy

Annemarie van Rossum
Department of Pediatrics, Division of Infectious Diseases and Immunology, Erasmus MC University Medical Center, Rotterdam, The Netherlands

Peter Rudd
Children's Centre, Royal United Hospital, Bath, UK

Manish Sadarangani
Department of Paediatrics, University of Oxford, Oxford, UK

Rebecca Salter
St Mary's Hospital, Imperial Healthcare, London, UK

Jo Seale
Barts Health NHS Trust, Department of Infection, London, UK

Shelley Segal
Oxford Children's Hospital, Oxford, UK

Tim Sell
Oxford Vaccine Group, Department of Paediatrics, Oxford, UK

Delane Shingadia
Department of Infectious Diseases, Great Ormond Street Hospital, London, UK

Hilary J Simons
National Travel Health Network and Centre, UK Liverpool School of Tropical Medicine, UK

Mary Slack
Institute of Hygiene and Microbiology, University of Würzburg, Germany

Mary Slatter
Great North Children's Hospital, Newcastle upon Tyne, UK

Matthew Snape
Oxford Biomedical Research Centre, Oxford University Hospital NHS Trust Department of Paediatrics, University of Oxford, UK

Nikos Spyridis
Faculty of Medicine, National and Kapodistrian University of Athens, Greece

Eda Tamm
Childrenäs Clinic of the Tartu University Hospital, Tartu, Estonia

Rahale Tavanayan Fard
Department of Paediatrics, Oxford Vaccine Group, Oxford, UK

Marc Tebruegge
Academic Unit of Clinical & Experimental Sciences, Faculty of Medicine, The University of Southampton, UK

Pat Tookey
UCL Institute of Child Health, London, UK

Maria Tsolia
Faculty of Medicine, National and Kapodistrian University of Athens, Greece

Stefi Vergnano
Paediatric Infectious Diseases Research Group, Institute of Infection and Immunity, St George's, University of London, London, UK

Lambrini Vogiatzi
3rd Department of Paediatrics, Medical Faculty, Aristotle University School of Health Sciences, Hippokration Hospital, Thessaloniki, Greece

Adilia Warris
Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, UK

Rosemarie Watson
Dermatology Department, Our Lady's Children's Hospital Crumlin, Dublin, Ireland

Steven Welch
Heart of England NHS Foundation Trust, Birmingham, UK

Lalith Wijedoru
Child and Reproductive Health Group, Liverpool School of Tropical Medicine, Liverpool, UK

Bhanu Williams
Department of Paediatrics, Northwick Park Hospital, London, UK

Eleri Williams
Paediatric Infectious Diseases and Immunology, Newcastle Upon Tyne Hospitals, NHS Foundation Trust, Newcastle upon Tyne, UK

Jane Wilson Howarth
Petersfield Medical Practice, Cambridge, UK

Lucinda Winckworth
Neonatal Unit, University College Hospital, London, UK

Tom Wolfs
Wilhelmina Children's Hospital, University Medical Center, The Netherlands

Austen Worth
Great Ormond Street Hospital, London, UK

Pablo Yagupsky
Clinical Microbiology Laboratories, Soroka University Medical Center, Israel

Theoklis Zaoutis
The Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Symbols and abbreviations

↓	decreased
↑	increased
→	leading to
>	greater than
<	less than
≥	greater than or equal to
≤	less than or equal to
=	equal to
≠	not equal to
~	approximately
±	plus or minus
%	per cent
♀	female
♂	male
1°	primary
2°	secondary
α	alpha
β	beta
γ	gamma
κ	kappa
ν	nu
−ve	negative
+ve	positive
°	degree
°C	degree Celsius
°F	degree Farenheit
®	registered trademark
AAP	American Academy of Pediatrics
ABLC	amphotericin lipid complex
ABPA	allergic bronchopulmonary aspergillosis
ACE	angiotensin-converting enzyme
AD	Anno Domini
ADA	adenosine deaminase
ADEM	acute demyelinating encephalomyelitis

ADH	antidiuretic hormone
AFBN	acute focal bacterial nephritis
AHC	acute haemorrhagic conjunctivitis
aHUS	atypical haemolytic–uraemic syndrome
AIDS	acquired immune deficiency syndrome
ALA	amoebic liver abscess
ALT	alanine aminotransferase
AML	acute myelogenous leukaemia
AMP	adenosine monophosphate
ANA	antinuclear antibody
ANC	absolute neutrophil count
ANCA	antineutrophilic cytoplasmic antibody
AOE	acute otitis with effusion
AOLC	acridine orange leucocyte cytospin
AOM	acute otitis media
APECED	autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy
ARD	acute respiratory disease
ARDS	acute respiratory distress syndrome
ARF	acute rheumatic fever
ARPEC	Antibiotic Resistance and Prescribing in European Children
ART	antiretroviral therapy
ARV	antiretroviral
ASD	atrial septal defect
ASP	antimicrobial stewardship programme
AST	aspartate aminotransferase
ATS	American Thoracic Society
AUC_{0-24}:MIC	ratio of area under concentration time curve at 24 hours over minimum inhibitory concentration
AV	atrioventricular
BAAF	British Association for Adoption and Fostering
BAL	bronchoalveolar lavage
BC	before Christ
Bcc	*Burkholderia cepacia* complex
BCG	bacille Calmette-Guérin
BDG	β-1,3-D-glucan
BMS	Bacterial Meningitis Score

BMT	bone marrow transplantation
BNF	*British National Formulary*
BNFC	*British National Formulary for Children*
BP	blood pressure
BPD	bronchopulmonary dysplasia
BPSU	British Paediatric Surveillance Unit
BSE	bovine spongiform encephalopathy
BSI	bloodstream infection
BYCE	buffered charcoal yeast extract
CAA	coronary artery aneurysm
CAKUT	congenital abnormalities of kidneys and urinary tract
CAP	community-acquired pneumonia
CAPS	cryopyrin-associated periodic fever syndromes
CARS	compensatory anti-inflammatory response syndrome
cccDNA	covalently closed circular deoxyribonucleic acid
CCHF	Crimean–Congo haemorrhagic fever
CDC	Centers for Diseases Control and Prevention
CDI	*Clostridium difficile* infection
CDT	*Clostridium difficile* toxin
CEMACH	Confidential Enquiry into Maternal and Child Health
CFS	chronic fatigue syndrome
CFU	colony-forming unit
CGD	chronic granulomatous disease
CHD	congenital heart disease
CHIPS	Collaborative HIV Paediatric Study
CHIVA	Children's HIV Association
CI	confidence interval
CI-HHV-6	chromosomally integrated human herpesvirus
CINCA	chronic infantile neurological, cutaneous, and articular syndrome
CJD	Creutzfeldt–Jakob disease
Cl^-	chloride
CL	cutaneous leishmaniasis
C_{max}:MIC	ratio of maximal drug concentration over minimum inhibitory concentration
CMC	chronic mucocutaneous candidiasis
CME	*Candida* meningo-encephalitis

cmH_2O	centimetre of water
CMV	cytomegalovirus
CNO	chronic non-bacterial osteitis
CNPA	chronic necrotizing pulmonary aspergillosis
CNS	central nervous system
CoNS	coagulase-negative staphylococci
COPD	chronic obstructive pulmonary disease
CPK	creatine phosphokinase
CRE	carbapenem-resistant *Enterobacteriaceae*
CRMO	chronic recurrent multifocal osteomyelitis
CRP	C-reactive protein
CRS	congenital rubella syndrome
CSF	cerebrospinal fluid
CT	computerized tomography
Ctx	cholera toxin
CVC	central venous catheter
cVDPV	circulating vaccine-derived poliovirus
CVP	central venous pressure
CXR	chest X-ray
CYP	cytochrome P
DAA	direct-acting antiviral
DALY	disability-adjusted life year
DAMP	danger-associated molecular pattern
DC	direct current
DEET	*N,N*-diethylmetatoluamide
DFA	direct fluorescent antibody
DGKE	diacylglycerol kinase–epsilon
DHF	dengue haemorrhagic fever
DIC	disseminated intravascular coagulation
DIRA	deficiency of interleukin 1-receptor antagonist
DLSO	distal and lateral subungual onychomycosis
DMARD	disease-modifying anti-rheumatic drug
DMSA	dimercaptosuccinic acid
DNA	deoxyribonucleic acid
DOT	days of therapy
DPT	diphtheria/polio/tetanus
DRESS	drug reaction, eosinophilia, and systemic symptoms

DTP	diphtheria, tetanus, pertussis
EB	elementary body
EBLV	European bat lyssavirus
EBNA	Epstein–Barr virus nuclear antigen
EBV	Epstein–Barr virus
ECDC	European Centre for Disease Prevention and Control
ECG	electrocardiography
ECMO	extracorporeal membrane oxygenation
EEA	European Economic Area
EEG	electroencephalography
EF	ejection fraction
EFSA	European Food Safety Authority
EHEC	enterohaemorrhagic *Escherichia coli*
EIA	enzyme immunoassay
ELBW	extremely low-birthweight
ELISA	enzyme-linked immunosorbent assay
ELISPOT	enzyme-linked immunospot
EM	electron microscopy
EMA	European Medicines Agency
ENA	extractable nuclear antigen
ENT	ear, nose, and throat
EORTC/MSG	European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group
EPTA	European Parliamentary Technology Assessment
ESBL	extended-spectrum β-lactamase
ESC	European Society of Cardiology
ESR	erythrocyte sedimentation rate
EU	European Union
EULAR	European League Against Rheumatism
5-FC	5-fluorocytosine
FBC	full blood count
FCAS	familial cold autoinflammatory syndrome
fCJD	familial Creutzfeldt–Jakob disease
FDA	Food and Drug Administration
FFI	familial fatal insomnia
$FFiO_2$	fraction of inspired oxygen

FH	factor H
FI	factor I
FMF	familial Mediterranean fever
FNA	fine-needle aspiration
FS	fractional shortening
ft	foot (feet)
FTA-ABS	fluorescent treponemal antibody-absorbed test
G6PD	glucose-6-phosphate dehydrogenase
g	gram
GABA	gamma-aminobutyric acid
GABHS	Lancefield group A β-haemolytic *Streptococcus*
GAS	group A *Streptococcus*
GBS	group B *Streptococcus*
GCS	Glasgow coma score
G-CSF	granulocyte colony-stimulating factor
GFR	glomerular filtration rate
GI	gastrointestinal
GM-CSF	granulocyte macrophage colony-stimulating factor
GP	general practitioner
GPEI	Global Polio Eradication Initiative
GSS	Gerstmann–Straussler–Scheinker syndrome
GUM	genitourinary medicine
GVHD	graft-versus-host disease
HAART	highly active antiretroviral therapy
HAdV	human adenovirus
HAI	health care-associated infection
HAV	hepatitis A virus
HBcAg	hepatitis B core antigen
HBeAg	hepatitis B envelope antigen
HBIG	hepatitis B immunoglobulin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDU	high dependency unit
HELLP	haemolysis, elevated liver enzymes, low platelets
HEV	hepatitis E virus

HEV-A	human enterovirus A
HF	haemorrhagic fever
HFMD	hand, foot, and mouth disease
HFRS	haemorrhagic fever with renal syndrome
HHV-3	human herpesvirus 3
HHV-5	human herpesvirus 5
HHV-6	human herpesvirus 6
HHV-7	human herpesvirus 7
HHV-8	human herpesvirus 8
Hib	*Haemophilus influenzae* type b
HIDS	hyperimmunoglobulinaemia D with periodic fever syndrome
HIV	human immunodeficiency virus
HLA	human leucocyte antigen
HLH	haemophagocytic lymphohistiocytosis
hMPV	human metapneumovirus
HMS	hyperreactive malarial syndrome
HNIG	human normal immunoglobulin
HPA	Health Protection Agency
HPS	hantavirus pulmonary syndrome
HPU	health protection unit
HPV	human papillomavirus
HRCT	high-resolution computerized tomography
HSCT	haematopoietic stem cell transplant
HSE	herpes simplex encephalitis
HSV	herpes simplex virus
HTLV	human T-lymphotropic virus
HUS	haemolytic–uraemic syndrome
IA	invasive aspergillosis
ICAF	inter-country adoption form
ICD	implantable cardioverter–defibrillators
ICGA	immunochromatographic assay
iCJD	iatrogenic Creutzfeldt–Jakob disease
ICP	intracranial pressure
ICVP	International Certificate of Vaccination or Prophylaxis
ID	infectious diseases
IDP	internally displaced person

IDSA	Infectious Diseases Society of America
IE	infective endocarditis
IFA	immunofluorescence assay
IFAT	immunofluorescence antibody test
IFI	invasive fungal infection
IFN	interferon
IgA	immunoglobulin A
IgD	immunoglobulin D
IgE	immunoglobulin E
IgG	immunoglobulin G
IgM	immunoglobulin M
IGRA	interferon-gamma release assay
IL	interleukin
IM	intramuscular; infectious mononucleosis
IMD	invasive meningococcal disease
IMPDH	inosine 5'-monophosphate dehydrogenase
INR	international normalized ratio
IPA	isopropyl alcohol
IPD	invasive pneumococcal disease
IPV	inactivated polio vaccine
IRT	immunoglobulin replacement therapy
ITU	intensive therapy unit
IU	international unit
IUGR	intrauterine growth retardation
IV	intravenous
iVDP	immunodeficiency-related vaccine-derived poliovirus
IVIG	intravenous immunoglobulin
JIA	juvenile idiopathic arthritis
kb	kilobase
kg	kilogram
KOH	potassium hydroxide
KPC	*Klebsiella pneumoniae* carbapenemase
L	litre
LAIV	live attenuated influenza vaccine
L-am	liposomal amphotericin
LDH	lactic dehydrogenase
LED	light-emitting diode

LFT	liver function test
LGV	lymphogranuloma venereum
LIP	lymphoid interstitial pneumonia
LN	lymph node
LP	lumbar puncture
LPS	lipopolysaccharide
LRTI	lower respiratory tract infection
LTBI	latent tuberculosis infection
m	metre
MAC	*Mycobacterium avium* complex
MALDI-TOF	matrix-assisted laser desorption/ionization time-of-flight
MAT	microscopic agglutination test
MCL	mucocutaneous leishmaniasis
MCP	membrane cofactor protein
MCUG	micturating cystourethrogram
MDR	multidrug-resistant/resistance
MDRGNB	multidrug-resistant Gram-negative bacteria
MDS	myelodysplastic syndrome
mg	milligram
MHC	major histocompatibility complex
MIC	minimum inhibitory concentration
MIF	microimmunofluorescence
min	minute
MKD	mevalonate kinase deficiency
mL	millilitre
MLVA	multilocus variable-number tandem-repeat analysis
mm	millimetre
MMR	measles, mumps, and rubella
MMRV	measles, mumps, rubella, and varicella
MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance imaging
MRMP	macrolide-resistant *Mycoplasma pneumoniae*
mRNA	messenger ribonucleic acid
MRSA	meticillin (INN)-resistant *Staphylococcus aureus*
MSM	men who have sex with men
MSMD	mendelian susceptibility to mycobacterial diseases

MSSA	meticillin (INN)-sensitive *Staphylococcus aureus*
MTB	mycobacterial tuberculosis
MTCT	mother-to-child transmission
MTOR	mammalian target of rapamycin
MWS	Muckle Wells syndrome
NA	nucleos(t)ide analogue
NAAT	nucleic acid amplification technique
NaDCC	sodium dichloroisocyanurate
NAP1	North American pulsed-field gel electrophoresis type 1
NaTHNaC	National Travel Health Network and Centre
NB	*nota bene* (take note)
NCRSP	National Congenital Rubella Surveillance Programme
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICU	neonatal intensive care unit
NITAG	National Immunisation Technical Advisory Group
nm	nanometre
NNU	neonatal unit
NOMID	neonatal-onset multisystem inflammatory disorder
NPA	nasopharyngeal aspirate/aspiration
NPC	nasopharyngeal carcinoma
NPV	negative predictive value
NRTI	nucleoside reverse transcriptase inhibitor
NSAID	non-steroidal anti-inflammatory drug
NSE	neuronal-specific enolase
NTM	non-tuberculous mycobacteria
NTS	non-typhoidal salmonellae
OCV	oral cholera vaccine
OLM	ocular larva migrans
OM	osteomyelitis
OMV	outer membrane vesicle
OPV	oral polio vaccine
ORS	oral rehydration solution/salt
$PaCO_2$	arterial carbon dioxide tension
PALE	post-transplant acute limbic encephalitis
PAMP	pathogen-associated molecular pattern

PANDAS	paediatric autoimmune neuro-psychiatric disorders associated with streptococcal infection
PAPA	pyogenic arthritis, pyoderma gangrenosum, and acne syndrome
PBP	penicillin-binding protein
PCP	pneumocystis pneumonia
PCR	polymerase chain reaction
PCT	procalcitonin
PCV	pneumococcal conjugate vaccine
PD	prion disease
PDA	patent ductus arteriosus
PDR	pandrug-resistant
peg-IFN	pegylated interferon
PEP	post-exposure prophylaxis
PET	positron emission tomography
PFAPA	periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis
PFGE	pulsed-field gel electrophoresis
pg	picogram
PGE2	prostaglandin E2
PHE	Public Health England
PICU	paediatric intensive care unit
PID	primary immunodeficiency disorder; pelvic inflammatory disease
PK-PD	pharmacokinetics–pharmacodynamics
p.m.	*post meridiem* (after noon)
PMA	post-menstrual age
PML	progressive multifocal leukoencephalopathy
PNP	purine nucleoside phosphorylase
PPD	purified protein derivative
PPE	personal protective equipment
PPGS	papular purpuric gloves and socks
PPI	proton pump inhibitor
ppm	part per million
PPS	point prevalence survey
PPV	positive predictive value; pneumococcal polysaccharide vaccine
PRNT	plaque reduction neutralizing test

PRP	penicillin-resistant pneumococcus
PRR	pattern recognition receptor
PSGN	post-streptococcal glomerulonephritis
PSO	proximal subungual onychomycosis
PT	prothrombin time
PTLD	post-transplant lymphoproliferative disorder
PTT	partial thromboplastin time
PUO	pyrexia of unknown origin
PVL	Panton–Valentine leukocidin
RADT	rapid antigen detection test
RAST	radioallergosorbent test
RB	reticulate body
RBT	Rose Bengal test
RCT	randomized controlled trial
rDNA	ribosomal deoxyribonucleic acid
RDT	rapid diagnostic test
Rh	rhesus
RIG	rabies immunoglobulin
RIPL	Rare and Imported Pathogens Laboratory
RNA	ribonucleic acid
RPR	rapid plasma reagin
rRNA	ribosomal ribonucleic acid
RRP	recurrent respiratory papillomatosis
RSV	respiratory syncytial virus
RT-PCR	reverse transcriptase polymerase chain reaction
RTX	repeats-in-toxin
RVPBRU	Respiratory and Vaccine Preventable Bacteria Reference Unit
SA	septic arthritis
SAFS	severe asthma with fungal sensitization
SaO_2	oxygen saturation
SARS	severe acute respiratory syndrome
SARS-CoV	severe acute respiratory syndrome coronavirus
SAT	standard agglutination test
SCID	severe combined immunodeficiency syndrome
sCJD	sporadic Creutzfeldt–Jakob disease
SD	standard deviation

SEM	skin–eye–mouth
SFI	superficial fungal infection
SIADH	syndrome of inappropriate antidiuretic hormone secretion
siRNA	short interfering ribonucleic acid
SIRS	systemic inflammatory response syndrome
SLE	systemic lupus erythematosus
SNHL	sensorineural hearing loss
SPF	sun protection factor
SpHUS	*Streptococcus pneumoniae* infection-related haemolytic–uraemic syndrome
spp.	species
SSPE	subacute sclerosing panencephalitis
SSSS	staphylococcal scalded skin syndrome
STEC	Shiga toxin-producing *Escherichia coli*
STI	sexually transmitted infection
Stx	shiga toxin
SVR	sustained viral response
SWO	superficial white onychomycosis
TB	tuberculosis
TBE	tick-borne encephalitis
TBEV	tick-borne encephalitis virus
TetX	tetracycline inactivation
TIV	trivalent inactivated vaccine
TLR	toll-like receptor
TMP-SMX	trimethoprim–sulfamethoxazole
TNF	tumour necrosis factor
TOE	transoesophageal echocardiography
TP	tonsillopharyngitis
TPHA	*Treponema pallidum* haemagglutination assay
TPN	total parenteral nutrition
TPPA	*Treponema pallidum* particle agglutination assay
TRAPS	tumour necrosis factor receptor-associated periodic fever syndrome
TREC	T cell receptor excision circle
TSE	transmissible spongiform encephalopathy
TSS	toxic shock syndrome
TSST-1	toxic shock syndrome toxin-1

TST	tuberculin skin test
TTE	transthoracic echocardiography
TTG	tissue transglutaminase
TTP	thrombotic thrombocytopenic purpura
U&Es	urea and electrolytes
U	unit
UASC	unaccompanied asylum-seeking children
UK	United Kingdom
ULE	unilateral laterothoracic exanthem
UPEC	uropathogenic *Escherichia coli*
URTI	upper respiratory tract infection
US	United States
UTI	urinary tract infection
UV	ultraviolet
VAD	ventricular-assist device
VAND	vaccine-associated neurologic disease
VAPP	vaccine-associated paralytic poliomyelitis
var.	variety
VATS	video-assisted thoracoscopy
VAVD	vaccine-associated viscerotropic disease
VCA	viral capsid antigen
vCJD	variant Creutzfeldt–Jakob disease
V_d	volume of distribution
VDPV	vaccine-derived poliovirus
VDRL	Venereal Disease Research Laboratory
VFR	visiting friends and relatives
VHF	viral haemorrhagic fever
VL	visceral leishmaniasis
VLBW	very low birthweight
VLM	visceral larva migrans
VLP	virus-like particle
VRE	vancomycin-resistant *Enterococcus*
VSD	ventricular septal defect
VTEC	verotoxigenic *Escherichia coli*
VUR	vesicoureteral reflux
VZIG	varicella-zoster immunoglobulin
VZV	varicella-zoster virus

WBC	white blood cell
WCC	white cell count
WGS	whole-genome sequencing
WHO	World Health Organization
WPV	wild poliovirus
XDR	extensively drug-resistant
ZN	Ziehl–Neelsen

Section 1

Clinical syndromes

Chapter 1

Antibacterials

Basic principles in the use of antibiotics

- Antimicrobial agents either kill (bactericidal) or inhibit (bacteriostatic) the growth of a microorganism, by targeting specific unique bacterial sites or metabolic pathways (Table 1.1).

Table 1.1 Classification of antibiotics and mechanism of action

Antibacterial class	Mechanism of action	Bactericidal/ bacteriostatic
β-lactams Penicillins, cephalosporins, monobactams, carbapenems	Cell wall inhibitors	Bactericidal
Glycopeptides Vancomycin, teicoplanin	Cell wall inhibitors	Bactericidal
Lipopeptides (daptomycin)	Cell membrane inhibitors	Bactericidal
Polymyxins (polymyxin B, colistin)		
Isoniazid	Mycolic acids inhibitors	Bactericidal
Macrolides	Protein synthesis inhibitor (subunit 50S)	Bacteriostatic
Chloramphenicol		Bacteriostatic
Lincosamide		Bacteriostatic
Linezolid		Variable
Streptogramins		Bactericidal
Aminoglycosides	Protein synthesis inhibitor (subunit 30S)	Bactericidal
Tetracyclines		Bacteriostatic
Fluoroquinolones	DNA synthesis inhibitors	Bactericidal
Metronidazole		
Rifampin	RNA polymerase inhibitor	Bactericidal
Trimethoprim/ sulfonamides Pyrimethamine	Folic acid synthesis inhibitors	Bactericidal

- Desirable antibiotics would achieve maximum toxicity for the microorganisms and minimal toxicity to humans. However, all antibiotics produce human toxicity to varying degrees.
- The therapeutic index (maximal tolerated dose divided by the minimum effective dose) provides a numerical expression of drug toxicity.
- Some antibiotics, such as penicillins, are very safe and thus have a very high therapeutic index. Others, e.g. gentamicin, have a low maximum tolerated dose and a therapeutic index that is low.
- Common antibiotic adverse effects and toxicities include allergic reactions, drug- or class-specific toxicities, alteration of human flora, drug interactions, and selection for antibiotic resistance. Several examples of these adverse effects are:
  - hypersensitivity/allergic reactions, including rash; practically, all types of antibiotics, but commoner with β-lactams
  - gastrointestinal (GI) disturbances, including abdominal pain, diarrhoea, nausea/vomiting, etc.; practically, all types of antibiotics, commoner with macrolides
  - nephrotoxicity (aminoglycosides, vancomycin)
  - ototoxicity (aminoglycosides, vancomycin)
  - drug fever (β-lactams and others)
  - liver toxicity (carbapenems, tetracyclines, and others)
  - photosensitivity (quinolones, tetracyclines, sulfonamides)
  - miscellaneous reactions; metallic taste (metronidazole), reddish-orange body fluids (rifampicin), nystagmus and muscle weakness (aminoglycosides), peripheral neuropathy (isoniazid), red man syndrome (glycopeptides), tooth discoloration in children <8 years (tetracyclines)
  - alteration of human flora:
    —antimicrobials alter the host's normal flora and affect the predominantly anaerobic flora of the large bowel, resulting in antibiotic-associated diarrhoea or promoting colonization by *Clostridium difficile*. Pseudomembranous colitis could result from different types of antibiotics, with clindamycin being the most 'classic' example
  - vaginal candidiasis (cephalosporins and others)
  - drug interactions (rifampicin)
  - antibiotic resistance (discussed in Antibiotic resistance).
- Choosing the right antibiotic for therapy of a given infection is more challenging than ever, and following the key steps listed below will allow for a systematic approach to antibiotic selection.
- Presumptive and empiric therapy:
  - Initial choice of an antibiotic is usually based on a clinical infection syndrome and the anatomical site of infection. The initial antibiotic choice can often later be changed to the most narrow-spectrum, yet effective, antibiotic with activity against the identified organism
  - For suspected (unproven) infections, presumptive therapy may be considered, even when a bacterial cause is not proven. This is especially true for patients with a severe/life-threatening clinical infections

  - Will treatment improve the outcome? For instance, a child will not benefit from treatment of normal bacterial colonization.
  - What is (are) the most likely causative pathogen(s) for the diagnosed clinical infection syndrome?
  - What is the probable susceptibility of the isolated (or suspected) pathogen, based on lab results or local epidemiological parameters?
- What is the appropriate dose and regimen of therapy, according to the host and the site of infection? Dosage and regimen consideration are largely based on pharmacokinetics–pharmacodynamics (PK/PD) considerations. The three most important PK/PD measures are:
  - duration of time a drug concentration remains above the minimum inhibitory concentration (MIC) (T > MIC)
  - ratio of the maximal drug concentration over the MIC (C_{max}:MIC)
  - ratio of the area under the concentration time curve at 24 hours over the MIC (AUC_{0-24}:MIC).
- Drug distribution. While serum levels of antibiotics are used to predict responses, the knowledge of the distribution of a drug is often important. For example:
  - passive diffusion to tissues, such as the lung or skin, and the skin structure
  - blood–brain barrier penetration into the cerebrospinal fluid (CSF) (may require higher than standard dosages of antibiotics)
  - poorly vascularized spaces, such as abscesses, depend on the passive diffusion of antibiotics for killing of bacteria. Surgical intervention to drain or debride infected tissue is frequently required for a good clinical outcome
  - intracellular accumulation allows for effective treatment of intracellular organisms
  - changes in volume of distribution (V_d) and elimination of antibiotics or hepatic and renal impairment may require adjustments of dosing, as well as re-dosing
  - protein binding may be relevant, e.g. in neonates in whom ceftriaxone should be avoided because it is highly protein-bound and may replace bilirubin from albumin-binding sites.
  - an antibiotic may be bactericidal (actively killing bacteria) or bacteriostatic (preventing bacteria from dividing), depending on the circumstances such as the infection site and dosing
  - post-antibiotic effect describes the phenomenon of an extended period of time of inhibition of bacterial growth, even after antibiotic concentrations drop below the MIC (e.g. with aminoglycosides, which allows less frequent dosing).
- The duration of antibiotic therapy is the least evidence-based part of antibiotic prescribing and is usually decided on the notoriously unreliable expert opinion. However, for some clinical syndromes, there is growing evidence allowing for standardization of duration. These include:
  - 10 days for group A streptococcal (GAS) pharyngitis
  - 3–5 days of treatment for pneumonia in resource-poor settings
  - bacterial meningitis from different pathogens: 4–7 days for *Neisseria meningitidis*, 7–10 days for *Haemophilus influenzae*, 10–14 days

for *Streptococcus pneumoniae*, 14–21 days for *Escherichia coli*, and ≥21 days for *Listeria*
  - Generally, the shortest duration should be used, wherever possible. Every antibiotic prescription should have a clear stop date.
- Host factors should always be considered when choosing an antibiotic.
  - The most likely aetiology of infections is typically age-dependent (e.g. need to cover *Listeria* in all neonates with meningitis, but not in older immunocompetent children with meningitis).
  - Prior use of antibiotics in a patient is critical information, because this may represent failure of treatment (and may thus provide clues to the aetiology), and, in some cases, it may have caused selective pressure on the patient's flora, making subsequent infections with resistant bacteria more likely.
  - The choice of route of administration is influenced by the host. Questions to ask include the child's ability to take antibiotics orally (palatability is a key part of this!), as well as enteric absorption. Oral antibiotics should be used, wherever possible. The need for intravenous (IV) antibiotics over 48 hours should always be questioned.
  - Underlying conditions may be associated with a large number of host factors; most importantly, this includes impaired defence mechanisms (e.g. immune deficiency, medical devices), abnormal flora, interactions with the patient's regular medications, and impaired clearance in some—if an underlying condition is known, it will inform about typical causative pathogens.
  - Abnormal renal or hepatic functions require dose adjustments, according to the estimated change in function (e.g. calculated creatinine clearance).
  - Age-related changes in physiology lead to significant pharmacokinetic changes; this needs to be reflected when dosing antibiotics (e.g. neonates).
  - Allergies to drugs and antibiotics need to be asked about routinely, and the type of reaction should be documented in detail. Specific allergy testing may be required for those drugs where it is available, especially if the risk of anaphylactic reactions cannot be clearly assessed based on the history. In some situations, desensitization is an option.
  - If a patient is not getting better on a regimen, a careful review of all microbiological and host factors is mandatory and frequently reveals potential causes of failure.
- Prophylactic use:
  - There are few absolute indications for the prophylactic use of antimicrobials, and this is one area where misuse is very common.
  - An example of appropriate prophylaxis would be rifampicin or ciprofloxacin for close contacts of cases of meningococcal or *H. influenzae* type b (Hib) disease.
  - Surgical prophylaxis should be as a single dose, wherever possible. Prolonged surgical prophylaxis is one of the commoner causes of serious misuse of antibiotics.

Antibiotic resistance

Useful definitions

- **Antibiotic susceptibility**. In laboratory testing, it is usual to test the organism in drug concentrations that can be easily achieved in body fluids. Organisms susceptible to this or lower concentrations are regarded as susceptible.
- **Antibiotic resistance**. Organisms able to grow under those drug concentrations *in vitro* are considered resistant.
- **Minimum inhibitory concentration**. This is the lowest concentration of the agent that prevents the development of visible growth of the test organism during overnight incubation.
- **Minimum bactericidal concentration**. This is the lowest concentration able to reduce the original inoculum by a factor of a thousand.

General concepts

- Microorganism fitness depends on their capacity to adapt to changing environmental conditions.
- Antimicrobial agents exert a strong selective pressure on bacterial populations, favouring those that have the ability to resist them.
- The main driver for the development of resistance is the inappropriate use of antibiotics. There is reasonably good evidence that rational (judicious) use of antibiotics can prevent, or at least slow, the development of resistance.
- Information about current local resistance should be readily available and considered in choosing antibiotics, especially for infections on high-risk units, e.g. neonatal intensive care or oncology wards.
- 24–48 hours after the initial administration of antibiotics, always review antimicrobial chemotherapy with microbiology results, and stop or rationalize, wherever possible.
- Wherever possible, switch from IV antibiotics to oral at 48 hours, and stop at 5 days.

Predictable and variable susceptibility

- The susceptibility of common pathogens may change over time under selection pressure (extrinsic resistance), although, for some of them, the resistance is often predictable (intrinsic resistance).
- Once the organism is known, and while waiting for susceptibility testing, the most likely effective antibiotic treatment can be chosen, based on the particular characteristics of the pathogen and local epidemiology.

Common Gram-positive bacteria predictable susceptibility

- β-haemolytic streptococci are usually susceptible to β-lactams, macrolides, and clindamycin.
- *S. pneumoniae* is usually susceptible to β-lactams, macrolides, and vancomycin.
- *Enterococci* are usually susceptible to β-lactams and aminoglycosides, but resistant to cephalosporins.

- *Staphylococcus aureus* (meticillin (INN)-sensitive, MSSA) is usually susceptible to anti-staphylococcal penicillins (e.g. oxacillin), co-amoxiclav, cephalosporins, rifampicin, and clindamycin.
- In contrast, meticillin (INN)-resistant *S. aureus* (MRSA) is usually susceptible to vancomycin, clindamycin, doxycycline, daptomycin, and linezolid, but resistant to all β-lactams.
- Coagulase-negative staphylococci (CoNS) are usually susceptible to vancomycin, but resistant to all penicillins.
- *Listeria* species (spp.) are usually susceptible to β-lactams and aminoglycosides, but resistant to cephalosporins.

Common Gram-negative bacteria predictable susceptibility

- *N. meningitidis* is usually susceptible to third-generation cephalosporins, but there is growing evidence for increasing resistance to penicillins.
- Gram-negative *Enterobacteriaceae*, like *E. coli, Proteus mirabilis, Enterobacter* spp., *Klebsiella* may be susceptible to extended-spectrum β-lactams, like extended-spectrum penicillins, second- and third-generation cephalosporins, carbapenems, and co-trimoxazole, quinolones, and aminoglycosides, but resistant to narrow-spectrum penicillins.
- Increasing resistance of these bacteria to β-lactams and other antimicrobials (see later) and the emergence of multidrug-resistant (MDR) bacteria with varied resistance mechanisms (extended-spectrum β-lactamase, ESBL; *Klebsiella pneumoniae* carbapenemase, KPC; and carbapenem-resistant *Enterobacteriaceae*, CRE) are a major concern, especially in the hospital setting.
- *Pseudomonas* spp. may be susceptible to extended-spectrum penicillins (like piperacillin/tazobactam), ceftazidime, cefepime and meropenem, aminoglycosides, and quinolones.

Other bacteria predictable susceptibility

- Anaerobes are susceptible to amoxicillin/clavulanate, piperacil-lin/tazobactam, clindamycin, metronidazole, cefotetan, and carbapenems.
- *Mycoplasma* and *Chlamydia* are usually susceptible to macrolides and tetracyclines.

Mechanisms of antibiotic resistance

Several mechanisms of antibiotic resistance have been described. These include antibiotic chemical modification, reduced uptake into the cell, active efflux from the cell, modifying target site, overproduction of the antibiotic target, and metabolic bypass of inhibited reactions.

Bacteria may be naturally resistant or may acquire resistance by means of DNA mutation or acquisition of resistance-conferring DNA from another source (e.g. plasmids).

Common examples of the mechanisms of antibiotic resistance are detailed in Table 1.2.

Table 1.2 Major mechanisms of antibiotic resistance

Mechanism	Antibiotics affected	Main bacteria
Enzymatic inactivation		
β-lactamases, including ESBL	β-lactams	*Enterobacteriaceae*
Aminoglycoside-modifying enzymes	Aminoglycosides	Enterococci
Chloramphenicol acetyltransferase	Chloramphenicol	Gram +ve and Gram −ve
Macrolide, lincosamide, and streptogramin-inactivating enzymes	Macrolide, lincosamide and streptogramin	Gram +ve and Gram −ve
Tetracycline inactivation (TetX)	Tetracycline	*Bacteroides* spp.
Reduced uptake		
Lipid bilayer outer membrane	Penicillins	Gram −ve bacteria
Mutations of porins	β-lactams and others	Gram +ve and Gram −ve
Active efflux	Tetracyclines	*E. coli*, *Shigella* spp.
	Macrolides and streptogramins	Gram +ve
	Fluoroquinolones	Gram +ve and Gram −ve
Modifying target sites		
Alteration of ribosomal binding sites	Macrolides, lincosamides, and streptogramins	Streptococci and staphylococci
Alteration of target enzymes—PBP	β-lactams	Gram +ve
Alteration of DNA gyrase	Fluoroquinolones	Gram −ve, *Pseudomonas*
Overproduction of antibiotic target	Sulfonamides	Various bacteria
Bypass of inhibited reaction	Sulfonamides	Enterococci

PBP, penicillin-binding protein.

Control of resistance

Antibiotic prescribing habits of clinicians and general practitioners (GPs) are largely responsible for the emergence of resistant pathogens. The unnecessary use of antibiotics acts as a strong selective tool for the emergence of resistant microorganisms, and restriction of use should lead to the opposite effect (although this is more difficult to demonstrate outside controlled environments).

Reducing antibiotic prescribing is far from easy, and a combined effort is mandatory. Adherence to prescribing guidelines (for hospital and community prescribing) and restriction policies that reduce the use of certain antibiotics (for hospital prescribing) may lead to the reduction in antibiotic overuse.

In addition to reducing antibiotic prescribing, judicious usage of antibiotics include considerations regarding choosing the right antibiotic class, taking into account factors like post-antibiotic effect and the tendency of certain antibiotic classes to induce resistance.

All children hospitals should develop an antimicrobial stewardship programme.

New agents and conservation of old drugs

There is a shortage of new antibiotics under development by pharmaceutical companies, especially for MDR Gram-negative infections. Clinicians should generally reserve new antibiotics for third-line use. Improved incentives to invest in new antimicrobial agents are underway in both the European Union (EU) and the United States (US).

Improved stewardship of current agents should be based on a better understanding of current resistance rates in children across Europe. Point prevalence surveys can be standardized to produce comparative prescribing data between and within countries.

Further reading

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Chapter 2

Antifungals

See also Chapters 17, 23, 35, 47, 51, 96.

Introduction

Conventional amphotericin deoxycholate, fluconazole, and 5-fluorocytosine (5-FC) have, for decades, been the mainstay of antifungal therapy in invasive fungal infection (IFI). Recently, a number of newer compounds with promising efficacy and/or improved safety profile have been introduced, increasing our options for optimal therapy. These include the lipid formulations of amphotericin, the second-generation triazoles voriconazole and posaconazole, and the echinocandins caspofungin, micafungin, and anidulafungin. The pharmacology of antifungal drugs often differs considerably between children and adults. This has significant implications for optimal dosing in children. For some of these agents, there is still a disappointing shortage of high-quality data on their efficacy and pharmacokinetics in children, making research in this field a key priority. For all drug doses, see Appendix 5.

Fungal classification

Yeasts:
- *Candida*
- *Cryptococcus*
- *Trichosporon*.

Moulds:
- Non-septate hyphae:
  - *Zygomycetes*
- Septate hyphae:
  - *Aspergillus*
  - *Fusarium*
  - *Scedosporium*.

Dimorphic fungi (can exist as a mould or yeast):
- *Blastomyces dermatitidis*
- *Coccidioides immitis*
- *Histoplasma capsulatum*
- *Paracoccidioides brasiliensis*.

Classes of antifungal drugs

Polyenes:
- Nystatin, amphotericin deoxycholate, lipid formulations of amphotericin
- Act on the ergosterol component of the fungal cell wall, causing cell membrane lysis (Fig. 2.1).

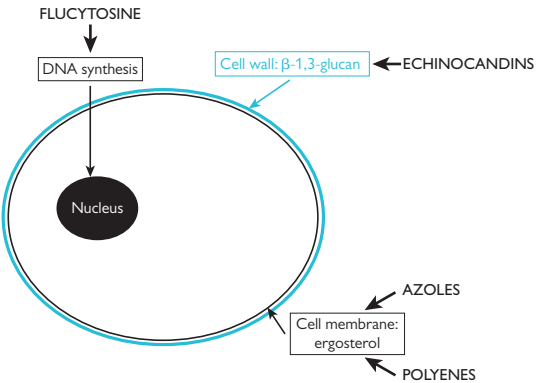

Fig. 2.1 Sites of action of antifungal drugs.

Pyrimidine analogues:
- 5-FC
- Converted to fluorouracil within susceptible fungal cells, which inhibits fungal DNA synthesis and protein synthesis.

Azoles:
- Fluconazole, itraconazole, voriconazole, posaconazole
- Inhibit fungal cytochrome P450-dependent lanosterol 14-α-demethylase, which is involved in ergosterol synthesis.

Echinocandins:
- Caspofungin, micafungin, anidulafungin
- Inhibit 1,3-β-D glucan synthase, an enzyme present in fungal, but not mammalian, cells, causing impaired cell wall synthesis.

Fungicidal versus fungistatic action

The differing mechanisms of action of the antifungal drugs lead to varying fungicidal and fungistatic activity (Table 2.1).

Table 2.1 Fungicidal versus fungistatic action of antifungal drugs against different fungi

Antifungal agent	*Aspergillus*	*Candida*	*Cryptococcus*
Amphotericin	Cidal	Cidal	Cidal
Fluconazole	Nil	Static	Static
Itraconazole	Cidal	Static	Static
Voriconazole	Cidal	Static	Static
Posaconazole	Cidal	Static	Static
Caspofungin	Static	Cidal	Nil
Micafungin	Static	Cidal	Nil
Anidulafungin	Static	Cidal	Nil

Amphotericin formulations

The major advantage of lipid-associated formulations, compared with amphotericin deoxycholate, is their significantly reduced nephrotoxicity. Lipid formulations are also thought to have better reticuloendothelial penetration (liver, spleen, and lung), although this difference has not been clearly confirmed in efficacy studies. Using different lipid carriers for amphotericin, three lipid-associated formulations have been developed:

- Liposomal amphotericin (L-am)
- Amphotericin lipid complex (ALC)
- Amphotericin colloidal dispersion (ACD).

Spectrum of action

- No difference between amphotericin deoxycholate and lipid formulations.
- Broad-spectrum activity against most *Candida* and *Aspergillus* spp., *Cryptococcus*, the dimorphic fungi, and other moulds such as *Zygomycetes* (*Rhizopus, Mucor*) and *Fusarium*.
- Resistance may be observed for some *Candida* spp. (*Candida krusei, Candida glabrata, Candida lusitaneae*) and commonly for *Aspergillus terreus* and *Scedosporium* spp.

Pharmacology

- All formulations are administered by IV infusion due to poor oral absorption.
- In tissues, higher concentrations are achieved in the liver and spleen, followed by the lung and kidney. Low penetration in the brain and CSF.
- Non-linear pharmacokinetics, with greater than proportional increase of serum concentrations with increasing dose.

- Fungicidal activity is concentration-dependent, requiring high drug concentrations at the site of infection. Antifungal activity continues when concentrations are below the MIC (post-antifungal effect). Thus once-daily dosing is effective.
- Dose adjustment is not necessary in patients with pre-existing renal impairment.
- Pharmacokinetic data in neonates are very limited but appear to be similar to data in older children. Therefore, similar dosing strategies can be used.

Efficacy

- Equivalent efficacy between amphotericin deoxycholate and lipid formulations. ABCD has been studied less than the other two lipid formulations.
- All have shown efficacy as empiric or targeted treatment of invasive fungal infections, including candidiasis, aspergillosis, cryptococcosis, mucormycosis, and other rarer mould infections.
- Despite *in vitro* susceptibility, infections caused by *Trichosporon* spp. appear to be clinically resistant to amphotericin.
- L-amB has also shown efficacy as prophylaxis in certain haematological patient groups at high risk for IFIs.

Toxicity

- Toxicity occurs because amphotericin binds not only to ergosterol in fungal cells, but also to cholesterol in human cells, e.g. the kidney. Binding to cholesterol is reduced by the lipids in lipid formulations, leading to reduced toxicity.
- The three lipid-associated formulations vary in their rates of toxicity, with L-amB associated with the lowest rates of discontinuation. Rates of fever, chills, and nephrotoxicity are all significantly lower with L-amB.
- Children can tolerate higher doses of L-amB for longer periods than adults. Rates of nephrotoxicity are lower, but tubular toxicity, such as hypokalaemia, can still be severe.
- Risk factors for nephrotoxicity include pre-existing renal impairment, hyponatraemia, hypovolaemia, and the concurrent use of nephrotoxic drugs.
- However, in neonates, amphotericin deoxycholate is tolerated relatively well, and nephrotoxicity is observed less frequently, compared to older children and adults.

5-fluorocytosine

5-FC is used mainly for cryptococcal meningitis, which is far less common since the introduction of effective antiretroviral regimens for childhood human immunodeficiency virus (HIV) infections. If used as monotherapy, antifungal resistance develops rapidly; thus, it should only be used as part of combination therapy. It probably enhances antifungal activity of amphotericin at sites where amphotericin has poor penetration such as the CSF and heart valves.

Spectrum of action

- *In vitro*, active against yeasts, such as *Candida* spp. (including *C. glabrata*) and *Cryptococcus neoformans*, and selected dematiaceous moulds (*Phialophora* and *Cladosporium* spp).
- Little or no activity against *Aspergillus* spp. under standard conditions. However, the activity may increase in acidic environment.

Pharmacology

- 5-FC has good oral bioavailability.
- Distribution is good, because of its small size and lack of protein binding, resulting in good penetration into the CSF, heart valves, and inflamed joints.
- It is excreted primarily by the kidneys. In patients with renal impairment, dose adjustment is needed.

Efficacy

- Adult data have shown 5-FC plus amphotericin to be more effective in treating cryptococcal meningitis than amphotericin alone.
- Longer treatment courses are required in immunocompromised patients, compared with immunocompetent patients (6 weeks versus 4 weeks).

Toxicity

- Due to a narrow therapeutic index, monitoring of drug levels is advised.
- Trough levels of >100 micrograms/mL are associated with bone marrow suppression and liver toxicity. Aim to maintain levels between 40 micrograms/mL and 80 micrograms/mL.

Fluconazole

One of the most widely used triazoles, due to its good activity against yeasts, excellent bioavailability, and relatively low cost.

Spectrum of action

- *In vitro*, active against *Candida* spp. (such as *Candida albicans, Candida parapsilosis, Candida tropicalis*), *Cryptococcus neoformans, Cryptococcus gattii*, and dimorphic fungi. *C. glabrata* shows variable susceptibility to fluconazole, and *C. krusei* is resistant.
- Fluconazole has no activity against *Aspergillus* and other moulds.

Pharmacology

- Fluconazole has 90% oral bioavailability.
- Distribution is good, because of its low protein-binding, resulting in CSF/vitreous concentrations of 80% of blood concentrations.
- Excreted by the kidney. Urinary concentrations are 10–20 times that of the blood, making it a very effective treatment for fungal urinary tract infections (UTIs).
- Paediatric and adult pharmacokinetics differ. Clearance is more rapid in children, leading to a shorter half-life, necessitating higher drug doses in

children. Pharmacokinetic modelling shows that 12mg/kg/day is required to achieve comparable plasma concentrations to adults receiving 400mg/day.
- Neonates require approximately 5 days to reach steady state, and maintenance doses of 12mg/kg/day of fluconazole achieve exposures similar to older children and adults. Therefore, a loading dose of 25mg/kg is suggested for neonates treated with fluconazole in order to achieve concentrations that are efficacious against *Candida* organisms more quickly.

Efficacy

- Fluconazole has shown efficacy in the treatment of invasive candidiasis, mucosal candidiasis (oropharyngeal and oesophageal candidiasis), cryptococcal meningitis, and endemic mycoses, particularly coccidiomycosis.
- It has also demonstrated efficacy as 1° prophylaxis of invasive candidiasis in certain groups of haematological patients such as haematopoietic stem cell transplant (HSCT) recipients and patients with acute myelogenous leukaemia (AML) or recurrent leukaemia. However, concerns exist about its lack of activity against moulds.
- Fluconazole administration at 3–6mg/kg/dose (IV or oral) twice weekly effectively prevents invasive candidiasis in high-risk neonates.

Toxicity

- Fluconazole causes less cytochrome P450 (CYP) inhibition than most other azoles. However, the possibility of drug interaction should always be considered in patients treated with fluconazole.
- Hepatotoxicity does occur but is rare (2/24 in one study); the commonest side effects are nausea and vomiting.

Itraconazole

Itraconazole is not only active against *Candida*, but also against *Aspergillus*, making it a more attractive prophylactic agent, compared with fluconazole. However, its unpredictable bioavailability and frequent drug interactions limit its role in the treatment of IFIs.

Spectrum of action

The spectrum of action of itraconazole includes species susceptible to fluconazole but also extends to include moulds such as *Aspergillus* spp., certain dematiaceous fungi, *Scedosporium apiospermum*, and *Penicillium marneffei*. It has no activity against *Zygomycetes, Fusarium* spp., and *Scedosporium prolificans*.

Pharmacology

- Available in oral (capsules, suspension) or IV formulations.
- Itraconazole has an unpredictable oral absorption. Absorption is increased in acidic environments such as when taken with food or acidic drinks. H2 blockers reduce absorption.

- Absorption varies with the drug formulation; capsules are better absorbed with food, while the suspension is better absorbed on an empty stomach. The suspension has a 30% better bioavailability, but this is reduced when it is given via a nasogastric tube.
- Itraconazole is highly protein-bound in the blood and has very poor CSF penetration.
- It has hepatic elimination; therefore, dose adjustment is not required in renal impairment.
- A higher V_d in children results in lower serum concentrations. Therefore, children require a twice-daily regimen, compared with once-daily in adults.
- Measurement of trough levels is necessary to ensure that adequate drug levels are achieved at the start of therapy, especially because drug interactions can affect blood levels. Aim for >0.5mg/L if the high-performance liquid chromatography assay is used. There is a different target level if a bioassay is used; consult the laboratory for clarification.

Efficacy

- Although itraconazole is active against *Candida* and *Aspergillus*, its variable absorption compromises its role in the treatment of invasive candidiasis or aspergillosis.
- It can be used, however, as 1° prophylaxis against IFIs in susceptible haematological patients, as well as those suffering from chronic granulomatous disease (CGD).

Toxicity

- Causes significant CYP inhibition, resulting in frequent drug interactions (rifampicin, carbamazepine, macrolides, warfarin, sirolimus, ciclosporin, etc.).
- Beware of high ciclosporin and tacrolimus levels.
- Dose-related GI toxicity commonly observed.

Voriconazole

Broader spectrum of activity to itraconazole with less erratic oral bioavailability.

Spectrum of action

- Potent activity against *Candida* spp., including *C. krusei* and *C. glabrata* that are resistant to fluconazole.
- Active against *Aspergillus* spp., including *A. terreus*, which is resistant to amphotericin B.
- Also active against *Cryptococcus*, endemic fungi, and less common fungal pathogens, including *Trichosporon* spp., *Penicillium marneffei, Fusarium* spp., and *Scedosporium apiospermum*.
- Less active against *Scedosporium prolificans*, and not active against the *Zygomycetes*.

Pharmacology

- Excellent oral bioavailability in adults (96%), but paediatric bioavailability is only about 45%, due to higher first-pass metabolism, and is markedly reduced when taken with food.
- Excellent central nervous system (CNS) penetration.
- Metabolized in the liver. Liver metabolism varies widely between individuals, correlating with the CYP2C19 genotype. Poor metabolizers (5–7% of Caucasians and 20% of non-Indian Asians) have far higher voriconazole levels.
- Children appear to have a higher elimination capacity of voriconazole than adults, requiring higher weight-based doses in order to achieve similar exposure to adults.
- Dose adjustment necessary for patients with hepatic impairment.
- No adjustment of oral voriconazole is needed in patients with renal dysfunction. In cases of moderate renal impairment (creatinine clearance <50mL/min), the IV formulation should be avoided due to accumulation of cyclodextrin carrier.
- Measurement of trough levels is necessary to ensure that adequate drug levels are achieved. Aim for ≥1mg/L. Levels may need to be rechecked when the route of administration is changed or if the patient is clinically unstable. Target levels may vary if different assays are used—always consult the laboratory for clarification.

Efficacy

- Voriconazole is currently the treatment of choice for invasive aspergillosis (superior activity over amphotericin deoxycholate in a randomized controlled trial (RCT)).
- Efficacious in the treatment of invasive candidiasis; it may also be used for treatment of infections caused by susceptible organisms, based on its spectrum of action.
- Also indicated for prophylaxis against IFIs in high-risk groups of haematological patients.
- Paucity of infantile and neonatal data.

Toxicity

- Causes CYP inhibition, resulting in a number of drug interactions. Sirolimus contraindicated because of markedly elevated levels.
- Reversible dose-dependent visual disturbance (especially blurred vision and increased brightness) can occur.
- Skin rash (10–20%), including photosensitive rashes (5%), and elevated liver enzymes (10–20%), especially with increasing doses.

Posaconazole

Posaconazole is the first of the newer triazoles, of which the activity extends to include the *Zygomycetes*. It therefore may have a potential advantage over other azoles as prophylaxis against IFIs in susceptible populations.

Spectrum of action

Similar to that of voriconazole, but also includes the *Zygomycetes*, in particular medically important members of the order *Mucorales* such as *Rhizopus, Mucor, Rhizomucor,* and *Absidia*. Susceptibility of *Mucorales* to posaconazole, however, is not universal, and resistant isolates may be observed.

Pharmacology

- Available recently as both an intravenous and oral formulation (suspension, tablets).
- Paucity of pharmacokinetic data in infants and children. Children >8 years appear to have similar pharmacokinetics to adults.
- Divided oral doses are thought to result in higher bioavailability in children.
- Less CNS penetration than voriconazole, but has been used successfully to treat CNS fungal infection.
- Administration with food increases absorption.
- Mostly excreted unchanged in the faeces, with only a small amount being metabolized, primarily to multiple glucuronide conjugates.
- It inhibits CYP3A4, but not other CYP450 enzymes.
- No dose adjustment in renal or liver impairment.
- Drug monitoring is recommended; aim for trough levels ≥0.7mg/L.

Efficacy

- Paucity of paediatric data; currently not approved for children <13 years.
- It may be used as salvage therapy in patients with invasive aspergillosis, fusariosis, coccidioidomycosis, and chromoblastomycosis, refractory or intolerant to other antifungal agents.
- Also as salvage therapy in patients with mucormycosis, refractory or intolerant to amphotericin formulations.
- It may be used as 1° therapy for oropharyngeal candidiasis (severe disease, immunocompromised patients).
- It is also efficacious as prophylaxis against IFIs in patients with AML, patients with myelodysplastic syndrome (MDS), HSCT recipients with graft-versus-host disease (GVHD), as well as those suffering from CGD in children >12 years.

Toxicity

- Less CYP inhibition, compared with other triazoles; however, clinically significant drug interactions may still occur.
- Generally milder side effects than other triazoles.

Caspofungin

Caspofungin is the first echinocandin that has been licensed for use. The activity of echinocandins against *Candida* and *Aspergillus*, together with their favourable safety profile and limited drug interactions, make them an attractive option for empiric or targeted treatment in many circumstances.

Spectrum of action

- Active against most *Candida* spp., including azole-resistant isolates of *C. glabrata* and *C. krusei*.
- The MICs of caspofungin tend to be higher for *C. parapsilosis* and *Candida guilliermondii* than for other *Candida* spp.; the clinical significance of these differences is currently being explored.
- Also active against *Aspergillus* spp.
- Variable activity against dimorphic fungi.
- No activity against *Cryptococcus, Trichosporon, Zygomycetes, Scedosporium*, and *Fusarium*.

Pharmacology

- Oral bioavailability is limited, therefore only available IV.
- Highly protein-bound with slow generalized distribution, which explains its poor CNS penetration.
- Metabolized by the liver, necessitating dose reduction in hepatic, but not renal, insufficiency.
- To achieve similar drug levels to adults, paediatric dosing is based on the body surface area.

Efficacy

- Efficacious for treatment of invasive candidiasis in children.
- Limited data exist for neonates, and therefore no firm recommendations can be made regarding caspofungin use in neonatal candidiasis.
- Indicated for salvage treatment of invasive aspergillosis in paediatric patients refractory to, or intolerant of, other antifungal agents.
- Also indicated as empiric therapy for presumed IFI (candidiasis or aspergillosis) in febrile, neutropenic patients.

Toxicity

- Minimal toxicity because echinocandins target 1,3-β-D glucan, which is not present in mammalian cells.
- Interactions with tacrolimus and ciclosporin. Monitor liver function tests (LFTs) when used with ciclosporin.
- Rifampicin, nevirapine, and efavirenz lead to increased clearance, necessitating an increase in the caspofungin dose.
- Drug interactions, however, are much fewer compared to azoles, as caspofungin is not metabolized through the CYP450 system.

Micafungin

Spectrum of action

- Similar to caspofungin.

Pharmacology

- Administered only as IV formulation.
- Highly bound to plasma proteins.
- Linear pharmacokinetics at usual doses.
- Increased clearance in young children, and even more in neonates.

- Good penetration to the lungs and abdominal organs.
- Concentrations achieved in the CSF are low at usual doses but appear to increase with increasing dose. A dose of 10mg/kg/day in neonates resulted in similar drug exposure with that required to treat *Candida* meningo-encephalitis (CME) *in vivo*.
- No dose adjustment required for patients with renal impairment or mild to moderate hepatic impairment.

Efficacy

- Efficacious in the treatment of invasive candidiasis in children, including neonates.
- May also be used as prophylaxis against invasive candidiasis or aspergillosis in haematological patients.

Toxicity

- Generally well tolerated; elevation of liver enzymes, infusion-related reactions, and rash have been reported, rarely necessitating discontinuation of treatment.
- Limited drug interactions; levels of sirolimus, nifedipine, and itraconazole increased with micafungin.

Anidulafungin

Spectrum of action

- Similar to other echinocandins.

Pharmacology

- Available only as IV formulation.
- Extensively (>99%) bound to human plasma proteins.
- No renal or hepatic metabolism; anidulafungin undergoes slow chemical degradation.
- Linear pharmacokinetics at the doses studied.
- No dose adjustment required for patients with hepatic or renal impairment.
- Administration of 0.75 and 1.5mg/kg/day of anidulafungin in children results in systemic exposure comparable to adults receiving 50 and 100mg/day, respectively.

Efficacy

- There are no paediatric efficacy data for anidulafungin; currently not approved for children.
- In adults, it has been efficacious in the treatment of invasive candidiasis, mainly in non-neutropenic patients.

Toxicity

- Very limited data for paediatric patients.
- Generally well tolerated; in adults, increased levels of hepatic enzymes, anaphylactic reactions, and infusion-related reactions have been observed.
- No significant drug interactions, as anidulafungin is not metabolized through CYP450 enzymes.

Future research

Well-designed studies of pharmacokinetics, safety, and efficacy are still needed for infants and young children, for some of the recently introduced antifungal agents, in order to guide appropriate dosing and indications for use. As the number of eligible paediatric patients to be recruited is expected to be limited, the establishment of paediatric networks and multicentre collaboration is of utmost importance for the implementation of such studies.

Further reading

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Chapter 3

Antiparasitics

Introduction

Antiparasitics are medicines indicated for the treatment of parasitic diseases. Such infections may broadly be divided into single-celled protozoa or helminths (worms) which are multicellular organisms.

Antiparasitic agents may be used in disease prevention (i.e. prophylaxis), control, and treatment, notably against malaria (see Chapter 87).

Protozoal diseases include amoebiasis and malaria. Diseases caused by worms may be due to gastrointestinal (e.g. roundworms and tapeworms) or systemic parasites (e.g. filaria and schistosomes).

While there are numerous antimalarial agents in clinical use or under development, the same tends not to be true for anthelmintics, as diseases caused by worms attract relatively less attention, often to the point of neglect.

However, there are a number of broad-spectrum agents effective against GI nematodes. Three of the most widely used are albendazole/mebendazole, ivermectin, and praziquantel.

Life cycles of helminths are complex, but most do not reproduce within the human host. This means that each individual parasite is the result of a separately acquired infection.

Children are particularly susceptible to GI infections caused by parasites, and this chapter will focus principally on treatments for such diseases. However, it should be remembered that treatment recommendations are often empirical or merely extrapolated from observations in adults.

The prevalence and intensity of infection with soil-transmitted helminths tend to be low in children aged <24 months, but there is accumulating evidence that severe and recurrent infections may have a detrimental effect on growth and development.

The World Health Organization (WHO) recommends that children as young as 12 months, originally excluded from de-worming programmes, should be treated, bearing in mind the relatively low toxicity of many of the available drugs and the positive outcome of risk–benefit analyses. For young children with intestinal worms, the health benefits of treating geo-helminthic infections include reduced likelihood of growth stunting and improved nutritional and cognitive outcomes.

Anthelmintic drugs

Anthelmintics can be divided into a variety of classes, dependent upon their chemistry and pharmacology. There are three broad-spectrum drugs in routine usage, i.e. albendazole (a benzimidazole), ivermectin (a macrocyclic lactone and one of the avermectins), and praziquantel (a pyrazinoisoquinolone).

Recent interest has focused on nitazoxanide, an analogue of metronidazole. This drug has a wide spectrum of activity against parasites (both protozoa and helminths) and viruses and presents an exciting new development in an area where there have been relatively few breakthroughs.

Note that the doses given in Table 3.1 refer to those recommended for children, except when there is no information available. However, in these cases, the drug in question has proven safe with minimal toxicity.

Table 3.1 The utility and recommended dosages of major anthelmintics

Helminth	Available drugs	Recommended dosage
Nematodes (GI)		
Ascaris lumbricoides	**Mebendazole**	(a) 100mg twice daily for 3 days, or (b) a single dose of 500mg
	Albendazole	400mg single dose
	Ivermectin	50–400 micrograms/kg single dose
	Piperazine	(See text)
Enterobius vermicularis	**Mebendazole**	Single dose of 100mg, repeated 2 weeks later, if needed
	Piperazine	(See text)
	Albendazole	400mg single dose
Hookworm		
• *Ancylostoma duodenale*	**Albendazole**	400mg single dose
• *Necator americanus*	Mebendazole	(a) 100mg twice daily for 3 days or (b) a single dose of 500mg
Trichuris trichiura	**Mebendazole**	(a) 100mg twice daily for 3 days or (b) a single dose of 500 mg
	Albendazole	400 mg for 3 days
Nematodes (systemic)		
Onchocerca volvulus	**Ivermectin**	150 micrograms/kg single dose with re-treatment at 6–12 months
Strongyloides stercoralis	**Ivermectin**	200 micrograms/kg daily for 2 days

(*Continued*)

Table 3.1 (*Contd.*)

Helminth	Available drugs	Recommended dosage
Wuchereria bancrofti	**Diethylcarbamazine**	6mg/kg single dose (see text)
	Albendazole	400mg single dose (in combination with either ivermectin (200 micrograms/kg) or diethylcarbamazine (6mg/kg))
	Ivermectin	150 micrograms/kg single dose with re-treatment at 6–12 months
Cestodes		
Taenia solium/saginata	Albendazole	400mg single dose
	Niclosamide	0.5 (<10kg) or 1g (10–25kg) orally single dose
Taenia solium (cysticercosis*)	Praziquantel	50–100mg/kg/day in three doses for 30 days
	Albendazole	7.5mg/kg twice daily for 8–30 days
Diphyllobothrium latum	**Praziquantel**	5–10mg/kg single dose (>4 years)
	Niclosamide	40mg/kg as single dose
Trematodes		
Clonorchis/Opisthorchis	Praziquantel	75mg/kg in three doses over 24 hours (see text)
Fasciola	Triclabendazole	10mg/kg administered as single dose after food (see text)
Fasciolopsis	Praziquantel	75mg/kg in three doses over 24 hours (see text)
Paragonimus	Praziquantel	75mg/kg in six doses over 2 days (see text)
Schistosoma haematobium	Praziquantel	20mg/kg initially, then 20mg/kg after 4–6 hours
Schistosoma mansoni	Praziquantel	20mg/kg initially, then 20mg/kg after 4–6 hours
Schistosoma japonicum	Praziquantel	20mg/kg initially, then two further 20mg/kg doses at 4- to 6-hour intervals

*Treatment with antiparasitic drugs is controversial, and trials have not been conclusive. They may cause irreparable damage if used to treat ocular or spinal cysts (even when corticosteroids are used). Check for ocular and spinal cysts before considering treatment (see Chapter 78, Infectious helminthiasis causing multisystem disease).

The note 'see text' may indicate that there is no specific paediatric recommendation, and the dosage is extrapolated from adult experiences where the drug has proven safe and effective. In other cases, it can be assumed that there is a specific paediatric dosage that has been identified through clinical experience.

Benzimidazoles

Thiabendazole was the first drug in this class to be described, and subsequently other benzimidazoles were introduced, notably mebendazole and albendazole.

There is an extensive clinical literature on these compounds, emphasizing their utility in a variety of GI and systemic diseases.

Their anthelmintic efficacy relates to their ability to interfere with the functions of the cytoskeleton through a highly selective interaction with parasitic β-tubulin.

Albendazole[a]

- Albendazole is the most important and clinically useful member of the benzimidazole class. Originally a veterinary product, it was first approved for human use in 1982.
- A single 400mg oral dose is usually recommended for clearance of gastrointestinal nematodes (i.e. *Ascaris, Trichuris* hookworm (*Ancylostoma* and *Necator*), and *Enterobius*) from children over 2 years of age. Fasting or purging is not required.
- Additional or more frequent dosage may be necessary in certain conditions, e.g. *Taenia* spp., and systemic infections such as *Strongyloides* and *Echinococcus*. This may relate to the relatively low bioavailability and rapid metabolism of albendazole. In children >2 years, albendazole (400mg) can be given once or twice daily for 3 days, and repeated after 3 weeks, if necessary. For *Echinococcus*, albendazole is given to children (>2 years) in a dosage of 7.5mg/kg (maximum 400mg) twice daily for 28 days, followed by a 14-day break, and then repeated for up to 2–3 cycles.
- Although albendazole has not been fully evaluated in children <2 years of age, no adverse effects or biochemical abnormalities were noted in children aged 9–23 months.

Mebendazole

- Mebendazole is used mainly in the treatment of intestinal parasite infections. Its main therapeutic indications are threadworms, roundworms, and whipworms.
- The most widely recommended dose regimens of mebendazole for the elimination of GI nematodes in children over 2 years of age are (a) 100mg twice daily for 3 days or (b) a single dose of 500mg.
- Tablets may be chewed, swallowed, or crushed and mixed with food. Additional or more frequent dosage may be advised in certain conditions, and fasting or purging is unnecessary.
- At therapeutic doses, the bioavailability of mebendazole tablets is only 1–2%. The low bioavailability is due to both the poor solubility of this formulation and an extensive first-pass metabolism in the liver.
- Mebendazole has not been fully evaluated and is unlicensed in children under 2 years of age, but it was well tolerated by children under 2 years given a dose of 500mg. Adverse effects were no higher in the week following treatment than in a placebo group.
- Mebendazole is recommended for the treatment of threadworms in children over 6 months of age.

Triclabendazole[b]

- Triclabendazole is a narrow-spectrum benzimidazole originally introduced into veterinary practice in 1983 for the treatment of fascioliasis, and was first used for this condition in humans in 1986. Its main therapeutic indication is *Fasciola* and *Paragonimus*.
- While most benzimidazoles have broad-spectrum anthelmintic activity, they exhibit minimal or no activity against *Fasciola hepatica*.
- The anthelmintic activity of triclabendazole is highly specific for *Fasciola* spp. and *Paragonimus* spp., with little activity against nematodes, cestodes, and other trematodes.
- The recommended dose of triclabendazole for the treatment of human fascioliasis is a single dose of 10mg/kg administered after food. In severe infection, a second identical dose is recommended 12 hours later. There are no specific recommendations for children.

Diethylcarbamazine[a]

- Diethylcarbamazine was shown to be an effective chemotherapeutic agent in 1947; yet its mechanism of action remains to be defined.
- While diethylcarbamazine is the drug of choice for the treatment of lymphatic filariasis and loiasis, it is no longer indicated in onchocerciasis due to a potentially fatal post-treatment reaction and the availability of ivermectin.
- Like its parent piperazine, diethylcarbamazine has some activity against the major intestinal nematode parasites of man. However, of the intestinal helminths, the roundworm *Ascaris* is the only one susceptible to diethylcarbamazine. Benzimidazoles offer a superior alternative.
- In filariasis, to minimize reactions to treatment in children over 1 month, treatment is started with a dose of diethylcarbamazine citrate of 1mg/kg in divided dosages on the first day, and increased gradually over 3 days to 6mg/kg daily (3mg/kg if <10 years) in divided dosages. The length of treatment varies according to infection. Heavy infection may lead to a febrile reaction, and, in *Loa loa*, there is a tiny risk of encephalopathy.
- It should be noted that single-dose therapy of 6mg/kg is effective in community-based therapy of lymphatic filariasis and is as effective as previously used higher multiple dosages. While such regimens may not result in total or rapid clearance of microfilaraemia, levels of microfilariae and the prevalence of infection are similar 12 months post-dose.

Ivermectin[a]

- Ivermectin (22,23-dihydroavermectin) is a semi-synthetic derivative of a family of macrocyclic lactones called avermectins, originally isolated from the soil-dwelling actinomycete *Streptomyces avermitilis*. Its main therapeutic indications are onchocerciasis (river blindness) and strongyloidiasis.
- Ivermectin is active against most nematodes, including onchocerciasis and strongyloidiasis. It can also be used in combination with diethylcarbamazine or albendazole for the treatment of lymphatic filariasis.

- It is usefully active against *Ascaris, Trichuris*, intestinal *Strongyloides*, hookworm (*Ancylostoma* and *Necator*), and *Enterobius* in single doses of 50–400 micrograms/kg.
- Ivermectin causes an influx of chloride (Cl^-) ions through the cell membrane of invertebrates by activation of specific ivermectin-sensitive ion channels, with a resultant hyperpolarization muscle paralysis.
- Ivermectin is a gamma-aminobutyric acid (GABA) agonist, but it does not cross the blood–brain barrier so has no central effects in humans.
- In children >5 years, ivermectin is generally administered as a single doses of 150 micrograms/kg for the treatment of human filariasis, with re-treatment at 6–12 months, dependent upon symptoms.
- Ivermectin given to children >5 years in a dose of 200 micrograms/kg daily for 2 days may be the most effective treatment for chronic strongyloidiasis.

Praziquantel[b]

- Praziquantel shows broad-spectrum activity against most trematodes, except *Fasciola*. Its main therapeutic indication is schistosomiasis where it is active against all major species.
- Other praziquantel-sensitive trematodes include *Clonorchis, Opisthorchis, Paragonimus, Metagonimus*, and *Heterophyes*. Praziquantel also shows useful activity against cestodes, including *Taenia, Hymenolepis*, and *Diphyllobothrium*. There are no specific recommendations for using praziquantel against cestodes in children, but the drug is considered safe.
- The exact mechanism of action of praziquantel is unknown, but an antiparasitic antibody response is required. Resistance to praziquantel is the subject of intense debate, and the position is currently unresolved.
- For liver, lung, and intestinal flukes, the adult dosage is 75mg/kg in 3–6 doses over 1–2 days, but there are no specific recommendations for children. For *Schistosoma haematobium* and *Schistosoma mansoni*, the suggested dose for children >4 years is 20mg/kg initially, followed 4–6 hours later by a further dose of 20mg/kg (20mg/kg three times daily for *Schistosoma japonicum*).
- Praziquantel is considered safe in children over the age of 2 years. It should be taken with food and plenty of water to prevent gagging or vomiting due to its bitter taste. The tablets can be divided but should not be chewed.

Other anthelmintic agents

Levamisole[a]

- Levamisole is a useful alternative to the benzimidazoles in roundworm infections, i.e. *Ascaris*.
- Levamisole appears to act by disrupting neuromuscular transmission in the nematode by causing sustained depolarization of the muscle membrane, resulting in paralysis of the worm.
- A single oral dose of 2.5–3.0mg/kg body weight (maximum 150mg) of levamisole is used for both individual treatment (1–18 years of age) and community-based campaigns. In severe hookworm infection, a second dose may be given after 1 week.

Niclosamide[a]

- Niclosamide is highly effective against various tapeworm infections such as those caused by *Taenia saginata* (beef tapeworm), *Taenia solium* (pork tapeworm), *Diphyllobothrium latum* (fish tapeworm), and *Hymenolepis nana* (dwarf tapeworm).
- Niclosamide acts as an oxidative phosphorylation uncoupler, thereby blocking the uptake of glucose by intestinal tapeworms, resulting in their death.
- Niclosamide is administered in tablets, which should be chewed thoroughly before swallowing and washed down with a small amount of water. When niclosamide is given to children, the tablet should be pulverized and then mixed with water.
- While niclosamide is given to adults orally as a single dose of 2g, children weighing 10–35kg are given a single dose of 1g orally. Those weighing <10kg are given a single dose of 0.5g orally.
- Niclosamide is not active against the larval form (cysticerci) of *T. solium* infection. Many recommend the use of laxatives, following treatment with niclosamide, to avoid any risk of acquiring cysticercosis through internal or external autoinfection. However, others believe them to be unnecessary, except in patients who are chronically constipated.
- Arguments against the use of laxatives in tapeworm infections include increased risk of autoinfection as a result of vomiting (internal) or passage of frequent and watery stools with increased risk of faecal contamination or hand soiling (external), dehydration, and electrolyte imbalance.
- For *H. nana* infection, treatment should be continued for 7 days. An initial dose of 2g is given orally on the first day, followed by 1g daily for the next 6 days.
- Niclosamide is considered safe, with minor GI upset the only issue.

Piperazine

- The anthelmintic activity of piperazine is restricted to *Ascaris* and *Enterobius*. Its main use is for threadworms in young infants (3–6 months).
- Piperazine causes flaccid paralysis of *Ascaris lumbricoides*. It is an agonist at extra-synaptic GABA receptors, causing an influx of Cl^- ions.
- Piperazine is available as a hydrate (750mg/5mL or 4g/30mL as citrate). In children 3 months to 1 year of age, a single level spoonful is given as a single dose in the morning and repeated after 2 weeks. For children 1–6 years, a level 5mL spoonful should be given.
- Dosages for *Ascaris* are the same as *Enterobius* but may be repeated monthly for up to 3 months if infection recurs.

[a] These drugs are unlicensed in the United Kingdom (UK) and only available from 'special-order' manufacturers or specialist importing companies (see *BNF for Children, BNFC*).

[b] These drugs are unlicensed in the UK and only available from the manufacturer.

Further reading

BNF for Children. Available at: http://www.bnf.org/bnf/org_450055.htm.

The Medical Letter. Available at http://secure.medicalletter.org/.

Yu VL, Edwards G, McKinnon PS, Peloquin C, Morse GD, eds. *Antimicrobial therapy and vaccines, volume II: antimicrobial agents*, second edition. Pittsburgh: ESun Technologies, LLC, 2005. Available at: http://www.antimicrobe.org.

Chapter 4

Antivirals

See also Chapters 14, 19, 46, 57, 62, 64, 75, 76, 79, 98, 107.

Introduction

The development of antiviral compounds has followed the improved understanding of the processes of viral replication and host–virus interactions. This knowledge has aided drug development by identifying viral or host-specific targets for antivirals at all time points of the viral life cycle: entry, uncoating, genome replication, protein synthesis, assembly, maturation, and release. The number of antiviral compounds available has greatly increased over the past 25 years, concurrent with significant developments in virology and genomic amplification techniques, and driven by an increased population of immunosuppressed patients highly susceptible to viral infections. In particular, those infected with HIV or immunosuppressed for treatment of malignancy or other conditions.

Host–virus interactions in the normal and immunocompromised host

Viruses can only replicate by using the host cell machinery. Thus, eradication of the viral infection may also lead to loss of the infected cell. Many viral infections are trivial or completely asymptomatic in the immunocompetent but can be devastating in those with immunodeficiency, e.g. cytomegalovirus (CMV) infections. Other viral infections are usually symptomatic but, in most hosts, cause minor symptoms, which are self-limiting, e.g. infections caused by rhinoviruses. Viruses that establish latency within the host after 1° infection, such as the herpesviruses, may only later cause symptoms, e.g. if they reactivate during a subsequent period of host immunosuppression. Families of viruses, such as the hepatitis viruses, may be rapidly cleared from some hosts after initial infection but, in others, go on to cause chronic infections that can lead to long-term organ damage, and even malignancy (e.g. hepatocellular carcinoma (HCC) with hepatitis B). Chronic virus infections, e.g. with retroviruses such as HIV, may only cause clinical symptoms after many years of viral replication that eventually lead to dysfunction of the host immune system and susceptibility to opportunistic infections.

Antiviral strategies appropriate for all these different types of infection are constantly being refined. More than one antiviral agent, acting at different points in the replicative life cycle, may be required to completely suppress viral replication (e.g. triple therapy for HIV), or the antiviral agent may

require to be supported by immune modulation with antibody or cytokine therapy (e.g. ribavirin with interferon (IFN) which used to be the standard of care for hepatitis C treatment).

RCT data confirming treatment efficacy are available for the commonest treatment regimes, but, for rare infections, clinical case series data may be all that are available.

Mechanisms of antiviral action

Antiviral compounds may act at many different stages along the viral replication cycle. Some require chemical activation by viral enzymes, and others by host cell enzymes. Thus, many antivirals can have significant side effects on host cells. The schema in Fig. 4.1 is a summary model of antiviral actions that can be adapted for each virus, its host cell, and its antiviral treatments.

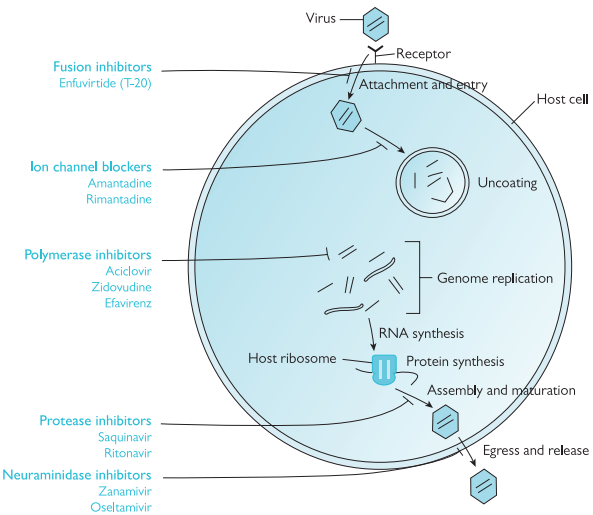

Fig. 4.1 A composite picture of potential sites of antiviral action along the replicative pathway of different viruses in an infected host cell.

(Kindly reproduced with permission, Fig. 14.1 from Knipe DM, Howley PM, Griffin DE, Lamb RA, Martin MA, Roizman B, eds. *Fields' Virology*, 5th edn. Philadelphia, PA: Lippincott Williams & Wilkins, 2007.)

Sites of antiviral action

Prevention of viral entry, absorption, and penetration

- *Maraviroc* blocks the CD4 cell surface CCR5 co-receptor for HIV, thus inhibiting viral entry to the cell.
- *Enfuvirtide* (T20) inhibits viral cell fusion, mimicking a homologous region in gp41, the HIV surface glycoprotein responsible for the fusion event.
- *Amantadine/rimantadine* block the influenza A M2 protein. The M2 protein is a viral transmembrane protein that functions as an ion channel, enabling the process of viral uncoating, so that viral nucleic acid can be transported to the host cell nucleus.
- *Pleconaril* binds to a pocket of the capsid (coating) of enteroviruses and rhinoviruses, and prevents virus attachment and uncoating.
- *Myrcludex-B: following the identification of the NTCP as the hepatitis B virus (HBV) entry receptor, inhibits viral entry. This class of antivirals is expected to significantly add to the armamentarium against HBV.*

Inhibition of viral genome replication

- *Aciclovir* is a guanine nucleoside analogue which is mono-phosphorylated by the thymidine kinase encoded by herpes simplex virus (HSV) and varicella-zoster virus (VZV), and then di- and tri-phosphorylated by host cellular kinases. The active compound aciclovir-triphosphate competes with the natural nucleoside guanine to bind to the viral DNA polymerase, and this terminates the elongation of the viral DNA—aciclovir is an obligate 'DNA chain terminator'.
- *Ganciclovir* is another guanine nucleoside analogue with activity against CMV. It is activated to the triphosphate GCV-TP form by HSV thymidine kinases and CMV protein kinases encoded by the viral *UL97* gene, as well as cellular kinases. It is both a substrate and a competitive inhibitor of the viral polymerase. However, ganciclovir is not an obligate 'chain terminator' like aciclovir and can inhibit cellular polymerases as well as the CMV polymerase. It is not as selective as aciclovir and is therefore more toxic (see ➔ Antiviral drug toxicity, p. 41–2).
- *Cidofovir* is a phosphonate-containing cytosine analogue so does not require the initial viral phosphorylation step, but it depends on cellular kinases to convert it to its active form. Although cidofovir can be taken up by both infected and non-infected cells, the viral DNA polymerase has a 25–50 × greater affinity for the molecule, compared with the host cell enzyme. Cidofovir is not a DNA 'chain terminator' but rather slows the elongation of the chain. It is effective against all the herpesviruses, as well as other DNA viruses such as adeno- and poxviruses.
- *Zidovudine, lamivudine, abacavir* (and others) are nucleoside analogues that are phosphorylated by cellular kinases and inhibit the reverse transcriptase enzyme of HIV. Lamivudine and the closely related drug emtricitabine are also effective against HBV.
- *Foscarnet* directly inhibits the DNA polymerase of all herpesviruses by binding to the site occupied by pyrophosphate. It is about 100 × more active against viral, than host cell, DNA polymerase. It is also effective against HIV reverse transcriptase.

- *Nevirapine, efavirenz*, and *etravirine* are non-nucleoside molecules that inhibit the reverse transcriptase of HIV.
- *Ribavirin* is a guanosine nucleotide analogue; it is phosphorylated to its active forms by cellular kinases. The mechanism of action is not well understood. Ribavirin has a wide spectrum of antiviral activity against both RNA and DNA viruses.
- *Direct-acting antivirals (DAAs) for hepatitis C virus (HCV). Polymerase NS5B inhibitors (i.e. sofosbuvir and dasabuvir). NS5a inhibitors (i.e. ledipasvir, daclatasvir, and ombitasvir).*

This is a fast-evolving area, and numerous compounds, in combination even as a single pill, are expected in clinical practice. Doses and the optimal time to treat children have not yet been defined.

Prevention of integration with host cell genome

- *Raltegravir and dolutegravir* block HIV integrase, the enzyme integrating viral linear DNA to the host cell genome. They therefore inhibit provirus formation.

Prevention of viral assembly and release

- *Lopinavir, ritonavir, darunavir* (and others) are protease inhibitors that disrupt maturation, an essential step for the production of infectious HIV virions.
- *Zanamivir and oseltamivir* are neuraminidase inhibitors that target the neuraminidase enzyme of influenza A and B. Inhibition of this enzyme prevents sialic acid cleavage and release of the viral particles from the cell membrane.
- *DAAs for HCV. Protease inhibitors that inhibit the maturation step: second generation protease inhibitors like simeprevir, paritaprevir, and simeprevir for genotype 1,4 infections.*

Combined antiviral effects

- *Type 1 IFNs* (α and β) are secreted by all nucleated cells after viral infection. IFN β is produced mainly by white blood cells (WBCs), and IFN α by fibroblasts. RNA viruses are more susceptible to IFNs than DNA viruses. The cellular effects of IFNs are mediated indirectly by >20 effector proteins. All elements of the viral replication cycle can be blocked including: cell entry, uncoating, messenger RNA (mRNA) synthesis, viral protein translation, assembly, and release. The main effects differ according to the virus and the viral families.

Families of viruses and their most appropriate treatments

Specific antiviral treatments exist for some, but not all, infections; these, in some cases, may also be augmented by additional interventions, e.g. IV immunoglobulin. See Table 4.1 and Table 4.2 for the most effective recommended treatments for infections with DNA and RNA viruses. For more details on individual conditions, see the specific infection chapters.

Table 4.1 DNA viruses and recommended treatments

Virus family	Antiviral drugs	Other treatments
Variola (smallpox)	Limited data—no human studies Cidofovir may be effective	Urgent vaccination of contacts may prevent or modify disease
Molluscum contagiosum	Topical or systemic cidofovir	Physical disruption (e.g. cryotherapy) Chemical disruption (e.g. topical podophyllin) Immune modulation (e.g. topical imiquimod)
Vaccinia virus	Limited data—no human studies Cidofovir may be effective	
HSV 1 and 2	Aciclovir/valaciclovir Famciclovir/penciclovir Foscarnet Cidofovir	
VZV	Aciclovir/valaciclovir Famciclovir/penciclovir Foscarnet Cidofovir	Varicella-zoster immunoglobulin as prophylaxis in selected populations
CMV	Ganciclovir/valganciclovir Foscarnet Cidofovir	Maribavir CMX001 recently shown to prevent CMV disease in transplant recipients
EBV	Ganciclovir/valganciclovir Foscarnet Cidofovir	Rituximab as anti-B-cell treatment or anti-EBV cytotoxic T-cell infusions for post-transplant lymphoproliferative disorder
Human herpesvirus 6 and 7	Ganciclovir/valganciclovir Foscarnet Cidofovir	
Human herpesvirus 8	Ganciclovir/valganciclovir Foscarnet Cidofovir	Augmentation of immunity (e.g. treating concurrent HIV infection) Chemotherapy for Kaposi's sarcoma
Adenoviruses	Cidofovir Ribavirin	IVIG
Human papillomaviruses		Excision/laser/cryotherapy/electrocautery Chemical disruption (e.g. topical podophyllin) Immune modulation (e.g. topical imiquimod) Intralesional IFN

(*Continued*)

Table 4.1 (*Contd.*)

Virus family	Antiviral drugs	Other treatments
JC and BK viruses		Augmentation of immunity (e.g. treating concurrent HIV infection) or reducing immunosuppression
HBV	Lamivudine[a] Adefovir/tenofovir[a] Entecavir	IFN α Entry inhibitors in development
Human parvovirus		IVIG

[a] May be used for those infected with HIV plus HBV.

CMV, cytomegalovirus; EBV, Epstein–Barr virus; HBV, hepatitis B virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; IFN, interferon; IVIG, intravenous immunoglobulin; VZV, varicella-zoster virus.

Table 4.2 RNA viruses and recommended treatments

Virus family	Antiviral drugs	Other treatments
Rotaviruses		IVIG
Togaviridae, e.g. Chikungunya virus		Avoid mosquito exposure
Yellow fever virus		IFN IVIG
West Nile virus	Ribavirin	IFN IVIG
HCV	Protease and polymerase inhibitors with or without ribavirin	IFN α—might still be used due to cost of DAAs
Rubella virus		
Coronaviridae, e.g. SARS	Ribavirin/lopinavir/ritonavir	IFN
Parainfluenza viruses	Ribavirin	
Mumps virus		
Respiratory syncytial virus	Ribavirin	Palivizumab—passive monoclonal antibody protection for specific vulnerable hosts (e.g. premature infants born <26 weeks)
Human metapneumovirus	Ribavirin	

(*Continued*)

Table 4.2 (*Contd.*)

Virus family	Antiviral drugs	Other treatments
Measles SSPE	Ribavirin	Vitamin A (in countries with morbidity/mortality from measles) IMIG, IVIG SSPE—IFN, isoprinosine
Rabies virus	A combination of sedation and immune modulation/ribavirin has been proposed but not universally followed	Post-exposure prophylaxis vaccine Human rabies immunoglobulin
Influenza viruses	Oseltamivir Zanamivir Amantadine (only effective against influenza A)	
Ebola and Marburg		
Lassa virus	Ribavirin	
Lymphocytic choriomeningitis virus	? Ribavirin	
Human T-cell lymphotrophic viruses	Nucleoside analogue reverse transcriptase inhibitors Protease inhibitors	
HIV	Nucleoside analogue reverse transcriptase inhibitors Non-nucleoside reverse transcriptase inhibitors Protease inhibitors Integrase inhibitors Fusion inhibitors Co-receptor inhibitors Fixed combinations (i.e. tenofovir/FTC/efavirenz or tenofovir/FTC/rilpivirine)	
Polioviruses	Pleconaril (n/a)	IVIG
Enteroviruses	Pleconaril (n/a)	IVIG
Hepatitis A virus		Vaccine for post-exposure prophylaxis
Rhinoviruses	Pleconaril (n/a)	IFN α
Caliciviruses, e.g. noroviruses		
Hepatitis E virus	Ribavirin in chronic cases	

DAA, direct-acting antiviral; FTC, emtricitabine; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; IMIG, intramuscular immunoglobulin; IVIG, intravenous immunoglobulin; SARS, severe acute respiratory syndrome; SSPE, subacute sclerosing panencephalitis.

Treatment dose recommendations of many antiviral drugs for neonates, infants, and children are often based on very small cohort studies of treated individuals. With the considerable changes in renal, hepatic, and gut function during growth and development, the doses are not always adequately optimized, especially those for infants. Maximizing doses is important for antiviral effect, but this must be balanced with the need to minimize potential toxic effects. The most up-to-date dosing schedules should be used (see *BNFC* or the drug information leaflet), and, if appropriate, drug levels may also be measured, e.g. for aciclovir or ganciclovir. Caution is required in interpreting serum levels of drugs that act principally at the intracellular level. Drug level monitoring is also an essential part in the follow-up of combination therapy, e.g. in HIV infections, to ensure adherence, safety, and efficacy.

Development of resistance to antiviral agents

Ongoing viral replication in the presence of antivirals promotes emergence of mutant viruses that are less sensitive to the drug treatment. Therefore, treatment must be optimized to achieve maximal viral suppression. Drug resistance is most problematic in relation to long-term treatment of persistent infections, including herpesviruses, HIV, and hepatitis. This is particularly a problem for infections caused by HIV and HCV, both RNA viruses exhibiting high turnover of infectious particles, with viral polymerases that lack proofreading ability and a consequent significant spontaneous mutation rate. Effective therapy of HIV depends on combination antiretroviral therapy (ART) that belongs to different classes. Inadequate treatment with sequential exposure to different drugs leads to complex drug resistance patterns. Molecular assays, as well as phenotypic and gene sequence databases, have been developed to aid the interpretation of ART resistance provided by expert clinical virologists (e.g. the *Stanford HIV Drug Resistance Database*, available at <http://hivdb.stanford.edu/>).

Drug resistance should always be suspected when there is lack of virological response with good adherence/absorption or evidence of viral rebound. Poor adherence to treatment makes the development of resistance more likely. Table 4.3 lists the patterns of viral drug resistance and alternative treatments.

Table 4.3 Patterns of viral drug resistance and alternative treatments

Antiviral drug	Mechanism of resistance	Clinical manifestation of resistance	Possible alternative treatments
Aciclovir/ valaciclovir Famciclovir/ penciclovir	Usually due to mutations in the HSV/VZV thymidine kinase gene, which lead to loss of enzyme activity (TK mutants), so that the active drug form is not produced. Rarely due to mutations in the viral DNA polymerase gene	Usually occurs in immunosuppressed patients on long-term suppressive therapy (e.g. post-BMT or those with AIDS). They may get more frequent HSV or VZV, recurrences often with increased severity, e.g. in the central nervous system	Foscarnet Ganciclovir Cidofovir
Ganciclovir/ valganciclovir	Reduced intracellular phosphorylation due to mutation of the CMV *UL97* gene, or due to mutations in the viral polymerase (*Pol*) *UL54* gene	Usually occurs in immunosuppressed patients on long-term suppressive therapy (e.g. post-BMT or those with AIDS). They get more frequent CMV recurrences, often with increased severity, e.g. in the eye	Foscarnet Cidofovir *Pol* mutants are resistant to famciclovir/ cidofovir *UL97* mutants are not
Cidofovir	Mutations in the viral DNA polymerase gene	Only very rarely reported	
Foscarnet	Mutations in the viral DNA polymerase gene	Only very rarely reported	
Amantadine	Mutations in the influenza A ion channel M2 gene Does not work for influenza B	May be found in treated individuals within 48h—uncertain clinical relevance	Oseltamivir Zanamivir
Oseltamivir	Neuraminidase mutations may occur after 4 days of treatment	Primary infection with oseltamivir-resistant strains has occurred—clinically similar to wild-type infection	The guidance varies, depending on susceptibility of seasonal/ epidemic strains Amantadine (for influenza A)

(*Continued*)

Table 4.3 (*Contd.*)

Antiviral drug	Mechanism of resistance	Clinical manifestation of resistance	Possible alternative treatments
Zanamivir	Neuraminidase and/or haemagglutinin mutations may cause reduced sensitivity	Occurs in immunosuppressed patient on >2 weeks of treatment, with persistent viral shedding	The guidance varies, depending on susceptibility of seasonal/epidemic strains Amantadine (for influenza A)
Lamivudine (for treatment of HBV) (should not be given as monotherapy for HBV due to high risk of resistance) (Can be used as part of combination ARV for patients with HIV plus HBV)	Commonest mutations affect the YMDD motif in the catalytic domain of the HBV polymerase (common mutations: rtM204V/I and rtL180M)	Occur in 42–70% of individuals treated for 2–5 years with lamivudine monotherapy Associated with HBV rebound	Adefovir Tenofovir Entecavir (not preferred for lamivudine-treated patients, unless necessary and no mutations) Patients already on lamivudine should receive add-on therapy with adefovir or tenofovir, not switch
Entecavir (for treatment of HBV) (must not be used for patients with HIV plus HBV)	L180M + M204V/I ± I169T ± V173L ± M250V or L180M + M204V/I ± T184G ± S202I/G	Rare in naive patients, but may occur in individuals who already have lamivudine mutations (requires three mutations). Resistance occurs in 0% and 1.2% at years 1 and 5, respectively	Tenofovir
Adefovir (for treatment of HBV) (must not be used for patients with HIV plus HBV)	Common polymerase mutations: rtN236T, rtA181T, rtA181V	Resistance occurs in 0%, 3%, 11%, 18%, and 29% at years 1, 2, 3, 4, and 5, respectively	Usually as add-on for patients already on lamivudine Entecavir

(*Continued*)

Table 4.3 (*Contd*.)

Antiviral drug	Mechanism of resistance	Clinical manifestation of resistance	Possible alternative treatments
Tenofovir (for treatment of HBV) (can be used as part of combination ARV for patients with HIV plus HBV)	Common polymerase mutations: rtN236T confers intermediate resistance to tenofovir	No resistance seen at 2 years	Entecavir
Ribavirin	Clinically significant viral resistance has not been observed		
ARVs	Complex patterns of ARV class-related resistance develop when full HIV suppression is not achieved		

AIDS, acquired immune deficiency syndrome; ARV, antiretroviral; BMT, bone marrow transplant; HBV, hepatitis B virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; VZV, varicella-zoster virus.

Antiviral drug toxicity

The serious side effects of some antiviral treatments mean that often these drugs are only used in critical situations such as to treat severely immunosuppressed patients. Over time, it is hoped that less host toxic drugs with equal or greater antiviral effect will emerge.

- *Aciclovir, valaciclovir* (prodrug of aciclovir with increased oral absorption): IV aciclovir may cause reversible renal toxicity when administered to patients who are poorly hydrated. Accumulation of aciclovir in such patients may also cause reversible neurotoxicity. High-dose IV aciclovir used to treat neonates may cause reversible neutropenia. Oral aciclovir may cause mild GI upset. To date, aciclovir has not been found to be teratogenic in humans.
- *Ganciclovir, valganciclovir* (prodrug of ganciclovir with increased oral absorption): IV ganciclovir causes reversible myelosuppression, with neutropenia in up to 40% of patients who receive the drug. This effect can be mitigated by the use of granulocyte colony-stimulating factor (G-CSF). Toxicity tests have demonstrated that ganciclovir is mutagenic, carcinogenic, and teratogenic in animals, so it is treated as a cytotoxic drug within the clinical setting. Close monitoring for such toxicities in humans is essential, and this drug should only be used when it is considered that benefits outweigh these potential risks. Oral valganciclovir (which causes less neutropenia, but also hepatitis) is now also available for children and may be used as continuation after IV use or as prophylaxis for CMV infection in the severely immunocompromised.

- *Cidofovir*: IV cidofovir has a long intracellular half-life and can be dosed weekly. Cidofovir is highly concentrated in the renal tubules, with a significant risk of nephrotoxicity, so treatment must be preceded by hyper-hydration, and the dose titrated to the renal function. Carcinogenic and teratogenic effects, as well as hypospermia, have been demonstrated in animal studies.
- *Foscarnet*: this causes severe, but reversible, nephrotoxicity in up to half of patients; the dose must be titrated to the renal function. Renal toxicity is often associated with other metabolic derangements of calcium, magnesium, and phosphate; this is aggravated by concomitant treatment with other nephrotoxic agents (e.g. amphotericin and aminoglycosides). CNS side effects and bone marrow suppression may also occur.
- *Ribavirin*: in low doses, ribavirin may cause haemolytic anaemia and, in high doses, anaemia due to bone marrow suppression. These effects do not occur with aerosolized treatment (e.g. for respiratory syncytial virus (RSV) bronchiolitis). Ribavirin has been demonstrated to be teratogenic and embryo-lethal in animals so is contraindicated for pregnant women.
- *Oseltamivir*: this may cause GI upset which is usually mild.
- *Zanamivir*: this may cause bronchospasm when administered by inhalation.
- *Pleconaril*: this has minimal side effects but unfortunately production currently is on hold.
- *IFN*: side effects are dose-related. Immediately after administration, flu-like symptoms with fever, myalgia, and headache are very common. In the longer term, after several weeks of therapy, depression or other neuropsychiatric effects, as well as bone marrow suppression, may occur. When used in combination with ribavirin, bone marrow toxicity must be monitored very closely. Pegylated IFN has a longer half-life and can be dosed less frequently; it also has less severe side effects.
- *ARVs*: the different families of ARVs have numerous side effects, and interactions with each other and other classes of drugs; these are important, as the ARVs must always be used in combination with each other to achieve sufficient potency for full HIV suppression. More details of side effects, toxicity, and interactions can be found at the Penta-ID website (<http://www.pentatrials.org>).

Future research

- Improved antiviral formulae for children, especially for better absorbed oral preparations.
- Development of treatment for severe manifestations of enterovirus infection (e.g. neonatal infection, myocarditis, encephalitis).
- Development of less toxic treatments for herpesvirus infections.
- Better understanding of host genetics (including metabolism and immune function) and how they affect responses to viruses, as well as antiviral treatments.

Further reading

Knipe DM, Howley PM, Griffin DE, Lamb RA, Martin MA, Roizman B, eds. *Fields virology*, fifth edition. Philadelphia: Lippincott Williams & Wilkins, 2007.

Chapter 5

Antimicrobial stewardship

Introduction

Antibiotic resistance threatens the remarkable health benefits achieved by antibiotics worldwide. WHO has identified antibiotic resistance as one of the major threats to human health. The Centers for Diseases Control and Prevention (CDC) estimates that, in the US, >2 million antibiotic-resistant infections occurred every year, with at least 23 000 people dying as a result. Resistance leads to inappropriate empirical therapy, delay in starting effective treatment, and the use of less effective, more toxic, and more expensive drugs, leading, in turn, to increased morbidity, mortality, and costs.

The overuse and misuse of antibiotics over recent decades has resulted in an unprecedented selection pressure that has made almost all disease-causing bacteria resistant to many of the antibiotics commonly used to treat them. Pharmaceutical development that previously kept us ahead of resistance is currently slow, with drugs for only two new antimicrobial targets (linezolid and daptomycin) introduced since 1998. As a result, reducing unnecessary antimicrobial use is now recognized as a global priority by prescribers, administrators, and the public. Yet, antibiotics continue to be misused in hospital and community settings. The neonatal and paediatric antimicrobial point prevalence survey of the Antibiotic Resistance and Prescribing in European Children project (ARPEC) revealed that almost half of hospitalized children received at least one antimicrobial during the survey date. With almost 50% of antimicrobial use estimated to be inappropriate, maintaining the effectiveness of currently available agents for as long as possible is an absolute priority. The most effective way of doing this is through prudent use of antibiotics or antibiotic stewardship.

Antimicrobial stewardship programmes (ASPs) are a coordinated set of interventions designed to monitor and direct antimicrobial use at health care institutions, providing a standard evidence-based approach to judicious antimicrobial use. Thus, ASPs ensure that every patient gets the right antibiotic only when needed, by the right route, at the right dose, and for the right duration.[1]

What are the goals of antimicrobial stewardship programmes?

- Improve patient outcomes.
- Optimize patient safety; e.g. decreasing *C. difficile* infections or adverse drug reactions.

- Reduce resistance, and preserve existing and future antimicrobial agents.
- Decrease or control costs without compromising the quality of medical care.

Antimicrobial stewardship programme models

ASPs may be generally classified, according to the core strategy by which they seek to affect antimicrobial use (Fig. 5.1, Table 5.1).[2]

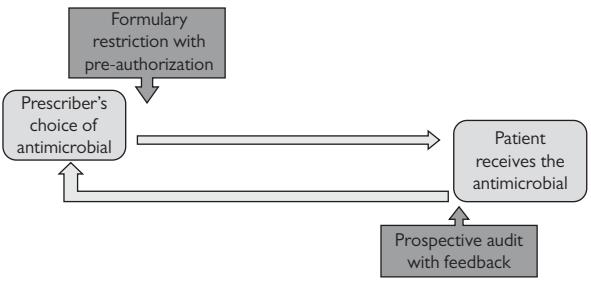

Fig. 5.1 ASP core strategy.

Published data support the role of either intervention in improving antimicrobial utilization and decreasing costs; yet there is still no consensus as to which strategy is better. The implementation of prospective audit interventions have been reported to be most successful in institutions with previously established ASPs based on formulary restriction with pre-authorization of select agents.

Each institution can use either of these types of interventions, based on local practices, resistance trends, and available resources. For instance, when resources are more constrained, some institutions might elect to classify antibiotic use as:

I. Unrestricted agents: dispensed by pharmacy for any indication
II. Controlled agents: dispensed for a limited period of time without prior approval (48–72 hours), but, when prolonged duration is desired, an automatic stop-order alerts physicians that authorization by an infectious diseases (ID) physician/clinical pharmacist should be obtained
III. Restricted agents: only available through prior approval.

Table 5.1 General classification of ASPs

Formulary restriction with pre-authorization of selected agents	Prospective audit with feedback to prescribers
Require clinicians to obtain ASP approval prior to initiating antibiotics	*Programmes review selected antibiotics and provide feedback to clinicians after a predetermined time (i.e. 48–72 hours)*
Most direct method of influencing antibiotic utilization and containing cost	Allows ASP time to gather more clinical information for feedback and has less impact on prescriber's autonomy
Hospital formularies need to be continuously updated in response to changes in local susceptibility patterns or new drug availability Can be labour-intensive, as approver must be available to provide immediate, real-time service to prevent delays in starting therapy Restriction strategies, when used alone, do not consider the appropriateness of prescribing non-restricted antimicrobials, losing an opportunity for education A challenge is to avoid paradoxical increases in use of other drug classes	Targets inappropriate continuation of therapy (more frequent than inappropriate initiation of therapy) by: 1. streamlining/de-escalation of therapy (selection of an agent with narrowest spectrum of coverage) 2. discontinuation of empiric therapy for diseases that do not require antimicrobial therapy (i.e. flu) 3. Dose optimization (i.e. extended infusion of β-lactam to treat higher MIC pathogens, extended-interval aminoglycoside dosing) 4. IV to oral conversion for highly bioavailable drugs 5. recognizing organism and antimicrobial mismatch 6. recognizing drug–drug interactions 7. undertaking therapeutic monitoring

Main antimicrobial stewardship programme strategies to improve antimicrobial use

See Table 5.2 for the key stakeholders to initiate and sustain ASP.

1. Appropriate and prompt initiation of antimicrobial therapy.
2. Appropriate selection of antimicrobials.
3. Appropriate administration and de-escalation of antimicrobial therapy.
4. Use of available expertise and resources at the point of care.
5. Continuous and transparent monitoring of antimicrobial use data.

Table 5.2 Who are the key stakeholders to initiate and sustain ASPs?

Participants	Role	Barriers
Clinical pharmacist	Develops the day-to-day activities	Clinical pharmacist trained in infectious diseases are scarce
Microbiology laboratory	Provides institution's antibiogram; aids clinicians interpreting patient's microbiology data	Uptake of new biotechnology-based tests, increasing centralization of lab services, shortage of skilled workers
Paediatric infectious diseases specialists	Provide clinical guidance Create institutional guidelines Promote education	Time constraints ASP ≠ infectious diseases consultation
Infection control and hospital epidemiologist	Expertise in surveillance and control of spread of antimicrobial-resistant organisms	Time constraints
IT specialists	Monitoring medication ordering and administration	Requires technological support
Prescribers	Antibiotic champions in different specialties can support and reiterate ASP recommendations	Lack of knowledge about antibiotics (i.e. newer = better) Decision-making autonomy Reluctance to change behaviour Patients' expectations
Hospital administration	Without positive endorsement by hospital administration, ASPs are unlikely to be implemented and to achieve compliance	Limited financial resources Institutional policy Physician autonomy

Other antimicrobial stewardship programme strategies

1. *Education*: this is recognized as the cornerstone of any ASP. However, there is little agreement as to what constitutes an optimal education programme. Passive approaches (posters or newsletters) are easy to implement, but, if not combined with more active approaches (academic updates), they are only marginally effective in changing antimicrobial prescribing practices and do not have sustained effects.
2. *Development of peer-reviewed clinical antibiotic prescribing guidelines*: useful in streamlining decision-making processes for clinicians. Must be continuously reviewed and updated. Adaptation of national

guidelines to local circumstances and collaboration with hospital specialists may improve compliance by promoting ownership. Their dissemination needs also to be combined with other educational approaches to increase adherence.

3. *Computer-assisted programs*: provide doctors with information, advice, and feedback concerning individual patients, antibiotics, and drug-related side effects. Unfortunately, these require sophisticated software so are not widely available. Antimicrobial orders forms are also an effective way to approve certain antibiotics for documented infections (e.g. vancomycin and ceftriaxone for bacterial meningitis) or by individual medical services (e.g. bone marrow transplant unit), but not for general use.

How to measure the outcomes of antimicrobial stewardship programmes

Like any other quality improvement intervention, it is essential to evaluate the programme's impact, including the possibility of negative unintended consequences. Documenting specific and measurable outcomes from ASP efforts to achieve its goals are urgently needed, as studies reporting only a reduction in antimicrobial use do not provide direct outcome data. Common variables related to antimicrobial usage are described in Table 5.3. All of these are a problem. There is no single accepted way of measuring antimicrobial use for children in hospital. Days of therapy really require e-prescribing, which is still not common across Europe. There is no accepted paediatric defined daily dose (DDD) method as yet. The Serial Point Prevalence Surveys of antimicrobial use may be helpful to demonstrate changes in condition-specific patterns of use.[3]

Table 5.3 How to measure the outcomes of ASPs

Process measures	Outcome measures
Quantity of total antimicrobial use*	Change in resistance rates
Quantity of targeted antimicrobial use	Antimicrobial drug expenditures
% oral versus IV drug administration	Length of stay, readmission rates
Length of therapy ('LOT')	*C. difficile* rates, adverse drug events
Adherence to clinical guidelines	Time to appropriate therapy

* The relationship between the amount of antimicrobial use and appropriateness of antimicrobial use is not known. Measurement of antimicrobial use can rely on:

- Daily dose (DDD); the usual daily dose for adults as defined by WHO; represents a poor estimate for children
- Days of therapy (DOT); one DOT refers to the administration of a single agent at least once that day; overemphasizes appropriate multidrug regimens. DOT/LOT can be used to complement DOT.

Current state of paediatric antimicrobial stewardship programmes

Initial ASP efforts were centred on adult patient populations. Although the key structural components of ASPs in paediatrics should be the same as for adults, important differences may exist in the types of agents and endpoints that are monitored. Adoption of ASPs in children's hospitals has accelerated over the past few years as a means to limit antimicrobial resistance and improve quality of care. In a recent US survey, ~40% of free-standing children's hospitals had an established ASP (more than half implemented after 2008), and another 35% were in the planning stages of implementing an ASP.

Neonatal units (*NNUs*) provide unique challenges for ASPs. Signs and symptoms of infections in infants are non-specific; cultures are sometimes not feasible to obtain, and treatment guidelines are often not established. Nevertheless, interventions to improve antibiotic stewardship have been successfully implemented in neonatal wards. Restricting the use of cephalosporin agents in neonatal intensive care units (NICUs) has been associated with a reduction in colonization with MDR Gram-negative bacteria or invasive candidiasis. Decreasing vancomycin use has been shown to be an important controlling factor in controlling vancomycin-resistant *Enterococcus* (VRE).

Chronic diseases, such as cystic fibrosis, or haemato-oncology also present distinct challenges. Providers' perceptions that their patients are intrinsically different and not represented by clinical guidelines are a common barrier for guideline implementation. Collaborative efforts between paediatric ID specialists and departmental opinion leaders, along with continuous education efforts, are recommended to achieve sustained behavioural changes.[4]

Future challenges

With the rise in antibiotic-resistant infections and limited new agents in the foreseeable future, the implementation of ASPs at all health-care facilities need to be prioritized. The optimal implementation and monitoring of paediatric ASPs need considerably more research.

Key references

1 Dellit TH, Owens RC, McGowan JE, *et al*. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis* 2007;**44**:159–77.

2 McGowan JE Jr. Antimicrobial stewardship—the state of the art in 2011: focus on outcome and methods. *Infect Control Hosp Epidemiol* 2012;**33**:331–7.

3 Tamma PD, Cosgrove SE. Antimicrobial stewardship. *Infect Dis Clin North Am* 2011;**25**:245–60.

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Chapter 6

Bacterial meningitis

See also Chapters 14, 28, 69, 70, 86, 105, 112.

Introduction

- Meningitis is inflammation of the meninges, although the arachnoid and pia mater are also usually inflamed, i.e. leptomeningitis.
- Most cases are culture-negative, i.e. aseptic meningitis, and are usually caused by viruses.
- Meningitis due to encapsulated bacteria has become less frequent since the introduction of highly effective conjugate vaccines against *N. meningitidis, S. pneumoniae*, and Hib since the 1990s.
- *The priority is prompt diagnosis and treatment of bacterial pathogens.*

Causative organisms

Bacterial meningitis

The predominant bacteria responsible vary, depending on age:

- *Neonates (<1 month)*: Group B Streptococcus (GBS) (50–60% of bacterial cases), *E. coli* (15–20%), other Gram-negative organisms (10%), *S. pneumoniae* (6%), *Listeria monocytogenes* (5%)
- *1–3 months*: GBS, *E. coli, S. pneumoniae, N. meningitidis*
- *>3 months: N. meningitidis, S. pneumoniae*, Hib.

Aseptic meningitis

- Characterized by CSF pleocytosis (raised white cell count, WCC) and raised protein, with absence of microorganisms on Gram stain and routine culture.
- Viruses are the commonest cause, most frequently enteroviruses. Other viral causes include parechoviruses, mumps, HSV, CMV, EBV, VZV, adenoviruses, HIV, measles, rubella, influenza, parainfluenza, and rotavirus.
- Other infectious causes of aseptic meningitis include:
  - Partially treated bacterial meningitis
  - Non-pyogenic bacteria, e.g. *Mycobacteria, Leptospira, Treponema pallidum, Borrelia, Nocardia, Bartonella*, and *Brucella*
  - Atypical organisms, e.g. *Chlamydia, Rickettsia*, and *Mycoplasma*
  - Fungi, e.g. *Candida, Cryptococcus, Histoplasma*, and *Coccidioides*
  - Protozoa and helminths, e.g. roundworms, tapeworms, flukes, amoebae, and *Toxoplasma*.

Epidemiology and the impact of vaccines

Bacterial meningitis

(Also see Chapters 70, 86, and 105.)

Neisseria meningitidis

- Peak incidence of meningitis occurs in children aged 6 months to 2 years, with a second smaller peak at 15–19 years.
- The incidence of meningococcal disease across Europe is 5–10 per 100 000 per year in children <5 years, with high rates in the UK and Ireland; 60–90% have meningitis, with or without septicaemia.
- The majority of disease in Europe is caused by serogroup B and C organisms. The serogroup C conjugate vaccine (introduced in the UK in 1999 and subsequently across Europe) resulted in a 10-fold reduction in the incidence of serogroup C meningococcal disease.
- Serogroup B organisms now cause 85–90% of cases in the UK. An outbreak caused by a new clone of serogroup W meningococci caused a rapid increase in cases from 2009.
- A new MenB vaccine was licensed in Europe, Canada, and Australia in 2013, and in 2015 was introduced in the UK. Another MenB vaccine has also been licensed in the US.
- Due to an increase in serogroup W in the UK an ACWY conjugate vaccine was introduced for adolescents in 2015 which also acts as a booster for MenC.
- Serogroup Y accounts for a substantial proportion of cases in North America. The ACWY conjugate vaccine is given to adolescents in the US.
- Epidemics in Africa are usually associated with serogroup A, and more recently serogroups W and X. A MenA conjugate vaccine has been in use in the meningitis belt of sub-Saharan Africa since 2010.

Streptococcus pneumoniae

- The peak incidence of invasive pneumococcal disease (IPD) is in children <2 years.
- In Europe, the incidence of pneumococcal meningitis was 1–8 cases per 100 000 per year in children <5 years prior to the widespread use of the 7-valent pneumococcal conjugate vaccine (PCV7).
- PCV7 contains polysaccharides from serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. The 10-valent vaccine PCV10 also covers serotypes 1, 5, and 7F. PCV13 includes these serotypes plus 3, 6A, and 19A. Higher valency conjugate vaccines are currently undergoing clinical trials.
- PCV7 was introduced into the routine UK immunization schedule in 2006, and replaced with PCV13 in 2010.
- Following the introduction of PCV7 in the UK and prior to the use of PCV13 in children <2 years:
  - The incidence of IPD decreased by 56% overall, from 54 per 100 000 per year to 24 per 100 000 per year
  - There was a decrease in PCV7-serotype IPD of 98%
  - The incidence of PCV7-serotype IPD was 0.9 per 100 000 per year, and of non-PCV7-serotype IPD was 23 per 100 000 per year
  - The commonest serotypes were 14, 6B, and 19F prior to the widespread use of PCV7 and 7F, 19A and 1 afterwards, all of which are included in PCV13.

- Two years after the introduction of PCV7 for vaccination of 'high-risk' children in France, there was a 39% reduction in the incidence of pneumococcal meningitis in all children <2 years.

Haemophilus influenzae type b

- Most Hib disease occurs in children <5 years.
- Before the use of Hib conjugate vaccines, the incidence of invasive Hib disease in Europe was 12–54 per 100 000 per year in children <5 years; ~60% had meningitis.
- Most European countries implemented routine Hib conjugate vaccination between 1992 and 1996, leading to >90% reduction of disease in all countries.
- From 1999, there was a resurgence in the number of cases in the UK, predominantly in children aged 1–4 years. In 2003, a further catch-up campaign occurred, and a routine booster dose was introduced into the immunization schedule in 2006, resulting in a decrease in disease.

Neonatal bacterial meningitis

- The incidence of bacterial meningitis has been 0.2–1 per 1000 live births in developed countries since the 1980s.
- Up to 30% of neonates with sepsis have associated bacterial meningitis.
- Vaccines to prevent GBS disease are currently undergoing phase 2/3 clinical trials.

Aseptic meningitis

- ~85–90% of children presenting with meningitis in the highly immunized populations of developed countries will have aseptic meningitis.
- The epidemiological pattern depends on the causative pathogen, which is often not identified because of incomplete diagnostic investigation.
- ~85% of cases where the aetiology is known are due to enteroviruses, which are commoner in summer and autumn in temperate climates.
- In a study in Finland, the annual incidence of viral meningitis was 219 per 100 000 in infants <1 year, and 27.8 per 100 000 in all children <14 years.
- The incidence of viral meningitis in neonates is ~0.05 per 1000 live births.
- Most tuberculosis (TB) cases in the UK occur in non-UK-born children (37 per 100 000 per year versus 2.5 per 100 000 per year), especially those born in Africa and those of South Asian ethnic origin, and rates of disease are increasing in these groups.
- TB meningitis has been reported in up to 6% of children with TB disease and is commonest in those <6 years. It usually occurs 2–6 months after the initial infection and is associated with miliary TB in 50% of cases.
- Fungal meningitis is usually associated with immunocompromised hosts and neonates.

Predisposing factors

- Young age.
- ♂ sex.
- Malnutrition or chronic illness.
- Recent head trauma, neurosurgery, or presence of a ventriculo-peritoneal shunt.

- Local anatomical defects.
- Close contact with:
  - A colonized carrier (*N. meningitidis, S. pneumoniae*, Hib)
  - An individual with disease (*N. meningitidis*, Hib, TB, viruses, rarely *S. pneumoniae*)
  - An individual with a sputum-positive smear (TB)
  - Certain animals (e.g. reptiles—*Salmonella*, domestic animals—*Listeria*).
- Environmental factors:
  - Household exposure to tobacco smoke
  - Household overcrowding.
- Consumption of unpasteurized dairy products in pregnancy (*Listeria*).
- Swimming in water contaminated by urine from infected animals (*Leptospira*).
- Recent tick bite (*Borrelia, Rickettsia*).
- Lack of immunization (mumps, Hib, *S. pneumoniae, N. meningitidis*).
- Immunosuppression:
  - Deficiencies in terminal complement components (*N. meningitidis*)
  - Hyposplenism, e.g. post-splenectomy, congenital asplenia (*S. pneumoniae, H. influenzae*)
  - Immunosuppressive drugs (fungi, TB)
  - Hypogammaglobulinaemia (enteroviruses)
  - HIV infection (*S. pneumoniae*, CMV, HSV, VZV, fungi, TB, *Toxoplasma*)
  - Defects in cell-mediated immunity (fungi, TB, CMV, HSV, VZV).
- Sickle-cell disease (*S. pneumoniae*, Hib, *Salmonella*).
- Malignant neoplasia.
- Risk factors for TB include:
  - Travel to an area with a high incidence of TB
  - Belonging to an ethnic minority originating from areas with a high incidence of TB.
- Risk factors for neonatal fungal infection include:
  - Prematurity (gestational age <32 weeks)
  - Very low birthweight (<1500g)
  - Prolonged intubation or indwelling vascular devices
  - Parenteral nutrition and delayed enteral feeding
  - Treatment with broad-spectrum antibiotics, corticosteroids, or H2-receptor blockers.

Clinical presentation

- *The classical manifestations of meningitis present in older children are rarely present in infants and young children.*
- Usually begins with fever, nausea and vomiting, photophobia, and severe headache. Occasionally, the first sign is a seizure, which can also occur later. Irritability, delirium, and altered level of consciousness develop, as CNS inflammation progresses.
- The most specific signs are neck stiffness, associated with Kernig's and Brudzinski's signs. These are often absent in children:
  - Kernig's sign—inability to fully extend the knee while the hip is flexed due to contraction of the hamstring muscles and pain
  - Brudzinski's sign—automatic flexion of the hips and knees after passive neck flexion.

- Focal neurological abnormalities may occur. In the absence of seizures, they indicate cortical necrosis, occlusive vasculitis, or venous sinus thrombosis.
- In infants and young children, symptoms are non-specific and include fever or hypothermia, poor feeding, vomiting, lethargy, irritability, jaundice, respiratory distress or apnoea, and seizures. A bulging fontanelle may be present.
- Additional manifestations tend to be associated with specific organisms:
  - Petechiae and purpura (*N. meningitidis*, possibly Hib or *S. pneumoniae*)—the rash may be blanching
  - Leg pain, cold extremities, abnormal skin colour, and shock (*N. meningitidis*)
  - Joint involvement (*N. meningitidis*, Hib)
  - A chronically draining ear or history of head trauma (*S. pneumoniae*)
  - Pleurodynia, herpangina, or unexplained rashes (enteroviruses)
  - Chronic symptoms (TB, fungi).
- Bacterial and viral meningitis cannot be reliably distinguished on clinical features alone; however, children with bacterial meningitis are more likely to have shock, seizures, an altered conscious level, and neck stiffness, compared to those with viral meningitis.
- TB meningitis can be staged on the basis of clinical features:
  - Stage 1—no reduced conscious level or focal neurological signs
  - Stage 2—reduced conscious level and/or focal neurological signs
  - Stage 3—coma.

Differential diagnosis

- Other CNS infection—encephalitis, intracranial abscess (cerebral, subdural, or epidural).
- Generalized sepsis from another focus.
- Leukaemia and solid CNS tumours.
- Connective tissue disorders, e.g. systemic lupus erythematosus (SLE), Behçet's disease.
- Kawasaki disease.
- Sarcoidosis.
- Drugs and toxins, including IV immunoglobulin (IVIG) and heavy metals.

Investigations

Lumbar puncture

- CSF should ideally be obtained prior to commencing treatment (see Box 6.1 for contraindications), but initiation of antimicrobial therapy should not be delayed if an immediate lumbar puncture (LP) cannot be performed.
- CSF analysis by microscopy, Gram stain, culture, and polymerase chain reaction (PCR) is the definitive method of diagnosis. Biochemistry for protein and glucose (with a plasma glucose taken at the same time) should also be performed (Table 6.1).

Table 6.1 CSF WBC count and protein and glucose values in normal children and changes that occur with meningitis

	Macroscopic appearance	CSF WBC count (per microlitre)[a]	CSF neutrophil count (per microlitre)	CSF protein (g/L)	CSF glucose (% of plasma glucose)
Normal CSF					
Neonate	Clear and colourless	0–20[b]	0–4[b,c]	0–1.3	>60
>1 month		0–5	0[c]	0–0.4	60–70
Children with meningitis					
Bacterial meningitis	Turbid or purulent	↑↑↑[d]	↑↑↑[d]	↑↑↑	↓↓
Viral meningitis	Usually clear	↑[e]	N/↑[e]	N/↑	↓/N
TB meningitis	Yellow or cloudy	↑↑[f]	N/↑[f]	↑↑↑	↓
Fungal meningitis	Usually clear	↑[f]	N/↑[f]	↑↑	↓

[a] In the case of a traumatic LP (>500 red blood cells, RBCs), one WBC per 500 RBCs can be subtracted from the total CSF WBC count; in very heavily bloodstained CSF (>25 000 RBCs), the WBC count may be uninterpretable, even after adjustment.

[b] WBCs in neonatal CSF is predominantly lymphocytes, although neutrophils may be present.

[c] Some experts regard the presence of any neutrophils as being abnormal.

[d] CSF WBCs in bacterial meningitis are usually mostly neutrophils, although lymphocytes can be predominant in early disease.

[e] CSF WBCs in viral meningitis are usually mostly lymphocytes, although neutrophils can be predominant.

[f] In TB or fungal meningitis, the majority of CSF WBCs are lymphocytes.

Box 6.1 Contraindications to lumbar puncture

- Signs of raised intracranial pressure (ICP):
  - Reduced level of consciousness (Glasgow coma score <9)
  - Relative bradycardia and hypertension
  - Unequal, dilated or poorly responsive pupils
  - Abnormal 'doll's eyes' movements
  - Abnormal tone or posture
  - Respiratory abnormalities
  - Papilloedema[a]
  - Evidence of raised ICP on computerized tomography
- Abnormal focal neurological signs
- Following a prolonged convulsive seizure *or* within 30 min of a short convulsive seizure *or* following any tonic seizure[b]
- Cardiorespiratory instability
- Abnormal clotting studies (if available) or concurrent administration of anticoagulant therapy
- Severe thrombocytopenia (platelet count $<100 \times 10^9$/L)
- Extensive or extending purpura
- Localized infection at the site of LP

If contraindications are present, LP should be delayed and performed when contraindications are no longer applicable.

[a] Papilloedema is an uncommon finding in acute meningitis, and its presence should prompt consideration of venous sinus thrombosis, subdural empyema, or brain abscess.

[b] Prolonged: >30 min; short: ≤30 min.

- Optimum sample volumes: 1mL for glucose, protein, and lactate; 0.5–1mL for cell count, Gram stain, and bacterial culture; 1mL+ for viral PCR (diagnostic yield is increased by use of a dedicated collection tube, separate to that used for bacteriology).
- Any child in whom meningitis is suspected and any drowsy or ill infant should have an LP, in the absence of any contraindications (Box 6.1).
- CSF should be examined as soon as possible, because WBCs start to degrade after ~90min.
- Initial Gram staining of CSF reveals an organism in 60–80% of bacterial meningitis cases.
- It is uncommon for CSF values to be normal and a pathogen identified later, although this occurs most often in meningococcal meningitis (up to 10%), viral meningitis (up to 15–60% for enterovirus and 98% for parechovirus), and in neonates. Some experts therefore advise a repeat LP after 24–48 hours if there remains a high suspicion of bacterial meningitis.
- Consider alternative diagnoses in a seriously unwell child with normal CSF variables.
- CSF cultures are negative 2 hours after appropriate parenteral antibiotics are given in meningococcal meningitis, after 6 hours in pneumococcal meningitis, and after 8 hours in neonatal GBS meningitis.

- CSF cellular and biochemical changes persist at least 48–72 hours after the start of treatment.
- If TB meningitis is suspected, CSF staining for acid-fast bacilli and appropriate culture should be done.
- *Cryptococcus* can be diagnosed by India ink staining of CSF.

Cranial computerized tomography and magnetic resonance imaging

- *A scan should not delay the use of antimicrobial therapy.*
- *A normal computerized tomography (CT) scan does not mean it is safe to do an LP.* This decision should be based on clinical assessment. However, if a scan shows clear evidence of raised intracranial pressure (ICP), an LP should not be performed.
- The main indication for cranial imaging is when the diagnosis is uncertain or to detect other possible intracranial pathology.
- If neuroimaging is required, it should be undertaken urgently after stabilization of the child.
- While CT is widely available and very useful for rapid assessment of hydrocephalus, mass lesions, haemorrhage, or cerebral oedema, magnetic resonance imaging (MRI) will detect more subtle findings, particularly of vascular infarction.
- Non-contrast CT or MRI can be normal in early cases of meningitis.
- CT in cerebral oedema may show slit-like lateral ventricles, areas of low attenuation, and absence of basilar and suprachiasmatic cisterns.
- Signs of TB meningitis include obstructive hydrocephalus, basilar enhancement, and parenchymal granulomas and is abnormal in the majority of cases.
- Cryptococcal meningitis usually has non-specific abnormalities on CT. There may be signs of raised ICP, hydrocephalus, or focal lesions, especially in the basal ganglia.
- Neonatal *Candida* meningitis may result in cerebral micro- or macro-abscesses.

Other investigations

- All children with suspected meningitis should have:
  - Blood culture (positive in 80–90% of antibiotic-untreated children)
  - Blood for PCR
  - Full blood count (FBC), C-reactive protein (CRP), clotting, urea and electrolytes (U&Es), LFTs, glucose.
- Bacterial meningitis is likely in those with abnormal CSF parameters who have a significantly raised WBC count and/or CRP. If bacterial meningitis is suspected clinically and an LP has not been performed, children should be managed as such, regardless of blood results.
- A normal CRP and WBC count do not rule out bacterial meningitis.
- If TB meningitis is suspected, tests should include a chest X-ray (CXR), tuberculin skin test (TST) ± an interferon-gamma release assay (IGRA) (see Chapter 112).

Molecular techniques

- For *N. meningitidis*, PCR from blood has a sensitivity of 87% and a specificity of 100%.
- For *S. pneumoniae*, PCR is sensitive and specific on CSF, but false positive results may be obtained from blood due to the high nasopharyngeal carriage rate in young children.
- Rapid antigen latex agglutination tests on CSF or blood (which can be used to detect *N. meningitidis, S. pneumoniae, Hib, E. coli*, or GBS) can be done locally and rapidly, but the lack of sensitivity has limited their clinical use.
- CSF can be sent for PCR for possible viral aetiologies.
- If TB meningitis is suspected, prolonged culture is required, and CSF should be analysed by specific PCR if acid-fast bacilli are seen on microscopy. Automated diagnostic tests (such as GeneXpert®) allow rapid detection of *Mycobacterium tuberculosis* and identification of major rifampicin-resistance mutations and have been specifically aimed at use in resource-poor settings, although cost remains an obstacle for many.

Clinical decision rules

- Meningitis in developed countries is predominantly aseptic, so clinical decision rules have been developed since the introduction of the Hib conjugate vaccine to distinguish bacterial from aseptic meningitis, to reduce antibiotic and corticosteroid use and hospitalization.
- The 'Bacterial Meningitis Score' (BMS) is the only rule which has been sufficiently validated in a large number of children and classifies patients with CSF pleocytosis (WBC count >10 per microlitre) as very low risk of bacterial meningitis if they fulfil the following criteria:
  - Negative CSF Gram stain
  - CSF neutrophil count <1000 per microlitre
  - CSF protein <80g/L
  - Blood neutrophil count $<10 \times 10^9$/L
  - No seizure prior to presentation.
- In a meta-analysis of eight studies, this score had a negative predictive value of 99.7% (95% confidence interval (CI) 99.3% to 99.9%), but a specificity of only 62.1% (95% CI 60.5% to 63.7%).
- In a very large study, only 1.3% of children with a CSF WBC count <300 per microlitre had bacterial meningitis, increasing to 10% and 28% for those with a CSF WBC count >500 per microlitre and >1000 per microlitre, respectively.
- Studies of the BMS underestimated the overall prevalence of bacterial meningitis in children with CSF pleocytosis, because they excluded children with critical illness, purpura, immunosuppression, and previous antibiotic administration.
- Clinical decision rules need further validation, before they can be routinely implemented to guide treatment of children with suspected meningitis.

Management

- *Any child with suspected meningitis should be transferred to a hospital immediately.*
- *All children should be assessed for dehydration, shock, and raised ICP.*
- Many children, particularly those with meningococcal meningitis, will have coexisting septicaemia and shock. Standard resuscitation guidelines should be followed, with the expectation that prompt and adequate fluid resuscitation may be required.

Antimicrobial therapy

- For suspected meningococcal disease (presence of a purpuric or petechial rash), antibiotic therapy (Table 6.2) with parenteral benzylpenicillin is often given before admission to hospital and is recommended in the UK. There is no reliable evidence to support or refute this practice, and the priority of transfer to hospital should remain.
- In hospital, antibiotic therapy for suspected acute bacterial meningitis must be started immediately, before the results of CSF culture and antibiotic sensitivity are available:
  - Initiate antibiotics if the CSF WBC count is abnormal (Table 6.1)
  - Bacterial meningitis should still be considered if other clinical features are present, irrespective of the CSF WBC count.
- IV antibiotics are required to achieve adequate serum and CSF levels.
- Choice of empirical agent(s) should consider current local data regarding circulating pathogens and their antibiotic resistance patterns. Specific therapy may need to be adjusted, once a pathogen is cultured and antibiotic susceptibility results are available.
- The possibility of TB meningitis should be considered in all cases.

Table 6.2 Empirical and specific therapy for bacterial meningitis

Age group	Empirical therapy	Specific therapy
>3 months	Ceftriaxone or cefotaxime ± vancomycin	Ceftriaxone: 7 days for *N. meningitidis* 10 days for Hib 14 days for *S. pneumoniae* ≥10 days for unconfirmed organism
<3 months	Amoxicillin/ampicillin	GBS: ≥14 days cefotaxime/penicillin (± gentamicin for first 5 days)
	Plus cefotaxime (or ceftriaxone or meropenem)	Gram-negative organisms: 21 days CNS-penetrating antibiotic depending on sensitivities (usually cefotaxime or meropenem)
	± vancomycin	*Listeria*: 21 days amoxicillin/ampicillin, with gentamicin for first 7 days
	Consider aciclovir	No confirmed bacterial diagnosis: ≥14 days amoxicillin/ampicillin plus cefotaxime

Empirical therapy for children aged >3 months

- Monotherapy with a third-generation cephalosporin, e.g. ceftriaxone or cefotaxime (ceftriaxone is preferred as once-daily dosing):
  - Ceftriaxone has broad-spectrum activity against Gram-positive and Gram-negative organisms, is highly resistant to β-lactamases, and penetrates the blood–brain barrier well at higher doses
  - Neonatal deaths have been reported due to an interaction between ceftriaxone and calcium-containing products, so ceftriaxone should not be administered simultaneously with calcium-containing infusions. In this situation, cefotaxime should be used.
- In 2011, 15–20% of *S. pneumoniae* strains in Europe were not susceptible to penicillin, with 5–10% being not susceptible to cefotaxime/ceftriaxone. Highest rates of resistance were reported in Romania, Cyprus, and Poland. In regions where there is a high prevalence of resistance, or in children with recent prolonged or multiple exposure to antibiotics, or those who have recently travelled to an area with a high rate of pneumococcal resistance (including North America), adding vancomycin should be considered.

Specific therapy for children aged >3 months

- Specific therapy with ceftriaxone is recommended for convenience and cost-effectiveness of once-daily dosing. The duration of antibiotic therapy depends upon the infecting organism: 7 days for *N. meningitidis*, 10 days for *H. influenzae*, 14 days for *S. pneumoniae*.
- Treat unconfirmed, uncomplicated, but clinically suspected, bacterial meningitis with ceftriaxone for at least 10 days, depending on the clinical features and course.

Empirical therapy for children aged <3 months

- Amoxicillin/ampicillin (to cover *Listeria*) plus cefotaxime.
- Ceftriaxone may be used as an alternative to cefotaxime but should be avoided in infants who are jaundiced, hypoalbuminaemic, acidotic, or born prematurely, as it may exacerbate hyperbilirubinaemia. Ceftriaxone should not be administered at the same time as calcium-containing infusions.
- Vancomycin should be added for indications as mentioned.
- Consider meropenem, instead of cefotaxime, in settings with high rates of community-acquired ESBL-producing Gram-negative organisms.
- Add aciclovir if there is a possibility of HSV infection.

Specific therapy for children <3 months

- There are no controlled clinical trials to guide the duration of therapy.
- GBS: cefotaxime/penicillin should be continued for at least 14 days after initiation but should be extended to at least 3 weeks in complicated cases. Some authorities advise adding gentamicin for the first 5 days.
- Gram-negative organisms: cefotaxime should be given for 21 days, but this may be modified, based on local resistance patterns and sensitivities of the specific organism.
- *L. monocytogenes*: therapy is recommended for 21 days with amoxicillin, adding gentamicin for at least the first 7 days.

- Unconfirmed, but clinically suspected: administer amoxicillin/ampicillin plus cefotaxime for at least 14 days. If the course is complicated, consider extending the duration of treatment and consultation with an expert in paediatric infectious diseases.
- Repeat LP should be performed in neonates after 48–72h, only if there is worsening or no improvement of the clinical condition and/or laboratory parameters.

Specific therapy for aseptic meningitis

- TB meningitis: current UK guidelines recommend treatment with rifampicin, isoniazid, pyrazinamide plus a fourth drug (e.g. ethambutol) for the first 2 months, followed by rifampicin and isoniazid alone for a further 10 months.
- Fungal meningitis: infection of HIV-affected children with *Cryptococcus* or *Histoplasma* involves treatment with amphotericin, fluconazole, and flucytosine. Amphotericin and fluconazole are the agents of choice for neonatal *Candida* meningitis.

Corticosteroid therapy

- The use of corticosteroid therapy in bacterial meningitis remains controversial, principally because of the lack of data relevant to the post-conjugate vaccine era. There are no studies examining the use of steroids in aseptic meningitis, and guidelines emphasize the need to target steroid use to children who are most likely to have bacterial meningitis.
- *Children >3 months should receive corticosteroids if they have*:
  - Bacteria on CSF Gram stain
  - *And/or* a CSF WBC count >1000 per microlitre
  - *And/or* CSF pleocytosis and CSF protein >1.0g/L (consider the possibility of TB meningitis if the protein is very raised).
- Corticosteroids should ideally be administered before or with the first antibiotic dose, but they may be beneficial up to 12 hours later.
- Corticosteroids reduce meningeal inflammation and modulate cytokine secretion to reduce pro-inflammatory responses.
- In clinical trials, corticosteroids reduced the rate of severe hearing loss in childhood bacterial meningitis from 11.4% to 7.4%. The majority of children in these trials had meningitis due to Hib and a CSF WBC count >1000 per mm^3, but there was also a trend for better outcome in non-*Haemophilus* meningitis.
- Most studies used a 4-day course of 0.1–0.15mg/kg/dose four times daily of dexamethasone.
- The safety of corticosteroids in aseptic or neonatal meningitis has not been adequately addressed.
- For children in low-income countries, the use of corticosteroids is not recommended, as there is no evidence of benefit.
- Children with TB meningitis should receive corticosteroids for 2–3 weeks, followed by gradual withdrawal.

Ongoing fluid management

- *Fluid therapy should be guided by clinical assessment of the hydration status, signs of raised ICP, and shock, combined with regular electrolyte measurements.*

- Both over- and underhydration are associated with adverse outcomes.
- Over 50% of children have hyponatraemia at presentation, attributed to increased concentrations of antidiuretic hormone (ADH), and this is a marker of severe disease. There are differing opinions as to whether hyponatraemia is due to dehydration or the syndrome of inappropriate antidiuretic hormone secretion (SIADH).
- Enteral fluids or feeds should be used, where appropriate, and isotonic fluid when IV therapy is required.
- After correction of dehydration, full maintenance fluid should be given to prevent hypoglycaemia and maintain electrolyte balance.
- In settings with high mortality and where children present late, full maintenance fluid therapy was associated with reduced spasticity, seizures, and chronic severe neurological sequelae. Where children present early and mortality rates are lower, there is insufficient evidence, so fluid restriction should not be employed routinely.
- If there is evidence of raised ICP or circulatory failure, initiate emergency management for these conditions, and discuss ongoing fluid management with a paediatric intensivist.

Other supportive treatment

- A possible need for management in a paediatric intensive care unit (PICU) setting should be considered.
- Adequate oxygenation.
- Treatment and prevention of hypoglycaemia.
- Anticonvulsant treatment for seizures.
- Reduction of raised ICP (treat if clinically evident or signs on CT scan):
  - 30° bed head elevation
  - Maintenance of normal pCO_2 through mechanical ventilation
  - Treatment with mannitol and furosemide.
- Children with severe sepsis will require circulatory support with inotropes.

Prevention of secondary cases

Local/national policies and experts should always be consulted due to variation in practice and regular policy changes as guidelines are updated in line with current data. The following summarizes UK policies (2014), but detailed guidance to cover all scenarios is beyond the scope of this book.

Neisseria meningitidis

- Chemoprophylaxis against meningococcal disease (usually with ciprofloxacin) should be given as soon as possible, and ideally within 24 hours of diagnosis, to:
  - Household members who have had prolonged close contact with the index case during the 7 days prior to illness onset
  - Those who have had transient close contact with the index case if they have been directly exposed to large particles or respiratory droplets/secretions (e.g. health-care workers).
- Once the serogroup is known, an appropriate meningococcal vaccine should also be offered to unimmunized close contacts.

Haemophilus influenzae type b

- Chemoprophylaxis against Hib disease is indicated up to 4 weeks after diagnosis if the index case is <10 years old or there is a vulnerable individual (immunosuppressed, asplenic, or <10 years of age) in the household. In such cases, rifampicin should be given to:
  - The index case
  - All household contacts if there is a vulnerable individual in the household.
- Following Hib disease, Hib immunization should be given to:
  - The index case if <10 years of age *and* incompletely immunized or convalescent antibody levels <1 microgram/mL or hyposplenic
  - All incompletely immunized children <10 years of age in the same household.

Mycobacterium tuberculosis

- Household contacts of a child with TB meningitis should be screened using a TST ± an IGRA, with further assessment, as indicated. Other close contacts should also be assessed for any child with smear-positive TB.
- Following contact with smear-positive TB:
  - All children <2 years should receive isoniazid, while screening tests are being performed
  - Children of any age should receive bacille Calmette-Guérin (BCG) if the Mantoux test is <6mm.

Group B *Streptococcus*

- Maternal intrapartum antibiotics for cases at high risk of neonatal GBS reduce early-onset GBS disease (first week of life) but have no effect on late-onset disease. Strategies for prevention vary between countries. Some countries have routine screening in late pregnancy and intrapartum prophylaxis for all who are GBS-positive, while others only give prophylaxis in the presence of specific risk factors (such as prolonged rupture of membranes, maternal fever during labour).

Outcomes

The outcome depends on multiple factors, including age, time and clinical stability prior to treatment, organism, and host inflammatory response.

Bacterial meningitis

- Early complications:
  - Seizures
  - SIADH
  - Subdural effusions in one-third, often asymptomatic with spontaneous resolution. They may manifest with enlargement of the head circumference, vomiting, seizures, bulging fontanelle, focal neurological signs, or persistent fever

  - Focal neurological abnormalities
  - Hydrocephalus, more often in younger infants
  - Venous sinus thrombosis
  - Brain abscesses, especially in newborns infected with *Citrobacter diversus* or *Proteus*
  - Vasculitis.
- Long-term complications (occur in 10–30% overall):
  - *Sensorineural hearing loss (SNHL)—all should have hearing screening after discharge*
  - Epilepsy
  - Motor and cognitive impairment
  - Blindness and optic atrophy
  - Learning and behavioural problems.
- In the developed world, case fatality rates are <10% overall and <5% for meningitis due to *N. meningitidis* or Hib.
- For neonatal bacterial meningitis, mortality is ~5–10% overall. Disability at 5 years is 50% for GBS and *E. coli*, and 78% following infection with other Gram-negative organisms.

Aseptic meningitis

- Full recovery is usual in uncomplicated viral meningitis, though there are few adequate studies, and neuropsychological sequelae can occur, including fatigue, irritability, reduced concentration, and muscle pain, weakness, or spasm. Some infants have an increased risk of delayed language development.
- HSV in neonates can result in severe neurological sequelae.
- TB meningitis has almost 100% survival in stage 1 disease, but only 80% in stage 3 disease, with significant long-term disability in survivors. Sequelae include hydrocephalus, blindness, deafness, motor and cognitive impairment, intracranial calcification, and diabetes insipidus.
- Invasive neonatal candidiasis has a mortality rate of around 30%.

Future research

- Prevention of neonatal GBS and *E. coli* infection through maternal vaccination.
- More sensitive microbiological tests for diagnosis in antibiotic-pretreated patients.
- Better blood and CSF biomarkers for the differentiation of bacterial from viral meningitis.
- Assessment of new antimicrobial agents against resistant pneumococcal strains.
- Benefit of corticosteroids in the era of widespread coverage of Hib, pneumococcal, and meningococcal serogroup C vaccine coverage, and in neonates.
- Further evidence regarding the risk or benefit from fluid restriction.

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Chapter 7

Bone and joint infections

Introduction

Empirical treatment of osteoarticular infection depends on the age of the child and the likely pathogen.

Pathophysiology

Osteomyelitis and septic arthritis

- Usually arises by haematogenous spread of bacteria, most commonly in the metaphyseal region of a larger bone.
- May be 2° to contiguous infection or due to direct inoculation.
- Acute septic arthritis (SA) may be an extension of osteomyelitis (OM) or by haematogenous spread seeding directly to the joint space without bone involvement.
- In neonates, bone infection affects the growth plate or joint in 76%.
- Discitis is an infection of the intervertebral disc space.

Osteomyelitis

- Haematogenous infection is the commonest, acute or subacute.
- Long bones are most often affected in children.
- Most unifocal; 5–20% multifocal.
- In neonates, OM is often multifocal with associated SA.

Septic arthritis

- Usually 2° to bacteraemia.
- The epiphyseal growth plate can be affected in young children.
- Permanent joint destruction can occur if treatment is not prompt.

Chronic recurrent multifocal osteomyelitis

- Rare inflammatory condition.
- Recurrent, sterile, lytic lesions.
- Often in the clavicle, humerus, and tubular bones.

Incidence

- Estimate: 5–12 cases per 100 000 children per year.
- Half of the children with acute OM are <5 years old.
- Boys are 1.2–3.7 times more likely to be affected by OM or SA than girls.

Aetiology

Neonates
- GBS, MSSA, *E. coli*/Gram-negatives, *C. albicans*.

<2 years
- MSSA, *Kingella kingae, S. pneumoniae*, GAS, non-typeable *Haemophilus* spp., *E. coli*, MSSA Panton–Valentine leucocidin (PVL) (uncommon in the UK), MRSA PVL (very rare in the UK).

2–5 years
- MSSA, GAS, *K. kingae*, GAS, *S. pneumoniae*, non-typeable *Haemophilus* spp., MSSA PVL (uncommon in the UK), MRSA PVL (very rare in the UK).

>5 years
- MSSA, GAS, MSSA PVL (uncommon in the UK), MRSA PVL (very rare in the UK).

Other much rarer organisms (consider in immunosuppressed children or other risk factors)
- Hib (unimmunized), CoNS (subacute), *Pseudomonas* spp., *Neisseria gonorrhoeae, N. meningitidis, M. tuberculosis, Salmonella* spp. (sickle-cell disease), *Bartonella henselae*, non-tuberculous mycobacteria (NTM), *Klebsiella* spp., *Fusobacterium* (often multifocal), *Aspergillus, C. albicans*.

Clinical features

Neonates
- Irritability, ± fever, widespread pain often difficult to localize on examination.
- Pseudoparalysis, erythema, bone or limb swelling. Several sites may be involved. (Note pseudoparalysis of the arm may be mistaken for delayed onset of Erb's palsy in late-onset GBS OM of the humeral head.)
- May be no focal signs, but unexplained sepsis or positive blood culture should warrant consideration of bone or joint infection.

Child
- Usually short history, with an ill child in pain.
- Fever frequent, but may be absent.
- Refusal to move the limb or to weight-bear, limp, erythema, bone or limb swelling, local tenderness.
- In SA, there is a unifocal hot, immobile, tender peripheral joint, with pain on passive joint movement.
- May have no focal signs.

Subacute or chronic osteomyelitis
- Longer history, may be weeks, with no systemic symptoms.
- Often no fever.
- Less acute local signs with limp, refusal to move the limb or weight-bear, local bony swelling or tenderness.

Discitis

- Insidious onset, no systemic illness, fever uncommon.
- Back pain; refusal to sit, stand, or walk.
- Refusal to flex the spine, local tenderness.
- Constipation or abdominal pain.

Chronic recurrent multifocal osteomyelitis

- Initially indistinguishable from acute/subacute OM.
- Histology non-specific.
- Pain may be severe, persistent, and debilitating.

Risk factors

- Trauma, sickle-cell disease, immunodeficiency, penetrating wounds, bone fixators or plates, varicella infection (GAS).

Differential diagnosis

- Trauma, including non-accidental injury, malignancy (osteosarcoma, leukaemia, neuroblastoma), reactive arthritis, haemarthrosis, Henoch–Schönlein purpura, juvenile idiopathic arthritis (JIA), TB.

Investigations and diagnosis

Blood tests

- CRP and erythrocyte sedimentation rate (ESR) are more reliably increased than WCC, but normal values do not absolutely exclude OM or SA (although osteoarticular infection is less likely if CRP and ESR are normal).
- Microbiological culture of blood (all cases), joint fluid (from aspiration), periosteal pus, or bone biopsy.
- Difficult cases may require molecular diagnostic techniques (e.g. 16S rDNA PCR, targeted multiplex PCR).

Imaging

- Plain radiographs are often unhelpful in acute presentations as osteolytic changes/periosteal elevation occur 10–21 days after the onset of symptoms. They are important as a baseline assessment to exclude trauma and in subacute presentations.
- Ultrasonography is useful for identifying deep effusions in SA and subperiosteal collections in OM.
- MRI with enhancement has the best diagnostic sensitivity and specificity.
- Technetium radionuclide bone scan (^{99m}Tc):
  - High sensitivity and specificity, but is now used rarely due to the radiation burden
  - May give false negative results in infancy.

Management

- Multidisciplinary, including paediatricians, orthopaedic surgeons, radiologists, and microbiologists.
- Little high-quality evidence to guide therapy, but established, consistent practice.

Surgical

- Often not required in OM with early radiographic signs.
- Surgical drainage in acute OM is indicated if no response to antibiotics after 48–72 hours or if radiological evidence of a substantial pus collection.
- Urgent washout and drainage of SA in hip, aspiration and irrigation in other joints, to reduce pressure on the growth plate.
- More aggressive surgical management if PVL MSSA or MRSA suspected or confirmed.
- Immobilize any surgically treated limb or focus of infection.

Medical

- Start empirical IV antibiotics on clinical diagnosis of acute OM or SA.
- In SA, start antibiotics following surgery, unless delay of >4 hours anticipated.
- *Use high doses*:
  - Neonates to <3 months: IV cefotaxime ± amoxicillin as in suspected sepsis/meningitis
  - ≥3 months to ≤5 years: IV cefuroxime monotherapy
  - ≥6 years: IV flucloxacillin or clindamycin monotherapy.
- Optimize antimicrobial treatment if organism is identified.
- In *simple unifocal disease*, a rapid switch to oral therapy may be appropriate:
  - Neonates to <3 months: consider IV to oral switch after 14–21 days if:
    —Afebrile plus pain-free for at least 24 hours, *and* CRP <20mg/L or CRP decreased by ≥2/3 of highest value
  - Child ≥3 months: consider IV to oral switch after 48–72 hours if:
    —Afebrile plus pain-free for at least 24 hours, *and* CRP <20mg/L or CRP decreased by ≥2/3 of highest value.
- When switching to oral antibiotics, dose, administration frequency, and palatability must be considered.
- Suggested pragmatic empirical oral antibiotic choices where organism remains unknown. Use high doses:
  - *Neonatal*: co-amoxiclav suspension three times daily
  - *1–2 months*: co-amoxiclav suspension three times daily
  - *2 months–2 years*: co-amoxiclav suspension three times daily
  - *2–5 years*: co-amoxiclav suspension three times daily
  - *6–8 years*: co-amoxiclav suspension three times daily or flucloxacillin four times daily (only if the child can take tablets)
  - *9–18 years*: flucloxacillin four times daily or clindamycin four times daily.

- Antibiotic therapy is continued for a total of 3–4 weeks in SA and 4–6 weeks in OM.
- Complex disease (multifocal, significant bone destruction, resistant/unusual pathogen, immunosuppressed, sepsis, or shock) requires prolonged IV antibiotic therapy, and the total length of antibiotic course may need to exceed 6 weeks. Treatment of complex disease should be managed in conjunction with experts in bone and joint infection.
- Prolonged IV therapy can be given in the community in some cases.
- If confirmed PVL-positive disease, use the latest guidelines from Public Health England (PHE; available at <https://www.gov.uk/government/organisations/public-health-england>.
- *Discitis*: antibiotics appear to speed resolution; length of therapy is usually 4–6 weeks.
- *Chronic recurrent multifocal OM*: use simple analgesia and non-steroidal anti-inflammatory drugs (NSAIDs); refer to paediatric rheumatologist if alternative or experimental therapies are considered necessary.

Outcome

- Most children with simple disease are discharged without long-term care or further assessment of growth or function.
- Significant risk of deep venous thrombosis and thromboembolism in children with OM.
- In severe diseases, risk of joint stiffness, limb shortening, dislocation (acutely neonates), and avascular necrosis of affected epiphysis.

Future research

- The optimal duration of therapy is unknown, and shorter treatment courses should be studied in randomized clinical trials.
- The safety of early oral switching in OM and SA should be further investigated in randomized clinical trials.

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Chapter 8

Cardiac infections

Introduction and definitions

There are three distinct forms of cardiac infection: endocarditis, myocarditis, and pericarditis. The last two often occur together and are considered later in the chapter.

Infective endocarditis (*IE*) is an infection of the endocardium, valves, or related structures of the heart.

Infective endarteritis is similar to IE. May involve: patent ductus arteriosus (PDA), shunts (native and constructed), aneurysms, stents, collateral closing devices, neonatal umbilical lines, damaged arterial walls.

Endocarditis classification

There are several recognized subtypes of IE (Table 8.1).

Epidemiology

- IE is rarer in children as compared to adults.
- The estimated cumulative incidence of IE in the adult general population per 1000 000 person-years is 15–60, compared to 3.9–6.4 in children.
- IE is more often seen in patients with congenital heart disease (CHD) than in the general population but is rarer in children with CHD, compared to adults with CHD.
- The estimated cumulative incidence of IE in adults with CHD is 11/10 000 person-years but is around three times lower in the paediatric population with CHD at 4.1/10 000 person-years (6.1 first cases per 1000 children from birth to 18 years).

Predisposing factors for paediatric infective endocarditis

- CHD: cyanotic, atrioventricular septal defect, severe left obstruction, small ventricular septal defect (VSD), PDA, post-operative <6 months. *Isolated atrial septal defect (ASD), repaired VSD, and repaired PDA do not increase the risk. IE is rare in the first month after operation, unless there is a persistent haemodynamic problem.*
- Prosthetic valve, prosthetic material.
- Intracardiac devices (permanent pacemakers, implantable cardioverter–defibrillators (ICDs), long-term catheters). *Closure devices after endothelialization in 6 months do not increase risk.*
- Previous IE.
- Hypertrophic cardiomyopathy.
- Acquired valvular heart disease with stenosis or regurgitation.

- IV drug abuse is unusual in children.
- About 10% of paediatric patients do not have an identifiable predisposing factor; such cases usually have *S. aureus* infection of the mitral or aortic valves.
- Immunodeficiency does not increase the risk of IE.

Table 8.1 Classification of IE

According to localization and presence/absence of intracardiac material		
Left-sided native valve IE		
Left-sided prosthetic valve IE	Early	<1 year after replacement
	Late	>1 year after replacement
Right-sided IE		
Device-related IE[a]	Permanent	Pacemaker, ICD
According to mode of acquisition		
Health care-associated IE	Nosocomial	Hospitalized >48 hours prior to onset of symptoms
	Non-nosocomial	Hospitalized <48 hours prior to onset of symptoms
Community-acquired IE		Onset of symptoms out of hospital or <48 hours after hospitalization if criteria for health care-associated IE not fulfilled
IV drug abuse-associated IE		IV injection drug user without alternative source of infection
Active IE		
IE with persistent fever or positive blood culture		
Active signs of inflammation at surgery		
Still on antibiotic therapy		
Histopathological evidence of active IE		
Recurrence of IE		
Relapse	Repeat episode with same microorganism <6 months after the initial episode	
Reinfection	Repeat episode with same microorganism >6 months after the initial episode	
	Infection with different microorganism	

[a] Related also to central venous lines as well as closure devices (atrial septal defect/ventricular septal defect/patent ductus arteriosus closing) before endothelialization.

ICD, implantable cardioverter–defibrillator.

Adapted from the European Society of Cardiology (ESC) guidelines (2009).[1]

Changing profile of paediatric infective endocarditis in developed countries

Changing predisposing factors

- ↓ Acquired rheumatic heart disease.
- ↑ Device/prosthesis-related.
- ↑ Previous operation for CHD repair.
- ↑ Previous IE (relapse, reinfection).
- ↑ IV drug abuse.

Changing microbiology

- ↓ Streptococcal.
- ↑ Staphylococcal.
- ↑ Blood culture-positive (>85%) (improved diagnosis: techniques, fastidious organisms).
- ↑ Intracellular organisms (improved diagnosis: sensitive serology, PCR from vegetations); fungi.

Changing mode of acquisition

- ↓ Community-acquired.
- ↑ Health care-associated.
- ↑ Recurrent IE.

Changing localization of lesions

- ↑ Multiple site (neighbouring and non-neighbouring).
- ↑ Right-sided.

Clinical presentation and diagnosis

Diagnosis is often a challenge due to the heterogeneous clinical manifestations and often multi-organ involvement. Symptoms and signs may be atypical in very young children. Presentations may be:

- Classic subacute presentation (over weeks and sometimes months), characteristic of infections caused by oral streptococci, is seen less often than previously
- Acute presentation due to infection with staphylococci has become commoner
- Prolonged indolent course of IE due to intracellular organisms (such as *Bartonella* and *Coxiella burnetii*).

Clinical features are related to:

- *Infection*: fever (>90%), positive markers of inflammation (elevated ESR/CRP, anaemia normocytic or microcytic with low serum iron and normal or high ferritin, leucocytosis with neutrophilia), positive blood culture (>85%)
- *Destruction* (>90%): new cardiac murmur, heart failure (30–60%), conduction abnormality:
  - New murmur may be difficult to differentiate from pre-existing murmurs
  - Heart failure caused by acute severe aortic or mitral regurgitation or intracardiac fistulae or rarely by valvular obstruction
  - Conduction abnormality (right/left bundle branch block or complete heart block) is due to spread of infection to the conduction system.

- *Embolism* (20–50%): systemic (brain, spleen, kidney, peripheral) or pulmonary.
- *Haematuria*: may be related both to immune complex deposition or small renal emboli.

See also Table 8.2.

Table 8.2 Revised Dukes' clinical diagnostic criteria for infective endocarditis (IE)

Major criteria	Minor criteria
Positive BC for IE:	• Positive BC (that does not meet a major criterion)
Typical microorganism consistent with IE from two separate BCs: *Viridans* group streptococci, *Streptococcus bovis*, HACEK group, community-acquired *S. aureus* or enterococci, in the absence of a 1° focus. Microorganisms consistent with IE from persistently positive BCs defined as: two positive BCs of samples drawn >12 hours apart OR all of three or a majority of four separate BCs with first and last sample drawn 1 hour apart OR one positive BC of *C. burnetii* or anti-phase I IgG antibody titre >1:800.	• Positive serological evidence for active infection for organism consistent with IE • Positive broad range 16S rDNA • Predisposing factor • IV drug abuse • Fever >38°C • Evidence of embolism • Immunological phenomena
Positive Echo for IE:	Positive Echo (that does not meet a major criterion)
Vegetation, new or worsening regurgitation, perforation, chordal rupture, new partial dehiscence of prosthetic valve, shunt occlusion, abscess, aneurysm or pseudoaneurysm.	

BC, blood culture; Echo, echocardiogram.

Definite clinical diagnosis: two major criteria OR one major and three minor criteria OR five minor criteria.

Possible clinical diagnosis: one major and one minor criteria OR three minor criteria.

Source: data from Li JS, Sexton DJ, Mick N, *et al*. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* 2000;**30**:633–8.[2]

Differential diagnosis

- Other chronic infections.
- Rheumatological and autoimmune diseases.
- Malignancy with systemic features. Cardiac myxomas can manifest with low-grade fever, immunological phenomena, and positive markers of inflammation.

Neonatal infective endocarditis

(See Box 8.1.)

- Most often related to intravascular catheters.
- Systemic hypotension.
- Signs of generalized sepsis.
- Particularly prone to septic embolization (focal neurological signs) and development of satellite infections (meningitis, OM).
- Candidal endocarditis is relatively commoner.

Box 8.1 When to suspect IE

- New regurgitant heart murmur.
- Embolic events of unknown origin.
- Sepsis of unknown origin (especially if associated with IE causative organism).
- Fever associated with:
  - Intracardiac prosthetic material (e.g. prosthetic valve, pacemaker, ICD, surgical baffle/conduit, central venous catheters (CVCs), ventricular-assist device (VAD))
  - Previous history of IE
  - Previous valvular or CHD
  - Other predisposition for IE (e.g. immunocompromised, IV drug user)
  - Recent cardiac intervention with associated bacteraemia
  - Evidence of congestive heart failure
  - New conduction disturbance
  - Positive blood culture with typical IE causative organism or positive serology for Q fever (microbiological findings may precede cardiological manifestations)
  - Vascular or immunologic phenomena: embolic event, Roth spots, splinter haemorrhages, Janeway lesions, Osler's nodes
  - Focal or non-specific neurological symptoms and signs
  - Evidence of pulmonary embolism/infiltration
  - Peripheral abscesses (renal, splenic, cerebral, vertebral) of unknown cause.

Adapted from the ESC guidelines (2009).[1]

Investigations

Cardiological investigations

- Echocardiography to look for: vegetations, regurgitation, valvular perforation, chordal rupture, fistula formation, prosthetic valve dehiscence, shunt occlusion, abscess, aneurysms, or pseudoaneurysms. Transthoracic echocardiography (TTE) is usually of high quality and has high diagnostic yield in children of >80%. If TTE is negative and of high quality, and suspicion remains high, it should be repeated in 7 days, as manifestations may appear only with progression. Transoesophageal echocardiography (TOE) is very rarely necessary and may be indicated in prosthetic valves, chest wall deformity, and obesity. *Absence of echocardiographic signs of IE does not rule out 100% IE.*

- Electrocardiography (ECG) to look for: conduction disturbances and arrhythmias.
- CT and MRI may be useful for visualization of embolic phenomena, paravalvar abscess. Nuclear imaging 18F-FDG PET/CT or radiolabelled leucocytes SPECT/CT might help find areas of inflammatory activity. These are especially important in prosthetic valve IE.

Microbiological diagnosis of infective endocarditis

For causative agents of bacterial IE, see Table 8.3.

Infective endocarditis

Blood culture still remains the cornerstone of the diagnosis of IE and a major criterion for Dukes' classification. It is imperative that, in cases of suspected IE, a sufficient number of correctly taken blood cultures are drawn. It is essential that the request indicates that IE is suspected, as the laboratory will prolong the incubation period accordingly.

In children, the following volumes and frequency are recommended:

- Volumes:
  - Infants and young children 1–3mL per bottle
  - Older children 5–7mL per bottle (up to 30mL blood/day).
- Frequency:
  - Three sets of separate venepunctures over 24 hours, ideally with one set 12h apart, but with at least the first and last set 1 hour apart
  - If patient is unstable and presentation acute, take *two* blood cultures at separate sites immediately, and a third at least 1 hour later, and commence empirical therapy *without delay*.

Table 8.3 Causative agents of bacterial IE

	Approximate frequency (%)
Viridans group streptococci	40
S. aureus	30
Coagulase-negative staphylococci	8
S. pneumoniae	6
HACEK[a]	5
Enterococci	5
Culture-negative (see Culture-negative infective endocarditis)	6

The commonest causative agents of IE in very low birthweight (VLBW) neonates are *S. aureus*, coagulase-negative staphylococci, and *Candida* spp., usually with long-term indwelling venous catheters.

[a] HACEK organisms grow slowly and can be difficult to identify. Sensitivity testing can be difficult and delayed. They include: *Haemophilus* spp. (*H. influenzae, parainfluenzae*), *Aggregatibacter actinomycetemcomitans, Aggregatibacter aphrophilus, Cardiobacter hominis, Eikenella corrodens*, and *Kingella kingae*.

Culture-negative infective endocarditis

- Applies to cases in which there is clinical and radiological evidence of IE, but blood cultures are persistently negative. Causes include prior antibiotic therapy or infections due to fastidious organisms (particularly HACEK group or nutritionally dependent organisms such as *Abiotrophia*). Sometimes, the organism can be cultured from vegetations.

Additional investigations

Serological testing

Serological testing can be very useful (and can sometimes be the only method available) for diagnosing IE caused by *Coxiella* (Q fever), *Bartonella, Legionella, Chlamydia*, and *Brucella* spp.

Molecular methods

- Molecular tests should be used as an adjunctive test to culture methods.
- Can be applied to both blood samples and infected lesions removed at surgery.
- Include broad range (16S ribosomal sequencing) or specific real-time methods (*S. aureus, Streptococcus pyogenes*, etc.).

Histological diagnosis

Still remains a major criterion if an organism can be demonstrated by appropriate staining methods in the resected lesion.

Immunological investigations

Immunological phenomena associated with long-standing infection may be seen and include: high immunoglobulin G (IgG) levels, positive antinuclear antibody (ANA) and rheumatoid factor, low C3/C4, and circulating immune complexes.

Treatment

Management of IE requires close collaboration between paediatricians, cardiologists, and ID/microbiology specialists. IE in children with implanted prosthetic material should be managed in centres with access to cardiothoracic surgeons, neurologists, and neurosurgeons as well as advanced imaging techniques. Revision surgery, whether immediate or delayed, is usually necessary. It is recommended that an 'Endocarditis Team' is formally established in any referral centre to provide expert advice on the treatment of non-complicated IE outside the referral centre, and to make decisions and coordinate the management of complicated IE in the referral centre.

Antimicrobial treatment

The determinants of choice of antibiotic regimen and length of therapy are:

- The identity of the pathogen
- Its antimicrobial sensitivity profile
- The nature of the infective lesion, i.e. native or surgically implanted prosthetic material
- Presence of septic embolic phenomena.

In IE, microbial pathogens are embedded in a fibrin–platelet matrix, with associated biofilm. Organisms in biofilms tend to be metabolically inactive and less susceptible to cell wall active agents such as β-lactams and glycopeptides. For this reason, doses of these agents tend to be high, and the duration of therapy long.

The general principles of antimicrobial therapy in IE are:

- Use at least one agent that is bactericidal for the organism concerned
- A cell wall active agent (β-lactam or glycopeptide), combined with an aminoglycoside, often provides synergy.

Tables 8.4, 8.5, and 8.6 summarize the drugs recommended in IE, depending on the presentation and causative organisms.

Treatment of culture-negative infective endocarditis

- In most instances, therapy should be directed against streptococci, staphylococci, and HACEK group organisms.
- In subcute cases (patient stable), use ceftriaxone and gentamicin.
- Acute presentation or a patient with prosthetic material requires staphylococcal cover—use vancomycin/teicoplanin plus gentamicin.

Table 8.4 Empirical antibiotic therapy based on clinical presentation

NVE Acute presentation	Vancomycin Plus gentamicin
NVE Indolent (sub-acute)	Amoxicillin OR cefotaxime Plus gentamicin
NVE β-lactam allergic	Vancomycin Plus gentamicin
NVE Acute presentation with risk factors for multiresistant Coliforms/Pseudomonas	Vancomycin Plus meropenem
PVE-presence of prosthetic intracardiac material	Vancomycin Plus gentamicin Plus rifampicin

Table 8.5 Antibiotic therapy for Staphylococcal IE

Site	Antimicrobial agents	Duration
Native valve methicillin sensitive *Staphylococci*	Flucloxacillin	4–6 weeks
Native valve methicillin resistant *Staphylococci* OR β-lactam allergic	Vancomycin Plus rifampicin	4–6 weeks 4–6 weeks
Prosthetic valve methicillin sensitive *Staphylococci*	Flucloxacillin Plus rifampicin Plus gentamicin (one or two divided doses)	6+ weeks 6+ weeks 2 weeks
Prosthetic valve methicillin resistant *Staphylococci* OR β-lactam allergic	Vancomycin Plus rifampicin Plus gentamicin (one or two divided doses)	6+ weeks 6+ weeks 2 weeks

For *Staphylococci* with Vancomycin MICs >2.0 mg/L, Daptomycin (with MIC ≤ 1.0mg/L) can be used, usually in combination with Rifampicin (4 weeks NVE and 6+ PVE) plus gentamicin (2 weeks).

Table 8.6 Duration of antibiotic therapy by organism

Organism	Antimicrobial agents	Duration
Oral *Streptococci* and *S. bovis*-penicillin susceptible (MIC ≤0.125 mg/L)	Benzylpenicillin OR amoxicillin OR ceftriaxone	4 weeks (6 weeks for PVE)
β-lactam allergy	Vancomycin	4 weeks (6 weeks for PVE)
Oral *Streptococci* and *S. bovis*-penicillin relatively resistant (MIC 0.25 to 2 mg/L)	Benzylpenicillin OR amoxicillin OR ceftriaxone	4 weeks (6 weeks for PVE)
	Plus gentamicin (once daily or divided)	2 weeks
β-lactam allergy	Vancomycin	4 weeks (6 weeks for PVE)
	Plus gentamicin (once daily or divided)	2 weeks
Oral *Streptococci* and *S. bovis*-penicillin fully resistant (MIC >4.0 mg/L)	Vancomycin	6 weeks
	Plus gentamicin	6 weeks
Granulicatella or *Abiotrophia* (nutritionally variant streptococci)	Benzylpenicillin OR amoxicillin OR ceftriaxone OR vancomycin	6 weeks
	Plus gentamicin (once daily or divided)	2 weeks
Enterococci-amoxicillin sensitive	Amoxicillin	4–6 weeks
	Plus gentamicin (once daily or divided)	2–6 weeks
Enterococci-amoxicillin resistant	Vancomycin	6 weeks
Or β-lactam allergic	Plus gentamicin	6 weeks
HACEK group	Ceftriaxone	4 weeks (6 weeks for PVE)
Enterobacteriaceae (coliforms) and other gram negatives (e.g. *Pseudomonas spp.*)	Cephalosporin, piperacillin/ tazobactam or carbapenem	6+ weeks
	Plus aminoglycoside	6+ weeks

- If known exposure history to *Coxiella* or *Bartonella* infection, treatment options are additionally directed against those pathogens.
- Usually 6 weeks' therapy is warranted for culture-negative IE (with the exception that *Coxiella* IE requires 2–3 years' therapy).

Treatment of fungal endocarditis

- Less common in children than adults.
- Neonates (mainly preterm) with disseminated candidaemia may have cardiac involvement such as valvular lesions or infected mural thrombi. Cardiac involvement should be excluded in all neonatal candidaemia.
- Infected prosthetic valves almost always require surgical revision.
- Most authorities recommend a combination of amphotericin and flucytosine. Echinocandins (e.g. caspofungin) and azoles (e.g. fluconazole) are alternatives. Duration is at least 6 weeks.
- In non-operable prosthetic material endocarditis, lifelong therapy may be warranted.

- IE due to filamentous fungi, such as *Aspergillus* spp., is usually only seen in highly immunocompromised patients and occasionally in patients with prosthetic valves. These cases are extremely difficult to diagnose (blood cultures rarely positive) and are often detected at post-mortem or after surgery. Treatment of filamentous fungal IE is rarely successful without surgical intervention. Both voriconazole and amphotericin are useful agents.

Surgical treatment

Surgery is potentially indicated for most of the cases of IE. Surgery is aimed at removing the infected tissue, with maximum effort to preserve a native valve; if this is not possible, then patches and homografts are preferred to prosthetic valves. The microbiological investigation of the excised vegetation and infected tissue, including with PCR, gives an invaluable tool for the aetiologic diagnosis in cases of culture-negative endocarditis.

Optimal timing for operation is crucial for improved outcomes in children. In some cases, there might be urgent indications.

Risk of emboli (systemic or pulmonary)

- Anterior mitral leaflet vegetation with significant size (>10mm).
- One or more embolic events during first 2 weeks of antimicrobial therapy.
- Increase of vegetation size after 4 weeks of antimicrobial therapy.

Intractable heart failure

- Acute insufficiency (especially mitral and aortic) with signs of ventricular dysfunction.
- Valve rupture or significant perforation.

Perivalvular extension

- Valvular dehiscence, rupture, or fistula.
- New heart block.
- Large abscess or extension of abscess despite therapy.

Most of these indications are extrapolated from the guidelines for adults and will need adjustment for children. *S. aureus* and *Aspergillus spp. IE* will need surgery without significant delay. Most cases with other types of fungal endocarditis will also need surgery. *Candida* mural endocarditis in neonates is more susceptible to antifungal therapy alone without the need for surgery.

The results of surgery have immensely improved the outcome for IE. Early lifesaving surgical therapy in children can be performed with relatively low risk. Neonatal surgery remains high-risk.

The timing of surgery for those without urgent indications is still a matter of debate. Infected prosthetic material-related IE will need surgery, as, even if antimicrobial treatment is effective, there is a significant risk of recurrence.

Percutaneous procedures

Percutaneous pacemaker and ICD lead extraction in patients with vegetations is safe. New devices can be implanted, provided the blood cultures remain negative. Infected long-term IV catheters causing IE can also be safely removed.

Antithrombotic therapy

There is no indication for the initiation of antithrombotic drugs (thrombolytic, anticoagulant, or antiplatelet) in patients with active IE.

Outcomes

Outcome has significantly improved, with mortality in developed countries as low as 10%.

Prophylaxis

Due to a lack of good scientific evidence for its efficacy, recommendations for antibiotic prophylaxis against IE have changed in recent years.

In the UK, the National Institute for Health and Care Excellence (NICE) guidelines for prophylaxis against IE, published in March 2008,[3] state that antibiotic prophylaxis solely to prevent IE should *not* be given to people at risk of IE undergoing dental and non-dental procedures.

The recommendations in the 2009 ESC guidelines[1] are similar but suggest that prophylaxis is still recommended for a small group of high-risk patients.

Myocarditis and pericarditis

Definitions

Myocarditis is characterized by an inflammatory infiltrate in the cardiac muscle, with or without necrosis of myocytes (Table 8.7).

Table 8.7 What is myocarditis?

Histopathology	Immunohistochemistry	MRI features
Cellular infiltrate (>14 leucocytes/mm^2)	T lymphocytes (CD3)	Tissue oedema
Myocyte necrosis	Monocytes/macrophages/natural killer (CD68)	Capillary leakage
	Antigen-presenting cells (human antigen-presenting HLA DR)	Necrosis/fibrosis

Pericarditis is an inflammation of the epicardium and/or the pericardium that leads to accumulation of excessive fluid in the pericardial sac (pericardial effusion). Not all pericardial effusions are due to inflammation. Non-inflammatory causes of effusions include congestive heart failure (hydropericardium), haemopericardium, and chylopericardium.

Constrictive pericarditis is a rigid, non-compliant pericardium due to fibrosis and calcification. There is usually small or absent pericardial effusion, with the exception of the effusive–constrictive subtype. The pericardium may not be thickened in up to 30%.

Acute pericarditis is of <1 month duration.

Chronic pericarditis is of >3 months duration.

Recurrent pericarditis is of:

- Intermittent type: symptom-free intervals without therapy
- Incessant type: discontinuation of therapy leads to relapse.

Aetiology

Many infections can cause both myocarditis and pericarditis. Viral causes are listed in Table 8.8. Coxsackie virus predominates in the newborn period, whereas, in older children, adenovirus is the commonest cause. Non-viral causes are listed in Table 8.9.

The detection of viral genomes by PCR appears to be of aetiopathogenic importance only in the presence of an immunohistologically proven reactive inflammatory infiltrate. In patients without inflammation, the finding may represent latent viral genome persistence.

Table 8.8 Viral causes of myocarditis and pericarditis

Enteroviruses	Influenza A
Coxsackie A	RSV
Coxsackie B	Mumps
ECHOvirus	Measles
Poliovirus	Rubella
Adenovirus	Rabies
Parvovirus B19	Hepatitis B, C
HHV-6	HIV
EBV	
CMV	
HSV	
VZV	

Table 8.9 Non-viral causes of myocarditis and pericarditis

Infectious	
Bacterial	*S. aureus*, Hib, *S. pyogenes* and *pneumoniae*, *N. meningitidis* and *gonorrhoeae*, *Salmonella* spp., *Pseudomonas aeruginosa*, *E. coli*, *M. tuberculosis*, *Borrelia burghdorferi* (Lyme disease), *Corynebacterium diphtheriae*
Fungal	*Candida*, *Coccidioides*, *Histoplasma*
Protozoa and helminths	*Entamoeba histolytica*, *Trypanosoma*, *Schistosoma*, *Trichinella*, *Toxocara*
Non-infectious	
Systemic inflammatory	Kawasaki disease, systemic lupus erythematosus and lupus-like, coeliac disease, juvenile idiopathic arthritis, scleroderma, inflammatory bowel disease, systemic vasculitis, Churg–Strauss syndrome
Toxic for myocarditis	Scorpion sting, snake venom, drug-induced
Other for pericardial effusion	Post-radiation, uraemia, hypothyroidism, tumours (lymphoma, metastatic), post-cardiotomy syndrome

Myocarditis

Epidemiology

Myocarditis is an underdiagnosed condition, and its true incidence is unknown. The reported incidence and prevalence largely depend on how strictly, and which, diagnostic criteria are applied. Up to 35% of paediatric dilated cardiomyopathy may be related to myocarditis.

Clinical manifestations

The presence and severity of clinical signs, as well as the course of disease, vary hugely (Table 8.10). A significant proportion of myocarditis probably remains undiagnosed (Table 8.11), as patients may remain asymptomatic and recover spontaneously. However, there may be rapid worsening, leading to haemodynamic compromise or death. In a proportion of patients, there is a chronic course, with dilated cardiomyopathy that may worsen or recover in months to years.

Table 8.10 The course of myocarditis

Preceding	Course	Outcome
Viral infection	Mild	Recovery
	Acute	Death
	Fulminant	Dilated cardiomyopathy
	Chronic	Transplant

Table 8.11 When to suspect myocarditis

Clinical features	Cause
Sudden death	Ventricular tachycardia/fibrillation
Syncope, cardiac collapse	Complete atrioventricular block
	Atrioventricular block grade II
	Atrial fibrillation
New-onset heart failure in the absence of previous structural heart disease	Left ventricular dysfunction
	Biventricular dysfunction
Palpitations	Compensatory sinus tachycardia, premature beats, supraventricular tachycardia
Chest pain	Concomitant pericarditis
	Coronary artery spasm
Chronic heart failure	Dilated cardiomyopathy
Asymptomatic	

In children, clinical manifestations are more often acute and severe; in neonates, they are often fulminant. Preceding viral symptoms, such as respiratory illness, are often not apparent.

Myocarditis is a difficult clinical diagnosis at onset:

- Up to 30% may have respiratory symptoms, 30% cardiac symptoms, and 6% GI symptoms
- Heart failure in infants is atypical, with decreased appetite, profuse sweating on feeding and crying, tachypnoea, cough on strain, poor perfusion with mottled skin. Systemic venous congestion may cause hepatomegaly, and consequently abdominal distension, pain, and vomiting; neck vein distension and peripheral oedema are characteristic of later age
- Chest pain is the rarest symptom and raises the suspicion only if some of the other symptoms is present.

Investigations

Investigations for myocarditis are described in Table 8.12.

While the CXR and ECG have a combined high sensitivity, echocardiography remains the cornerstone of diagnosis.

- Ventricular diameter is reported as an absolute value as well as a z-score (number of standard deviations from the mean i.e. a z-score > +2.0 suggests dilation).
- Systolic function of the left ventricle is assessed by the indices of pump function, and a hypocontractile left ventricle has fractional shortening (FS) <30% and an ejection fraction (EF) <55%.
- Enteroviral myocarditis causes segmental severe hypokinesia and thinning, similar to myocardial infarction.
- Fulminant myocarditis causes severe hypokinesia, but with normal left ventricular diameter and increased septal thickening.

Laboratory biomarkers of myocytolysis are important in the acute phase.

- Transaminases, especially aspartate aminotransferase (AST), are highly sensitive, but of very low specificity.
- Troponin T and I are highly sensitive and may persist up to a week.

The absence of positive markers of myocytolysis does not rule out the presence of the disease.

MRI may visualize affected areas but is not validated in paediatric patients:

- Tissue oedema, which may result in an elevated T2 signal
- Capillary leakage, which is speculated to be associated with an increased T1-weighted signal on early gadolinium enhancement
- Myocardial necrosis or scarring, as indicated by the presence of late gadolinium enhancement.

Endomyocardial biopsy (Box 8.2) with conventionally stained heart tissue samples has been abandoned from the routine panel of the diagnostic work-up because of low sensitivity (about 10%). There is increasing interest in investigating older patients, as the rate of complication falls. *A negative endomyocardial biopsy does not rule out myocarditis.*

Table 8.12 Investigations for myocarditis

Investigation	Findings
Chest X-ray	Cardiomegaly
	Pulmonary venous congestion
ECG	Sinus tachycardia
	Low voltage QRS
	Inverted/flat T-waves in left precordial leads
	Myocardial infarction pattern (localized wide Q, ST-segment depression/elevation)
	Axis deviation
	Pericarditis pattern (wide spread ST-segment elevation)
	Conduction abnormalities (AV block, LBBB)
	Arrhythmias (VT, SVT)
Echocardiography	Hypocontractile left or both ventricles with variable dilation[a]. Mitral regurgitation (papillary dysfunction). Global or less frequently segmental myocardial deformation abnormalities. Intracavitary thrombi. Concomitant pericardial effusion
Laboratory biomarkers	Cardiac myocytolysis: cardiac troponin I, creatine kinase-MB isoform
	Heart failure: NT-pro-BNP
Cardiac MRI	Global or regional
	Oedema (increased intensity on T2-weighted)
	Capillary leak (gadolinium early enhancement)
	Necrosis/scarring (gadolinium late enhancement)
Endomyocardial biopsy	Focal inflammatory infiltration with/without necrosis
	Immunohistology (anti-CD3, CD4, CD8, CD20, CD68, HLA class II)
PCR/RT-PCR	Viral DNA/RNA[b]
Serology and immunology	For *Borrelia*
	IgM or rising titre IgG antiviral antibodies
	Anti-myosin antibodies

[a] The more acute forms have less significant dilation; right ventricular dysfunction is a sign of severity and bad prognosis.

[b] Highly specific; lower sensitivity in blood, higher sensitivity in tissue samples.

AV, atrioventricular; HLA, human leucocyte antigen; LBBB, left bundle branch block; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; SVT, supraventricular tachycardia; VT, ventricular tachycardia.

Box 8.2 When is endomyocardial biopsy necessary?

Acute or fulminant heart failure of unknown aetiology

- Rapid deterioration
- Ventricular arrhythmias
- Atrioventricular block
- No response to conventional heart failure therapy

Suspected fulminant myocarditis

- Unexplained new-onset heart failure of <2 weeks after infection
- Haemodynamic compromise
- Normal-sized hypocontractile left ventricle with septal thickening

Suspected giant cell myocarditis

- Unexplained new-onset heart failure of 2 weeks to 3 months duration
- Ventricular arrhythmias and atrioventricular block grade II (Mobitz type II), complete heart block
- No response to conventional heart failure therapy with progressive worsening

Establishing the cause of myocarditis may be difficult:

- The development of highly sensitive and specific PCR assays that can detect viral DNA/RNA in both blood and tissue has improved the diagnostic yield, especially in the acute phase of enterovirus myocarditis.
- This enhanced capacity to detect the viral genome is not without controversy, as the detection of the viral genome, even on myocardial biopsy, does not necessarily imply that this is the aetiologic agent. This is particularly so when parvovirus is detected by PCR. Transcriptome studies may help distinguish between active infection and latency.
- Serological studies for viral infections can also be useful, either with detectable immunoglobulin M (IgM) antibodies for recent infection or rising titre of IgG.
- Serology is still the mainstay of diagnosis of myocarditis due to *Borrelia* and should be considered, especially in the presence of conduction disturbances.
- Protozoal and parasitic diseases (such as trypanosomiasis) should be considered if there is a history compatible with exposure.
- Diphtheria is now almost never seen in Europe/US; however, it should be considered in any patient with appropriate signs who is from an endemic region.

Treatment

Specific antiviral treatment is of limited use because of the significant period between the infection and the myocarditis. IFN has been used with variable success.

The use of immunosuppressive and anti-inflammatory treatments (corticosteroids, ciclosporin, IVIG) is controversial, and the effect is not proven. However, immunosuppression is indicated in giant cell and eosinophilic myocarditis.

Management of heart failure

- Drugs: diuretics, inodilators (phosphodiesterase 3 inhibitors: milrinone), inotropes (catecholamines), vasodilators, calcium sensitizers (levosimendan).
- Mechanical ventilation.
- Mechanical circulatory support: extracorporeal membrane oxygenation (ECMO) or VADs.
- Treatments aimed at providing a bridge to recovery or to allow time for cardiac transplantation. Explantation of VAD following recovery might be possible in up to 24%.

Management of arrhythmias

- Should be treated immediately.
- Sustained ventricular tachycardia often leads to haemodynamic compromise and may require direct current (DC) cardioversion.
- Amiodarone infusion is often effective.
- Oral amiodarone should be used for several months.
- ICD implantation may be necessary, but usually this is delayed in the hope of recovery.
- Complete heart block requires urgent pacemaker therapy. Atrioventricular (AV) block in giant cell myocarditis is progressive, and second-degree block is an indication for pacemaker use.

Outcome

- There is no validated set of criteria to predict which patients will recover, die, or be chronically ill, with dilated cardiomyopathy requiring possible later transplantation.
- Recovery is the most frequent outcome; there is no good estimate for children, but the rate of spontaneous recovery in adults is 58%.
- Fulminant lymphocytic myocarditis, with a distinct onset within 2 weeks of a viral infection, has an early mortality of about 10% and a favourable prognosis with aggressive support.
- Acute lymphocytic myocarditis, with an unclear onset and a more indolent course, more often has a poor outcome (Box 8.3). Acute myocarditis in newborns has a poor prognosis with a mortality rate of up to 75%, with most of the deaths occurring very soon after onset of disease.
- In older infants, mortality varies between 10% and 25%.
- Availability of mechanical support and transplantation significantly improves outcome.

Box 8.3 Predictors of unfavourable outcome

- Neonatal age
- Pathologic Q-waves
- Left bundle branch block
- Right ventricular dysfunction
- Giant cell myocarditis

Future research

The use of immunohistochemistry and MRI will allow more specific epidemiological studies in the future. The use of quantitative PCR and the assessment of replicative viral intermediates are needed to differentiate between replicative viral infection and viral latency.

New and validated biomarkers for prognostic purposes are needed.

Miniaturization of continuous-flow VADs will make possible wider use for younger patients.

Study of the mechanisms of spontaneous recovery may reveal completely new ways of treatment of heart failure and dilated cardiomyopathy.

Myocarditis may trigger the initial manifestations of genetic dilated cardiomyopathies, and research into that is ongoing.

Pericarditis[4]

In developed countries, idiopathic pericarditis comprises about 80% of all cases. These cases are presumed to be viral; as patients recover, no further investigations are required, and the aetiology remains unconfirmed. Pathogenesis involves both direct infection and an indirect associated immune/inflammatory response.

Epidemiology

No good population studies are available in the UK. In a study in Italy, published in 2008, an incidence of 27.7 cases per 100 000 of the population per year was found.

- Tuberculous pericarditis is rare in developed countries.
- Up to 5% of HIV-infected patients may have pericarditis in the absence of additional infection.
- Bacterial purulent pericarditis is a rare isolated disease, and immune deficiency should be ruled out. It is more often part of a generalized infection (sepsis, OM) or spread from a neighbouring organ (lungs, mediastinum).
- Parasitic causes should be considered when eosinophils predominate in the pericardial fluid.
- Recurrent pericarditis occurs in about 30% and is most probably an autoimmune disease.
- The incidence of paediatric constrictive pericarditis has fallen in developed countries with the waning of TB and improved management of purulent pericarditis.

Clinical manifestations and course

(See Box 8.4.)

Box 8.4 When to suspect pericarditis

- Chest pain
- General infection (pyrexia, malaise)
- Tachypnoea, breathlessness, often without crackles
- Systemic venous congestion (jugular venous distension, hepatomegaly, abdominal pain, vomiting, oedema)
- Pericardial rub
- Muffled heart sounds
- Pulsus paradoxus (reduced volume pulse on inspiration)
- Reduced cardiac output (tachycardia, high capillary refill time, hypotension, bradycardia)

- *Chest pain* is a highly sensitive symptom but is non-specific and can be reported only in older children. Pericardial rub is specific but is less pronounced in bigger effusions and in those containing less fibrin.
- Children often present with respiratory or abdominal symptoms.
- Large effusions that develop slowly can be asymptomatic, while smaller effusions that accumulate rapidly can present with tamponade.

Investigations for pericarditis are described in Table 8.13, and the differential diagnosis of specific forms in Table 8.14.

Table 8.13 Investigations for pericarditis

CXR	Cardiomegaly (normal to water bottle shadow)
	Additional pulmonary/mediastinal pathology
ECG	Early:
	Widespread concave ST-segment elevation (J-point elevated >25% of T, may be anterior *plus* inferior only)
	PR segment deviation opposite to P
	Late:
	T-wave flattening and depression
Echocardiography	Pericardial effusion
	Size (small, moderate, large)
	Distribution (even, collections)
	Characteristics (streaks of fibrin, roughness of epicardial surface)
	Pre-tamponade, tamponade
Plasma biomarkers	Inflammation (high CRP, ESR, fibrinogen, WBC)
	Cardiac myocytolysis (cTnT/I, CK-MB, AST, ALT, LDH)

(*Continued*)

Table 8.13 (*Contd.*)

Pericardial fluid	Microscopy and culture (including for TB)
	Cell count (blood cells, unusual cells)
	Protein, albumin, triglycerides
	For TB: ADA >50U/L, IFN, pericardial lysozyme, PCR
Aetiology specific	PCR/RT-PCR blood/fluid for viral and bacterial causes
	Serology for IgM or rising titre of IgG antibodies
CT chest	Adjacent organs and tissues
MRI	Pericardial thickening (>4mm in 70% of constrictive pericarditis)

ADA, adenosine deaminase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; IFN, interferon; LDH, lactate dehydrogenase; RT-PCR, reverse transcriptase polymerase chain reaction; TB, tuberculosis; WBC, white blood cell.

Table 8.14 Differential diagnosis of specific forms of pericarditis

	Viral	Bacterial	TB	Autoimmune
Aetiological evidence	PCR	Gram stain	Ziehl–Neelsen	Ig binding to epi/pericardium
		Bacterial culture	PCR	Negative viral PCR
		16S PCR	Culture	
		PCR for *Borrelia* and *Chlamydia*		
Clinical	Usually Mild	Severe	Chronic	Chronic
		Fulminant		
Tamponade	Infrequent	80%	Frequent	Infrequent
Fluid macroscopic	Serous/ serosanguinous	Purulent	Serosanguinous	Serous
Leucocyte count	>5000/mL	>10 000/mL	8000–10 000/mL	<5000/mL
Protein	>30g/L	High	Intermediate	Intermediate
Additional	Activated lym/ macro (sparse)	Neu/macro	ADA >40U/L	Activated lym/ macro
			PCR positive for *M. tuberculosis*	
Pericardial biopsy	Lymphocytic	Neutrophilic	Caseous granulomata, PCR	Lymphocytic
Recurrence	30–50%	Rare	Frequent	Frequent
Mortality if left untreated	Low, depends on agent	100%	85%	25% in untreated tamponade
Constriction	Rare	Frequent	30–50%	Rare

Echocardiography (Fig. 8.1) is the mainstay of diagnosis and impacts management.

- Pericardial effusion is seen on two-dimensional sections as echolucent areas around the heart.
- Size is assessed by measuring the separation in diastole; for adults and big children—small ≤10mm, moderate = 10–20mm, and large ≥20mm; for infants and small children, these values are halved, i.e. small = 5mm, moderate = 5–10mm, large ≥10mm.
- The predominant location and presence of collections are very important to guide the decision about the type of pericardiocentesis.
- For echocardiographic signs of tamponade, see Box 8.5.

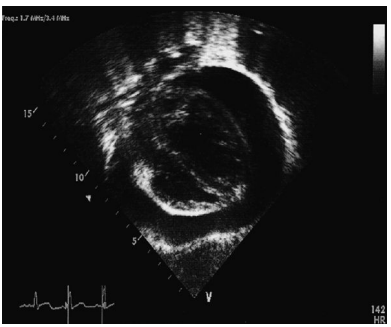

Fig. 8.1 Echocardiogram demonstrating pericardial effusion.

Box 8.5 Echocardiography signs of tamponade

- Freely floating 'swinging' heart
- Diastolic collapse of the right ventricle/atrium, less frequently left atrium and least frequently left ventricle
- Respiratory variation of inflow >25% (inspiratory increase on right and decrease on left)

These usually coincide with clinical signs:

- Worsening tachypnoea, breathlessness (often without crackles)
- Worsening tachycardia
- Low cardiac output
- Hypotension and bradycardia signal a life-threatening stage

Treatment

- Treatment of acute viral pericarditis aims to relieve symptoms and prevent relapses. Anti-inflammatory drugs are the mainstay of therapy of acute non-purulent pericarditis.

  - NSAIDs: ibuprofen or diclofenac, as well as nimesulide (selective cyclo-oxygenase-2 inhibitor), are preferred and should be continued for a minimum of 2 weeks or at least 1 week after the effusion and symptoms resolve.
  - Corticosteroids (necessary in autoimmune diseases, usually not needed in viral).
  - Biologic agents use in recurrent pericarditis is under investigation.
- Percutaneous pericardiocentesis is indicated in tamponade, pre-tamponade, and ineffective conservative management of large effusions. It is echo/fluoroscopy-guided, unless in emergency, and a pigtail catheter may be left *in situ*, usually for 24h or until drainage is <25mL/day or 1mL/kg/day.
- Purulent bacterial pericarditis is fatal if left untreated (Table 8.15).

Table 8.15 Treatment of purulent pericarditis

Surgical drainage of pericardium	Local antibiotics	Systemic antibiotics	Pericardiectomy
Investigate the cause	Intrapericardial helpful, but not sufficient	Start with flucloxacillin (vancomycin if reason to suspect MRSA) and cefotaxime/ceftriaxone tailored to the culture results Duration: 4 weeks	Late in some cases with dense adhesions

- Fungal pericarditis should be treated with the appropriate antifungal agent for at least 4 weeks. TB is treated with quadruple antituberculous regimen (see Chapter 121) for 12 months. Most centres use additional adjunctive corticosteroids for the initial 1–2 months.
- In chronic pericarditis, treatment should be aimed at eradicating the cause. Pericardiocentesis and anti-inflammatory drugs are supportive treatment. Pleuropericardial window or pericardectomy may be considered.
- Recurrent pericarditis should be treated with corticosteroids, with a starting dose of 1.0–1.5mg/kg/day for at least 1 month, then tapering slowly over 3 months. If relapse occurs, the last effective dose should be used for at least 3 months. NSAIDs should then be started. Colchicine is reported as being helpful.
- Chronic constrictive pericarditis requires pericardectomy, which is usually a safe and effective procedure. However, it may be difficult and risky if adhesions between the epicardium and myocardium are present.

Outcome

- The majority of acute viral pericarditis resolves uneventfully and quickly. Incessant pericarditis is defined as having symptoms lasting for >4–6 weeks and chronic pericarditis for >3 months. Recurrent pericarditis is a new episode after a symptom-free interval of 4–6 weeks. Recurrence may occur in up to 30% of cases, and, after the first relapse, there is a 50% chance of this continuing.

- Purulent pericarditis still carries a mortality risk, although reduced from the previously reported 25%. It may evolve into constrictive pericarditis.
- Recurrent pericarditis, although difficult to manage, has a favourable prognosis and usually resolves eventually.

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Chapter 9

Central venous catheter infections

Introduction

IV catheters are widely used to support the administration of drugs, fluids, electrolytes, blood products, and feeding solutions, and for haemodynamic monitoring.

Definition of a central venous catheter

A CVC is a catheter that is passed through a vein to end up in the thoracic (chest) portion of the vena cava (the large vein returning blood to the heart) or in the right atrium of the heart. Ultrasound-guided insertion is now the standard means of elective CVC placement. Midlines are not strictly central venous but share many of the functions of CVCs, representing a potential alternative to CVC use in some cases.

Types of central venous catheters

The type used depends on the indication for insertion and the duration of use:

- Tunnelled: line placed through a subcutaneous tunnel (such as Broviac, Hickmann, Groshong). These have a Dacron cuff, which anchors the catheter and may become enmeshed in fibrous tissue
- Port: both line and port are subcutaneous. Access to the port is via a transdermal needle
- Peripherally inserted central catheter: uncuffed lines placed through a peripheral vein
- Non-tunnelled
- Single or multi-lumen
- Materials used include plastics, metals, silicone, and polyurethane
- Antimicrobial-impregnated CVCs and heparin-bonded CVCs
- Midline venous catheter: peripheral line usually placed in the brachial or cephalic vein; the tip ends below the level of the axillary line. An alternative to a CVC, but not suitable for some types of infusates (e.g. parenteral nutrition and hyperosmolar solutions).

Advantages of central venous catheters over peripheral cannulae

- Painless and convenient vascular access.
- Reduced chance of phlebitis.
- Potential for multiple access channels.
- Large bore.
- Delivery of high-concentration drugs too irritating for peripheral veins, including high-osmolality drugs.
- Can remain in place for months or years (if tunnelled or port).

Disadvantages

- Mechanical, thrombotic, and infective complications.
- Midlines are associated with reduced levels of complications, compared to CVCs.

Relative contraindications to central venous catheter insertion

- Coagulopathy.
- Thrombocytopenia.
- Venous thrombosis or stenosis.
- Infection over insertion site.

Complications associated with central venous catheters

- Attributable mortality associated with severe complications may exceed 25%.
- *Mechanical*:
  - Bleeding, haematoma, thrombosis
  - Venous stenosis, catheter occlusion
  - Haemothorax, pneumothorax
  - Cardiac arrhythmias, cardiac tamponade
  - Air embolism
  - Local tissue damage associated with reaction to device components or extravascular leakage of infusate.
- *Infective*: CVCs are a risk factor for:
  - Hospital-acquired bloodstream infection (BSI)
  - Endocarditis
  - Septic emboli
  - Septic shock
  - Exit site infection
  - Phlebitis.

Risk factors for central venous catheter-associated infection

- Site of insertion: risk lowest for subclavian; highest for femoral.
- Number of lumens: increased number of lumens increases risk.
- Type of needleless connector: decreased risk for neutral, compared to positive displacement, connectors.
- Type of CVC:
  - Port probably lower risk than tunnelled CVC
  - Antimicrobial CVCs lower risk than non-antimicrobial
  - Midline lower risk than central.

- Host factors:
  - Extremes of age
  - Chronic illness
  - Co-morbidities that compromise immunity, e.g. neutropenia
  - Loss of skin integrity.
- Total parenteral nutrition (TPN) administration.
- Poor compliance with insertion and post-insertion 'best practice'.
- Frequency of catheter manipulation.
- Duration of catheter placement.

Causative organisms

- Most commonly bacteria, less commonly fungi (e.g. *Candida* spp.).
- The causative agent is an important consideration in treatment decisions.
- The commonest are skin commensals:
  - CoNS
  - *S. aureus*.
- Others include opportunistic pathogens:
  - Enterococci
  - *E. coli*
  - *Klebsiella* spp.
  - *Pseudomonas* spp.
  - *Enterobacter* spp.
  - *Serratia* spp.

Routes of central venous catheter colonization

- Contamination at the time of insertion.
- Migration of bacteria from contaminated connections.
- Migration from the skin surface.
- Haematogenous or contiguous spread.
- Contaminated infusates.
- Early infections (within 2 weeks of implantation) more likely to result from outer surface contamination.
- Late infections from intraluminal contamination often arising from connectors/infusates.

Frequency of infection

- Usually measured as rate/numbers of days at risk (device days): rates of <1 to >15/1000 CVC days reported.
- Rates of infection vary with patient population and risk factors.
- Midline risk: 0.3–0.8/1000 catheter days.

Clinical presentation

- Inflammation, induration, discharge at exit site or along tunnel.
- *Exit site infection* usually has local induration only of 0.5–1cm around CVC skin exit site.

- *Tunnel infection* has pain and induration >2cm from the skin exit site.
- Fever and/or rigors and/or hypotension associated with device manipulations/flushing.
- Septic shock or persistent fevers with a CVC in place and without alternative explanation.
- Evidence of septic emboli.
- Vomiting, limb pains, and rigors in immunocompromised children with a CVC, and fever is associated with a high probability of line infection/BSI.

Differential diagnosis for suspected central venous catheter infection

- Infection arising from another source.
- Thrombosis.
- Superficial cellulitis over exit site.
- Infusate reaction.
- Contamination of blood culture.

Investigations

Suspect CVC infection when raised inflammatory markers (CRP, WCC, procalcitonin (PCT)) without other explanation.

Blood cultures

Collection

- Good collection technique is imperative to increase the possibility of isolating causative organism(s) and reduce risk of contamination.
- Ensure an adequate blood volume is collected (depends on the size of the patient).
- Try to collect before the initiation of antibiotic therapy.
- Ideally collect blood from a peripheral vein and CVC (although this is rarely done).
- Collect blood from all CVC lumens.
- Decontaminate skin or hubs with 2% chlorhexidine in 70% isopropyl alcohol (IPA), and allow to dry before sampling.
- Decontaminate the top of the blood culture bottles with 2% chlorhexidine in 70% IPA after removing the caps.
- Use aseptic non-touch technique.

Diagnostic criteria

- Isolation of skin bacteria from two or more blood cultures (multisite or multisample) collected within a 48h period.
- Isolation of indistinguishable bacteria from the CVC tip and blood cultures.
- Quantitative blood cultures:
  - Blood from CVC with >1000 colony-forming units (CFU)/mL
  - Difference >5-fold in CFUs between blood collected from CVC and peripheral sample or between blood samples from different lumens of a CVC
  - Differential time to positivity between blood collected from CVC and periphery of >2h.

- Isolation or visualization of microbes on the CVC post-removal.
- Presence of bacteria in blood drawn through the CVC detected by microscopy (e.g. acridine orange leucocyte cytospin (AOLC) test).
- Quantitative molecular detection of bacterial components (16S rDNA).
- Semi-quantitative CVC tip culture with >15 CFUs from a 5cm segment rolled on an agar plate.

Treatment

- Depends on the agent of infection.

Line removal

Advised in the following:

- The CVC is the suspected source of infection and is no longer critically required or is relatively straightforward to replace
- Clinical evidence of infection persists despite 48–72 hours of appropriate antibiotic treatment, or clinical deterioration
- Tunnel infection (extending >2cm from exit site) not responding to antibiotics
- Evidence of serious complications (suppurative thrombophlebitis, septic shock, endocarditis, septic emboli)
- Persistent fever, bacteraemia, or fungaemia despite appropriate antibiotic treatment
- CVC infection with *S. aureus* (high risk of endocarditis, etc.), antibiotic-resistant species (e.g. *Pseudomonas* spp., *Stenotrophomonas* spp., *Mycobacterium* spp., *Acinetobacter* spp., *Corynebacteria*), *Candida*, or other fungi
- Port-associated infection (particularly if it involves the subcutaneous pocket) may be harder to eradicate without CVC removal than infection associated with a tunnelled CVC.

Antimicrobial treatment

- ~80% of CVC-associated infections caused by CoNS can be treated without CVC removal.
- Antimicrobials must be administered through the CVC.

Antibiotic choice

- Empirical treatment in patients with suspected CVC-associated infection should include a glycopeptide (such as vancomycin) and an agent active against Gram-negative bacteria.
- Consider empirical use of antifungals only in patients at high risk of fungal infection (severely immunocompromised, those with femoral CVCs, and those with multi-site *Candida* colonization).
- Antimicrobial choice should be rationalized, following the isolation of causative organism and antibiotic sensitivities.

Duration

- Duration of therapy is defined as starting from the time that the blood cultures become negative.
- Optimum duration unknown.
- Uncomplicated infection with CoNS—duration around 7 days.

- Prolonged durations may be required when bacteraemia/fungaemia persists despite CVC removal.
- Prolonged durations may be required with *S. aureus* infection, unless the CVC is removed promptly in an immunocompetent patient where there is no evidence of complications, in which case 2 weeks may be sufficient.

Antimicrobial lock solutions

- May be used for catheter salvage in uncomplicated CVC infections in which there are limited access sites in a patient dependent upon intravascular access for survival such as in haemodialysis or TPN.
- Optimal antimicrobial dosing for lock therapy is uncertain.
- Not warranted when CVC removal is required.
- Examples:
  - Vancomycin 2.5mg/mL or 5.0mg/mL, with or without heparin 2500 or 5000IU/mL
  - Gentamicin 1.0mg/mL, with or without heparin 2500IU/mL.

Prevention

There is considerable evidence from quality improvement programmes that many CVC-associated infections can be prevented by the following.

Infection control

- Introduction of care bundles for CVC insertion and maintenance.
- The use of maximal sterile barrier precautions at the time of CVC insertion.
- Standardization of equipment and techniques (CVC insertion pack/trolley).
- Chlorhexidine in 70% IPA-based skin disinfection (2% probably better than 0.5%).
- Good hand hygiene every time pre- and post-care.
- Use of needleless injectable hubs on all ports, decontaminated with 2% chlorhexidine in 70% IPA prior to accessing.
- Use of neutral displacement connectors.
- Aseptic non-touch technique for drug administration and blood sampling.
- Daily chlorhexidine washes of intensive therapy unit (ITU) patients has been associated with a reduction in CVC infection.

Central venous catheter factors

- Limit disconnections and reconnections to essential only.
- Tunnelled or port CVCs for longer-term CVCs.
- Slow-release chlorhexidine dressing at the exit site probably reduces the risk of infection, particularly with short-term CVCs.
- Antimicrobial CVCs reduce the risk of infection.
- Considerable evidence that antimicrobial locks can prevent >50% of CVC-associated infections.
- Early removal of line when no longer indicated.
- Use of midlines for infusates not requiring central venous access.

Follow-up and outcome

- Blood cultures should be considered following CVC removal to ensure resolution of bacteraemia.
- A TTE, as a minimum, is advised following CVC infection due to *S. aureus*.

Further research

- RCT comparing CVC replacement with the use of a novel antibiotic lock solution (consisting of *N*-acetylcysteine, tigecycline, and heparin) in haemodialysis patients with catheter related BSIs.
- Randomized multicentre trial comparing the effect of four different skin disinfection strategies in reducing CVC colonization and/or CVC-related BSIs in ITU patients.
- Prospective study assessing the use of F-18-FDG positron emission tomography (PET)/CT for the diagnosis of CVC infection.

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Chapter 10

Chronic fatigue syndrome

See also Chapter 65.

Introduction

The aetiology of chronic fatigue syndrome (CFS) is unclear, and it is likely that a number of factors are involved. There is limited evidence that infective, immunological, familial, and psychological factors all have some part in the causation of CFS.

Causative organism/evidence of infection

- A subgroup of children with apparent chronic fatigue will describe a viral infection at the onset of symptoms.
- When there is laboratory evidence of such an infection, then the diagnosis of post-viral fatigue can be made.
- These cases form a minority of cases of CFS.
- In a study from Australia, involving adults (16 years and over), chronic fatigue followed infection with *Coxiella burnetii* (Q fever), EBV (glandular) fever, and Ross river virus (epidemic polyarthritis) in 28/253 (11%) of patients assessed 6 months after infection.
- There is no evidence that minor upper respiratory or GI infections lead to post-viral fatigue.

Epidemiology

- A UK-based GP survey of medically unexplained fatigue for >3 months suggested a prevalence of 62/100 000.
- Surveys from elsewhere have suggested a wide range of prevalence in teenagers from 2.7 to 48/100 000.
- In a study of 301 Monospot-positive adolescents in the US, the risk of CFS was estimated as 20 times the background rate. The rates of fatigue were 13%, 7%, and 4% at 6, 12, and 24 months, respectively. This and other studies have shown a ♀ preponderance.

Clinical presentation and differential diagnosis

- The most commonly reported symptom is severe fatigue (mental and/or physical) exacerbated by exercise, activity, or intercurrent infection.

- Often associated features include: severe malaise; headache; sleep disturbance; depressed mood; myalgia; muscle pain at rest and on exercise; nausea; sore throat; tender lymph nodes; abdominal pain; and arthralgia.
- Patients seen in primary care reported a mean of three symptoms at presentation, but those seen attending a tertiary clinic, who had been ill for longer, reported eight symptoms.
- Some children have symptoms or a diagnosis of depression and anxiety. Others also exhibit school phobia, somatization, and social withdrawal.
- A number of specific diagnostic criteria have been proposed.[1]
- The main symptom in these criteria is disabling, disruptive fatigue that is persistent, and a diagnosis is made when other causes of fatigue have been excluded by clinical examination and laboratory tests.
- The differential diagnosis of post-viral fatigue can be made in those with a history of a virus infection at the onset of symptoms and confirmed laboratory evidence of this. However, the main differential diagnosis is of psychiatric illness such as depression.
- Other diagnoses to consider:
  - Anaemia, chronic disease such as renal failure
  - Chronic infections, e.g. chronic sinusitis
  - GI conditions, e.g. Crohn's and coeliac disease
  - Endocrine conditions, e.g. hypothyroidism and Addison's disease
  - Rarely, in some of the more persistent cases, in which no improvement occurs over a long period, or parents seem unwilling to comply with treatment, child abuse should be considered.
- A full physical examination should include: measurement of height and weight; assessment for anaemia; neurological examination, including that of the fundi and assessment of muscle wasting; assessment of lymph nodes, including spleen; palpation of the sinuses to identify chronic sinusitis; measurement of blood pressure (BP); and examination of the neck to exclude a goitre, and abdomen for signs of inflammatory bowel disease. In children with CFS, there are very rarely any objective clinical signs, despite many clinical symptoms.

Investigations

- There is no specific diagnostic test, but investigations are required to exclude conditions within the differential diagnosis.
- Even if the clinical picture makes anything other than CFS unlikely, parents often find it reassuring for investigations to be performed.

Recommended blood tests for chronic fatigue syndrome

- FBC and film.
- Ferritin, vitamin B_{12}, and folate.
- Viscosity or ESR.
- CRP.
- Blood glucose.
- U&Es.
- Creatine kinase.

- Thyroid function.
- LFTs.
- Viral serology—for EBV IgM and IgG, and EBV nuclear antigen (EBNA).
- Coeliac disease screening (tissue transglutaminase (TTG) or anti-endomysial antibodies).

Treatment

Part of the treatment is a clear clinical diagnosis of CFS and a thorough explanation of the diagnosis and outcome.

- Although there are claims made for the effectiveness of many different types of treatment, including anti-infective agents, antibiotics, immunoglobulin, and complementary therapy (e.g. acupuncture, aromatherapy), these are not based on any supportive evidence.
- The recommended treatment involves activity management—establishing a baseline of activity level and gradual increases as appropriate; clear psychological support giving advice, and symptomatic treatment, as required, and a regular clinical review of progress. It helps families to see the same person with regular planned appointments every few months, with a thorough clinical examination every time. It is not usually necessary to repeat blood tests.
- In children with a more severe and prolonged illness, a multidisciplinary team approach is recommended, including a paediatrician, physiotherapist, occupational therapist, and psychologist.
- The outcome overall is good, with most studies reporting 75–90% improvement over 2–3 years. There are often periods of relapse associated with intercurrent viral upper respiratory infections, especially in the winter. Children with CFS are usually better in the summer periods. Families should be encouraged towards slow, but steady, progress over time, recognizing that relapses and setbacks will occur. Continued attendance at school (even if only for a few mornings a week) is very important, as is social contact with friends. A positive attitude towards eventual recovery is realistic, based on the literature.

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Chapter 11

Congenital infections

See also Chapters 30, 57, 58, 62, 64, 92, 100, 106, 107, 111.

Introduction

- Pregnant women represent a vulnerable population with an increased risk of infection and consequent adverse outcomes for themselves and their infant. Maternal infections that have the potential of infecting the fetus or newborn include bacterial, viral, and protozoal causes (Table 11.1).
- Maternal infection during pregnancy can cause devastating short- and long-term consequences for the fetus.
- *In utero* infections can cause resorption of the embryo, abortion, stillbirth, congenital malformations, intrauterine growth retardation (IUGR), prematurity, and congenital infection.
- Infections acquired during labour and birth can lead to severe systemic disease and death or long-term disease and disability.
- For some congenital infections, there may be no signs or symptoms in early life, and it can take weeks to years for consequences to become apparent.
- Intrauterine infection is also a frequent and important mechanism leading to preterm birth.
- Premature infants are themselves at higher risk of infections, including septicaemia, pneumonia, and meningitis, as well as being susceptible to intrauterine and perinatal infections.

Table 11.1 The most important congenital and perinatal infections

Bacteria	Virus	Protozoa
GBS	HIV 1, 2	*Toxoplasmosis gondii*
Listeria monocytogenes	Rubella	Malaria
E. coli	CMV	
N. gonorrhoeae	Parvovirus B19	
Chlamydia trachomatis	HTLV-1	
Treponema pallidum	Hepatitis B and C	
	Varicella-zoster	
	Herpes simplex	

HTLV-1, human T-lymphotropic virus.

Epidemiology

- In the UK, infection in the first 7 days of life occurs in 1 per 1000 live births. Different congenital infection rates are explained further shortly.

Mechanisms of infection

See Fig. 11.1 for mechanisms of infection.

Intrauterine infection

- Transplacental spread after maternal infection and invasion of the bloodstream is the usual route by which the fetus becomes infected.
- Sometimes the placenta may become infected without fetal spread.
- The effect of maternal or placental infection on the fetus may be due to direct actions of toxins or organisms, or they may be indirect and a consequence of interference with placental or uterine function.
- Infections affecting the placenta may compromise normal placental function, e.g. a reduction in the transplacental transfer of antibody or fetal malnutrition due to reduced blood flow.
- Children born with congenital infections, such as rubella, often have multisystem disease.
- The infant often secretes large amounts of the pathogen for prolonged periods.
- There may be long-term tissue damage as a result of these infections, especially in the brain, ears, and heart, and sensorineural deafness is the commonest outcome of congenital infection.

Ascending infections

- The genital tract may be colonized by a transmissible pathogen (e.g. GBS, *Chlamydia*, or gonococcus).
- These pathogens can ascend to the amniotic sac, causing amnionitis by the cervical amniotic route, especially if there is a delay in delivery after the rupture of membranes, as this increases the time the fetus is exposed to the potential pathogen.

Intrapartum infections

- Infection may also be acquired as a result of exposure to infected cervical secretions, maternal blood, or faeces during passage through the birth canal. For example, gonococcus or HIV may be acquired at birth if the infant ingests infected genital tract secretions or maternal blood during vaginal birth.
- Scratches on the infant's skin may also provide a portal of entry, e.g. in the case of neonatal herpes where the risk of infection may be increased by invasive procedures such as scalp electrodes.
- Intrapartum and perinatal infections rarely result in severe or multisystem disease, and the signs of infection may not be immediately apparent.
- In some circumstances, there is a role for intrapartum prophylaxis, e.g. intrapartum antibiotics for women known to be colonized with GBS.

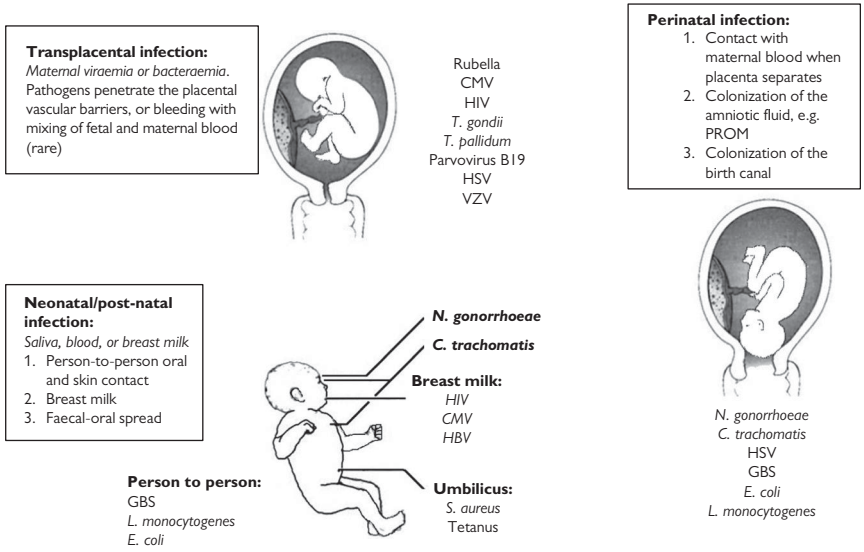

Fig. 11.1 Common mechanisms of mother-to-child transmission of infection and associated pathogens.

CMV, cytomegalovirus; GBS, group B *Streptococcus*; HBV, hepatitis virus B; HIV, human immunodeficiency virus; HSV, herpes simplex virus; PROM, premature rupture of membranes; VZV, varicella-zoster virus.

Post-natal infections

- During the first weeks of life, an infant is in intimate contact with its mother.
- Transmission of infection can occur from saliva or other body fluids.
- Breastfeeding may be responsible for the passage of infection, e.g. in post-natal acquisition of CMV, hepatitis B, or HIV. Additionally, if the mother has an infection, this may pass to the infant in breast milk. Cracked, bleeding nipples may be another source of potential infection, as infants may ingest infected maternal blood.
- In countries, such as the UK, where there is a high proportion of hospital births, health care-associated infections are another potential source of pathogen acquisition during the neonatal period.

The importance of timing of infection

The gestational age of the pregnancy when infection occurs may influence the risk of vertical transmission and/or the fetal or perinatal consequences. For example, the risk of serious congenital defects following rubella infection is greatest in the first trimester of pregnancy when the virus affects organogenesis and is associated with a high risk of serious congenital defects, including cataracts, heart defects, and sensorineural deafness. Exposure to rubella late in pregnancy or after birth poses little risk. Maternal toxoplasmosis infection also affects organogenesis, and the outcome of infection is most likely to be severe between the second and sixth months of pregnancy, when the risk of cerebral calcification, cerebral palsy, and epilepsy is greatest. In contrast, the risk of severe disease in varicella or herpes infection is greatest at the time of delivery.

Fetal exposure to CMV infection poses a risk of adverse sequelae at any stage of pregnancy. Although congenital CMV is associated with a significant risk of adverse sequaelae at any stage, infection acquired by the infant during birth from exposure to infected cervical secretions or in the post-partum period from infected breast milk is not associated with adverse outcomes, except in the very premature or immune-compromised infant.

Some perinatally acquired infections, such as HIV or hepatitis, do not present as acute infection in the newborn period but present subsequently with symptomatic disease.

Clinical presentation

Congenital infection may be apparent at birth, but some infections take months or years to manifest. The differential diagnosis of a neonate who presents severely unwell with multisystem involvement includes: sepsis, metabolic disorders, and malignancy. Some presenting features that may direct investigations include:

- *Skin/mucous membranes*: petechial rash of thrombocytopenia, 'blueberry muffin' ecchymotic rash of intradermal haematopoiesis, ulcerating/blistering lesions from herpetic or syphilitic infection
- *CNS*: signs of long-term and ongoing damage, with microcephaly, calcification, hydrocephalus, migration defects, microphthalmia, cataracts, retinitis, hearing loss

- *Reticuloendothelial system*: lymphadenopathy, hepatosplenomegaly, bone marrow failure with cytopenias
- *Lungs*: pneumonitis
- *Heart*: multiple structural defects
- *Gut*: hepatitis, jaundice, luminal strictures, malabsorption
- *Bones*: osteochondritis in syphilis.

Approach

- Investigation of congenital infection involves testing the mother and infant.
- Test the placenta where possible.
- Every effort should be made to specifically detect the infection, whether by culture or PCR.
- It is important to take samples as soon as possible in a symptomatic infant, as the yield will be greater.
- Previously a 'TORCH' screen was ordered. However, these serological tests have now been superseded by a multipronged investigational approach that includes blood tests, radiology, and other screening (Table 11.2).

Table 11.2 Investigations for suspected congenital infection

	Mother	Fetus	Neonate	Placenta
Blood tests	1. Immunoglobulin and IgG avidity High avidity—previous infection Low avidity and IgM—recent infection 2. Viral load and PCR	Fetal blood tests for: serology, culture, and PCR	1. Cultures, PCR 2. Paired quantitative serology at birth, from mother and newborn	
Radiology		Serial ultrasound scanning, MRI		
Other tests		Amniocentesis	1. PCR and culture from: skin, mucous membranes, any vesicular lesions, urine, CSF 2. Dark ground microscopy of ulcerated skin or mucosal lesions—syphilis	Histology, culture, PCR

Specific congenital infections to consider

Cytomegalovirus

Epidemiology

A total of 0.7% of infants are born with CMV worldwide; 11% of infants with early signs and symptoms of CMV disease are most at risk of permanent neurological impairment, including sensorineural hearing loss (SNHL). CMV accounts for ~20% of all SNHL and is the commonest non-genetic cause of SNHL.

Clinical features

- *Fetus*: 40% of infants born to a mother with CMV infection during pregnancy are CMV-infected. Where the fetus has early *in utero* evidence of CNS damage (e.g. calcification, hydrocephalus, microcephaly, etc.), the long-term prognosis is poor. Echogenic bowel on fetal ultrasound scan can be a sign of congenital CMV infection.
- *Infant*: At birth, 5–10% of CMV-infected infants present with multisystem disease; the remainder are clinically asymptomatic.

Congenitally and perinatally infected infants may asymptomatically excrete high levels of CMV in the urine for months or even years.

Management

Currently, antiviral treatment is recommended for infants with CNS involvement presenting in the first 30 days of life. A recent RCT has demonstrated that 6 months of oral valganciclovir therapy has superior neurodevelopmental outcomes, compared to 6 weeks, and this is now the standard of care therapy. Valganciclovir has short-term, and potential long-term, toxicities, so treatment should always be discussed with a paediatric ID team.

Rubella

Epidemiology

Since the introduction of the measles, mumps, and rubella (MMR) vaccine to the UK, congenital rubella syndrome is now very rare. There have only been 16 cases in the UK since the year 2000, of which 11 were born abroad.

Transmission and incubation period

The incubation period is 13–20 days. Transplacental spread occurs during periods of viraemia.

Clinical features

- *Fetus*: 51% of infants born to mothers infected during the first trimester will be affected. The risk of multisystem damage is far less after 16 weeks' gestation.
- *Neonates* with congenital rubella syndrome may be born with IUGR, microcephaly, structural cardiac anomalies, cataracts, deafness, and focal inflammatory damage in the bone marrow, liver, lungs, and brain.

Asymptomatic neonates may later develop abnormal neurology, and haematological and immunological dysfunction.

Management

Symptomatic and supportive.

Parvovirus B19

Epidemiology

- Parvovirus is extremely common, and seroprevalence in the under 5s is 5–10%. Seroprevalence is high in pregnant women, and the fetus may be at risk of fetal hydrops.

Clinical features

- *Fetus*: Infection without fetal loss or hydrops is common. There is no evidence of B19-associated congenital abnormality in the newborn or developmental abnormalities appearing later in childhood.

Management

- Maternal serum should be collected as soon after contact as possible.
- On diagnosis of parvovirus B19 infection, ultrasound scanning of the fetus is started 4 weeks post-onset of illness or date of seroconversion, and then at 1- to 2-weekly intervals until 30 weeks' gestation. Fetal hydrops may develop due to infection of the fetal bone marrow with subsequent suppression and severe anaemia; in such cases, *in utero* transfusion may be required.

Varicella-zoster virus

Congenital varicella syndrome

This is very rare. The risk of congenital varicella syndrome if a pregnant woman gets chickenpox is:

- <1% prior to 13 weeks' gestation
- 2% between 13 and 20 weeks.

Clinical features

- Cataracts and chorioretinitis.
- Limb hypoplasia.
- Cortical and muscular atrophy.
- Low birthweight.
- Dermatomal skin scarring—unique to VZV.

Neonatal varicella syndrome

If chickenpox occurs in a pregnant woman from 1 week before, or up to 1 week after delivery, a severe or fatal infection may occur in the neonate due to transplacental infection causing disseminated VZV.

Management

- Varicella-zoster immunoglobulin (VZIG).
- If any symptoms develop, despite VZIG, high-dose IV aciclovir.
- Most neonatologist give prophylactic IV aciclovir in neonates whose mothers develop varicella from 4 days before to 3 days after delivery (these babies are at highest risk of fatal outcome despite VZIG prophylaxis).

Syphilis

Epidemiology

A Public Health England (PHE)/British Paediatric Surveillance Unit (BPSU) UK prospective study of congenital syphilis determined prevalence in the UK of 0.0025 per 1000 live and stillbirths in 2011.

Transmission and incubation period

Infants are much more likely to be infected if the mother has 1° (100%) or 2° syphilis during pregnancy than if she acquired syphilis months or years before conception.

Clinical features

- *Fetal*: 30–40% of fetuses with congenital syphilis are stillborn. Infection of the fetus occurs most commonly in the second/third trimesters.
- *Neonatal*: two-thirds of infected infants are asymptomatic at birth but present with symptoms within the first 5 weeks.

Hepatosplenomegaly (nearly always present), prematurity, IUGR, generalized lymphadenopathy, osteochondritis, mucocutaneous blistering lesions, and renal, CNS, and ocular manifestations may be present.

Management

- Treat infants who are symptomatic and/or Venereal Disease Research Laboratory (VDRL)-positive.
- Treatment: aqueous crystalline benzylpenicillin for 10–14 days (IV or intramuscular (IM)).
- After treatment, 70% should be VDRL-negative by 1 year.

Toxoplasmosis

Epidemiology

Three per 100 000 live births in the UK.

Transmission and incubation period

The risk of fetal infection increases with gestation, but the severity of infection is correspondingly reduced.

Clinical features

Congenital infection: features vary widely and include hydrocephalus, cerebral calcification, microcephaly, microphthalmia, chorioretinitis, hepatosplenomegaly, and jaundice.

Up to 85% of congenitally infected babies seem normal at birth but may later develop retinitis, epilepsy, and learning difficulties.

Treatment

This is controversial and potentially toxic, and should be discussed with an ID team.

Herpes simplex virus 1 and 2

Epidemiology

- Incidence of neonatal herpes infection 0.2/1000 live births.
- Both HSV 1 and 2 perinatal infections may cause severe neonatal disease.

Transmission and incubation period

- Maternal infection may be 1° or due to reactivation of HSV (viral load higher in 1°).
- Symptoms may appear 4–5 days after birth—most disseminated infections becoming apparent by 11–12 days.

Clinical features

- *Skin, eye, and mouth disease*: vesicles/crusted lesions on the skin or mucous membranes; some may progress to CNS disease in the second week. Skin recurrences are frequent, and up to 30% have long-term neurological sequelae.
- *Encephalitis*: infants usually become symptomatic in the second week of life. A rash is only present in up to 30%. The baby may be encephalopathic with seizures.
- *Disseminated infection*: severe sepsis at around days 4–6; in 50%, there is a rash. Other manifestations include: pneumonitis, liver failure, coagulopathy, encephalitis.

Management

- IV high-dose aciclovir is the recommended treatment for disseminated neonatal herpes/herpes encephalitis and skin, eye, and mouth disease. Treatment must be started immediately on suspicion; do not wait for test results. High-dose aciclovir should be given for at least 3 weeks, or longer if there are ongoing symptoms. Relapses are common, and many clinicians will give long-term oral suppressive therapy to prevent recurrence for up to the first year of life.

Chlamydia trachomatis

Epidemiology

Two to 10% asymptomatic infection in young women; 25% of infants develop conjunctivitis within 7 days.

Clinical features and sequelae

Up to 5% of infants with eye disease may develop pneumonia (after 4–12 weeks). Fever and hypoxia may or may not be present.

Management

Treat the infant with erythromycin (20% relapse rate). Arrange genitourinary screening and treatment for the mother and partner.

Future research

- Improved antenatal diagnostic tests.
- Further clinical trials in the antenatal and post-natal treatment.
- Improved evidence base for screening for rarer infections.

Further reading

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Chapter 12

Diarrhoea and vomiting

Introduction

Diarrhoea and vomiting, alone or together, are extremely common presentations to health care in childhood. Diarrhoea is often defined as loose or watery stools at least twice as frequent as normal for that child. While acute gastroenteritis is the commonest cause of diarrhoea and vomiting, other causes must be considered. Vomiting may be the presenting feature of surgical conditions such as intussusception or appendicitis, systemic illness, and non-enteric sepsis.

Epidemiology

- Acute gastroenteritis presenting with diarrhoea and/or vomiting is extremely common in childhood.
- Diarrhoeal deaths have decreased over the last 15 years but are still responsible for at least 700 000 deaths annually in children under 5 years due to dehydration.[1]
- In Europe, each year, 0.2–0.7% of children <5 years are admitted to hospital with gastroenteritis, with those between 6 and 24 months at especial risk.[2]
- Only a small proportion of cases present even to primary health care, with most treated at home.
- Gastroenteritis occurs all year round, with seasonal winter/spring peaks in temperate climates due mostly to rotavirus.
- Where rotavirus vaccine programmes have high coverage, admissions have reduced markedly for rotavirus gastroenteritis, and moderately for non-rotavirus-coded gastroenteritis.
- In tropical settings, there are less seasonal patterns, with less predictable timing of outbreaks.[3]
- Risk factors for developing gastroenteritis include non-breastfeeding and out-of-home childcare.
- Asymptomatic infection with many gastroenteritis pathogens are common, including rotavirus and norovirus.

Aetiology

- An infectious agent can be identified in up to 70% of episodes of community-acquired gastroenteritis.
- Rotavirus is the commonest cause of sporadic gastroenteritis in children—95% of rotavirus infections are due to the four most frequent serotypes.

- Norovirus is next commonest and dominates where rotavirus vaccines are widely implemented.
- Other viral causes include astroviruses, adenovirus (types 40 and 41), and sapoviruses. More recently, other viruses, including bocaviruses, coronaviruses, picobirnaviruses, and toroviruses, have been proposed as aetiologic gastroenteritis agents.[4]
- *Campylobacter, Salmonella*, and *Aeromonas* spp. are significant enteric pathogens in the UK, while, in developing settings, *Shigella* is a major pathogen.
- In developing settings, bacterial pathogens assume greater importance for residents (*Campylobacter, Shigella*, and *Salmonella* spp.) and tourists (especially enterotoxigenic *E. coli*).
- *Cryptosporidia* and *Giardia* are important pathogens, especially in childcare and resource-poor settings, but rarely cause severe acute disease.
- *C. difficile* infection is increasingly recognized as a paediatric and adult nosocomial pathogen, and community diarrhoea incidence has also increased.

Pathophysiology

- Most enteric pathogens are transmitted by faecal–oral transmission—viral pathogens transmit person to person or via fomites, with norovirus also transmissible in aerosolized vomit.
- Contaminated food is a risk factor for bacterial pathogens and norovirus. Water-borne transmission is commoner with bacteria and protozoa.
- Rotavirus infects mature enterocytes of jejunal and ileal villi. Cell destruction and loss of villous architecture result in a massive reduction in the absorptive surface area and exposure of the immature enterocytes at the base of the villi, increasing fluid loss. Net loss of water and salt in the faeces manifests as diarrhoea. On days 2–5 of symptoms, adjacent villi fuse to help reduce the surface area of immature cells and decrease fluid loss. Between days 6 and 10, the villous architecture is restored. Rotavirus enterotoxin NSP4 also contributes to the enteritis.
- Invasive bacteria (*Shigella, E. coli, Salmonella, Campylobacter, Yersinia, Aeromonas*) typically cause an enterocolitis, with white cells and blood more commonly present in the faeces.
- Bacterial enterocolitis can result from a number of mechanisms, including mucosal ulceration and inflammation, and toxin production affecting cellular processes.
- Enteritis-producing *Bacillus* spp. and *S. aureus* have preformed toxins, while *Vibrio cholerae* and *E. coli* produce toxins following infection, including the enterohaemorrhagic *E. coli* toxin responsible for haemolytic–uraemic syndrome (HUS).
- *C. difficile* toxin-associated disease has become more important as a cause for nosocomial diarrhoea in childhood but can be a normal commensal in up to 40% of neonates.

Clinical manifestations

- Acute diarrhoea and/or vomiting in early childhood may also be associated with common primary infections of other organs, including upper and lower respiratory tract infections (LRTIs), as well UTIs.
- In childhood, it is extremely difficult to differentiate between community-acquired gastroenteritis pathogens, based upon the clinical presentation.
- Seizures with gastroenteritis strongly indicate *Shigella* as a likely cause in *Shigella*-prevalent areas; seizures have also been described with rotavirus.
- Rotaviral gastroenteritis classically occurs following a short 1- to 3-day incubation period. Vomiting is common early in the illness, with hospital studies describing it in up to 97% of patients. Fever is common, with fever >39°C present in up to one-third.
- Dehydration (usually isotonic) varies in frequency; it is seen in 7% of cases in community cohorts, and up to 63% admitted to hospital.
- Upper respiratory tract symptoms and signs may be seen in up to 40% of cases of gastroenteritis.

Investigations

- The decision to test for gastroenteritis pathogens is based upon several factors, including:
  - To allow the assessment of the organism epidemiology
  - To detect potential food-borne outbreaks that may require intervention
  - For unusual presentations (such as significant bloody diarrhoea)
  - To enable cohorting in hospitals to minimize nosocomial transmission
  - For nosocomially acquired cases to detect hospital outbreaks.
- Faecal culture remains important for the diagnosis of bacterial pathogens, and microscopy of a fresh faecal concentrate for protozoal pathogens.
- Antigen detection tests, including latex agglutination assays and enzyme-linked immunosorbent assays (ELISAs), are less sensitive than molecular assays for viral pathogens but may have the advantage of lower cost and decreased risk of detecting asymptomatic carriage. The clinical significance of PCR-detected *Dientamoeba fragilis* and *Blastocystis hominis* is uncertain.
- *C. difficile* assays usually detect the toxin or the gene coding for the toxin.

Management

- Oral rehydration therapy remains the cornerstone of gastroenteritis management, using recommended oral rehydration solution (ORS) to facilitate the co-transport of glucose and sodium across the small bowel epithelium.[5]
- The use of ORS can reduce gastroenteritis mortality by up to 93%.
- Even in acute bacterial gastroenteritis, antibiotics are rarely used.
- Bowel antispasmodic agents may be used in many adult cases but are contraindicated in children.

Prevention

- Community-level interventions, including handwashing, improved water quality, and disposal of faeces, are each thought to have reduced infectious diarrhoea, especially bacterial and protozoal gastroenteritis.
- Hand hygiene, using soap or ethanol-based preparation implementations, reduces viral loads of rotavirus and norovirus on the skin, but it is unclear whether these are reduced to non-infectious levels.
- Limitation of antimicrobial use in hospital patients reduces the risk of *C. difficile* colitis.
- The introduction of rotavirus vaccines in 2006 has seen their implementation in developed and developing settings, with 30 Gavi-eligible developing countries expected to include rotavirus vaccine in their national immunization programmes by 2015. All vaccines licensed to date have shown highest efficacy (up to >90%) in developed settings against severe rotavirus gastroenteritis, with efficacy in developing settings around 50%.[6]
- Rotavirus vaccines to date are oral, live attenuated vaccines, with some making use of the segmented rotaviral genome to create multiple strain reassortant vaccines.
- A small increased risk of intussusception has been observed following the first and/or second doses of rotavirus vaccine in the 3 weeks following dosing.
- Reduction in diarrhoea mortality has been demonstrated following rotavirus vaccine implementation in developing settings.[7]
- Interestingly, a 20% reduction in febrile seizure presentations has also been observed in rotavirus-vaccinated US children.[8]
- Breastfeeding near dosing does not impair immune responses to rotavirus vaccination.

What's new?

- Implementation of rotavirus vaccines has decreased diarrhoea mortality in developing settings, and severe rotavirus gastroenteritis requiring admission in all settings.
- Noroviruses are the commonest cause of childhood diarrhoea in most developed settings where the rotavirus vaccine has been introduced.
- Rotavirus may be responsible for up to 20% of febrile seizures in childhood.

What's next?

- Multiple rotavirus vaccines of differing design and dosing strategies are in late-stage clinical trials, many produced by low-cost manufacturers.
- Norovirus vaccines have reached clinical trials.
- Newer molecular techniques are continuing to 'close the diagnostic gap' in identifying causes of gastroenteritis.

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Chapter 13

Emerging infections and pandemic preparedness

See also Chapters 14, 45, 63, 79, 115.

Emerging infections

Introduction

- Among infectious diseases, a number of infections remain a constant threat to humans. Additionally, there are the *emerging, re-emerging* (or re-surging), *newly recognized*, and *deliberately emergent* infectious diseases.
- Emerging and re-emerging infections are often a consequence of complex interactions between the pathogen, host, and the environment:
  - Pathogens, particularly viruses, have a selective advantage in adapting to new ecological niches because of their high replication rates and their genetic plasticity, which allows them to acquire new biological characteristics through mutation, recombination, and reassortment
  - Host factors include: population growth and migration; increase in international travel, trade, technology, and industry; behavioural changes; ageing population; the use of broad-spectrum antibiotics and immunosuppressive drugs; breakdown of public health measures; war; poverty and social inequality; and intentional biological attacks
  - Environmental factors (many of them induced by humans) include: climate and weather changes; agricultural development and land use; changing ecosystems; livestock farming; changing relationships between humans and animals; deforestation; reforestation; urbanization; famine; and flooding.
- *Emerging infections* refer to infections that have newly emerged in a population:
  - Around 75% of emerging infections are zoonotic and arise when humans encroach on environments where they become exposed to microbes that they would otherwise not have encountered, or when there is close and prolonged contact between humans and animals, which allows microbes the opportunity to jump the species barrier (Box 13.1).
- *Re-emerging or resurging* infections refer to emergence of a known infection in a different form or in a different location (Box 13.2).

Box 13.1 Examples of recent emerging infection

Severe acute respiratory syndrome (SARS): the first emerging infection of the new millennium began in the Guangdong province of South China, which has a high population density of humans and wild and domestic animals. The aetiological agent, a previously unknown coronavirus, jumped across the species barrier from its natural reservoir, the bat, to susceptible animals such as civets and raccoons, and then to humans. The infection spread so rapidly across the world that, in a short period of time, it was responsible for over 8000 cases and almost a thousand deaths in 30 different countries.

New variant Creutzfeldt–Jakob disease (vCJD): transmissible spongiform encephalopathies (TSEs) are a rare group of progressive neurological conditions characterized by the loss of neuronal tissue, causing a typical sponge-like appearance of the brain. Unlike our common perception that all pathogens required nucleic acid to direct their replication, the aetiological agent in TSE is the prion protein, which is normally found on the surface of many cells in the body, including the brain. In TSE, the normal form of the prion protein undergoes a spatial conformation that makes it resistant to normal cellular degradation and sets up a chain reaction that induces other normal prion proteins to fold into the abnormal form. TSEs are unique in that their aetiology may be sporadic (sporadic CJD), genetic (familial CJD), iatrogenic (blood transfusions, neurosurgery), or infectious (ingestion of infected material). In the UK, in the 1980s, the bovine spongiform encephalopathy (BSE) epidemic, commonly known as mad cow disease and affecting over 200 000 cows, was most likely a result of cattle being fed the remains of other cattle with BSE. Contrary to all expectations, the disease crossed the species barrier, and the first human case of 'mad cow disease', termed variant CJD (vCJD) was reported in the mid 1990s. Because of its prolonged incubation period (up to 40 years), the true burden of infection is not known. By October 2009, vCJD had killed 166 people in Britain and 44 elsewhere.

Viral haemorrhagic fevers: haemorrhagic diseases caused by viruses, such as Ebola and Marburg, which were identified in the 1960s and 1970s, are often classed as emerging infections, because they appear suddenly and cause severe disease with a very high case fatality (75–90%). However, these episodes are rare, usually occur in a well-defined geographical location and, because of their rapid onset and high fatality, usually 'burn out' rapidly and return to their, as yet unidentified, natural host.

Box 13.2 Examples of factors that have contributed to emergence and re-emergence of specific infections

International travel: the classic example of an infection emerging in a new region is the West Nile virus which is a well-known cause of meningoencephalitis in Africa and the Middle East. In 1999, the virus appeared in New York through an unknown route, possibly via an infected bird or mosquito and, since then, has spread throughout the US, Canada, Mexico, the Caribbean, and Central America. Similarly, the chikungunya virus was first described in 1952 in Tanzania. In 2004, localized outbreaks on the coast of Kenya resulted in a rapid spread of the infection to the Indian Ocean islands and, from there, to many parts of the world. In particular, the disease caused an outbreak of unprecedented magnitude in India, affecting over a million people.

Breakdown in public health measures: infections that were previously well controlled may re-emerge if there is a reduction in public health measures, either because of a change in service provision (including immunization programmes) or reluctance in accepting a service.

Antibiotic pressure: the accidental discovery of the first antibiotic in 1928 was heralded as one of the triumphs of modern medicine. Extended use of broad-spectrum antibiotics, however, has resulted in the emergence of pathogens that were previously considered to be well controlled, such as multiresistant *M. tuberculosis* and *Plasmodium falciparum* infections worldwide, MRSA, VRE, and certain multiresistant Gram-negative bacilli.

Immunosuppression: the development and successful use of immunosuppressive drugs for the treatment of malignancies and autoimmune disorders has seen a rise in opportunistic bacterial, viral, fungal, and parasitic infections, such as *Pneumocystis jirovecii* (previously known as *Pneumocystis carinii*) infections, toxoplasmosis, aspergillosis, cryptococcosis, atypical mycobacterial infections, disseminated adenovirus and CMV infections, and histoplasmosis, among many others.

Other factors: other factors that may play a role in emerging and re-emerging infections include population growth and migration (e.g. *Plasmodium knowlesi* malaria in South East Asia); climate and habitat changes (e.g. *Sin nombre* virus causing acute cardiopulmonary syndrome in south-west US); migratory patterns of animals and birds (avian influenza); changes in agriculture practices (Argentine haemorrhagic fever; Korean haemorrhagic fever); and human practices such as building dams (Rift Valley Fever), among many others.

- *Newly recognized infectious diseases* refer to conditions that are now recognized to be caused by infections (Table 13.1).

Table 13.1 Examples of newly recognized infectious diseases recently associated with chronic diseases

Disease	Pathogen
Gastritis, gastric ulcers and stomach cancers	*Helicobacter pylori*
Cervical cancer	Human papillomavirus
Liver cancer	Chronic hepatitis B and hepatitis C
Bladder cancer	Schistosomiasis
Kaposi's sarcoma	HHV-8

- *Deliberately emergent pathogens* are those that are intentionally planned by humans through bioterrorism (Table 13.2):
  - These agents are usually found in nature but may be altered to make them difficult to detect, increase their ability to cause disease, make them resistant to treatment, and/or increase their ability to propagate in the environment
  - Bioterrorism is often used to create mass panic and cause disruption to society, out of proportion to the actual number of deaths or illness caused
  - Pathogens with a potential for use in bioterrorist attacks have been classified into category A (high-priority agents such as anthrax, smallpox, botulinum toxin, bubonic plaque, tularaemia, and viral haemorrhagic fevers (VHFs)), category B (moderate-priority agents such as brucellosis, ricin, melioidosis, and cholera), and category C (emerging pathogens that could be engineered for mass spread in the future).

Table 13.2 Examples of recent notable bioterrorist attacks

Year	Event
1984	The Bhagwan Shree Rajneesh religious group attempted to control a local election by infecting 11 restaurants and grocery stores with *Salmonella typhimurium* in Oregon, US; more than 750 people developed severe gastroenteritis, and several hundreds were hospitalized, although none died
1993	The Aum Shinrikyo religious group released anthrax spores in Tokyo, Japan. Although not a single person was infected in that attack (because anthrax spores are so difficult to aerosolize at high concentrations), the same group was also responsible for subsequent deadly attacks using sarin gas, a deadly nerve agent, in 1994 and 1995
2001	Letters deliberately laced with anthrax were sent to news media offices and the US Congress, killing five people

Conclusions

- Human beings have been under constant threat of emerging and re-emerging infections, and this is likely to continue in the foreseeable future.
- As our understanding of the factors associated with emergence and re-emergence of infectious diseases increases, it is becoming clear that an increasingly modern world will provide more opportunities for new and old pathogens to thrive.
- We must recognize that the emergence of new transmissible pathogens is a global risk, and international collaboration is vital for surveillance, containment, and control of emerging infections.
- In the UK, Public Health England regularly reports on national and international outbreaks and incidents of new and emerging infectious diseases (see Further reading, p. 124).

Pandemic preparedness

A pandemic (from Greek πᾶν *pan* 'all' and δῆμος *demos* 'people') defines an epidemic of an infectious agent that has affected a significant number of people in a large region. Seasonal flu is excluded from this definition.

Pandemics have been a constant fear of mankind. Back at the very beginning of civilization, when humans began to settle, epidemics came with the domestication of animals, as happened with influenza and TB. In the Middle Ages, infections that wreaked havoc among the American population were spread by European explorers when they made contact with natives who never suffered from diseases like measles, smallpox, and influenza.

Phases of a pandemic

A document on pandemic preparedness guidance was published by the WHO in 1999. Revisions were made in 2005 and 2009, prior to the 2009 H1N1 pandemic, so the virus is not mentioned, but all the documents work on a basis that the next pandemic will be due to influenza. This organization developed a 6-stage classification for pandemics (Table 13.3). The first two stages make the inter-pandemic period when a novel strain has been detected only in animals, but not in humans. The third, fourth, and fifth stages are part of the 'pandemic alert period' where the first strains of that virus are detected in people. If the situation worsens and human-to-human transmission is seen at a fast rate in a wide geographic zone, a pandemic will be declared.

This 6-stage pandemic classification can be applied to any infectious agent. WHO has also published a document on assessing the risk of the next influenza pandemic and how to respond to each phase of the pandemic, as well as the steps to follow in the inter-pandemic period.[2] In this document, the 'pre-pandemic period' is called the 'alert phase', and a new 'transition phase' (Fig. 13.1) is added when the strength of the pandemic phase is starting to decline.

Table 13.3 The WHO phases[1]

Inter-epidemic period	
1	No new influenza virus subtypes have been detected in humans. An influenza virus subtype that has caused human infection may be present in animals. If present in animals, the risk of transmission is considered to be low
2	No new influenza virus subtypes have been detected in humans. However, a circulating animal influenza virus subtype poses a substantial risk of human disease
Pre-pandemic period	
3	Human infection(s) with a new subtype, but no human-to-human spread, or, at most, rare instances of spread to a close contact
4	Small cluster(s) with limited human-to-human transmission, but spread is highly localized, suggesting that the virus is not well adapted to humans
5	Larger cluster(s), but human-to-human spread still localized, suggesting that the virus is becoming increasingly better adapted to humans but may not yet be fully transmissible (substantial pandemic risk)
Pandemic period	
6	Pandemic phase: increased and sustained transmission in general population

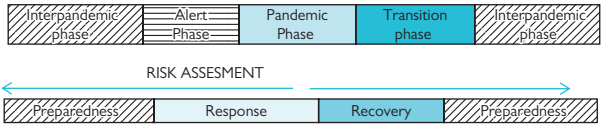

Fig. 13.1 The continuum of pandemic phases with indicative WHO actions.
(Source data from 'Figure 2. The Continuum of pandemic phases with indicative WHO actions' from the WHO document "Pandemic influenza risk management", published the 10th of June, 2013, <http://www.who.int/influenza/preparedness/pandemic/influenza_risk_management/en>.)

Current concerns about pandemics

- Actual pandemic threats: viral haemorragic fever—Ebola/SARS coronavirus (SARS-CoV)/Middle East respiratory syndrome—coronavirus/influenza.
- Current infectious diseases public health concerns: HIV—acquired immune deficiency syndrome (AIDS)/TB.[3]
- Superbugs: antibiotic resistance and lack of new antibiotics, multidrug-resistant Gram-negative bacteria (MDRGNB). Half a million new cases of MDR-TB are being seen worldwide.
- Biologic warfare: anthrax, Ebola, Marburg virus, plague, cholera, typhus, Rocky Mountain spotted fever, tularaemia, brucellosis, Q fever, yellow fever, and smallpox.

- Missed opportunities of integrating research and clinical trials in a new infectious disease outbreak. A FP7 programme called PREPARE is addressing this problem in the EU (🔗 <www.prepare-europe.eu>).

Preparing for a pandemic

There are a number of phases that should be taken to prepare for a pandemic. All of them should be coordinated by an international health organization as a pandemic is, by definition, a disease that crosses boundaries between countries.

Inter-epidemic period (WHO action—preparedness)

- Develop and carry out exercises in order to prepare for a future pandemic (exercises can be table-top exercises, functional exercises, and full-scale exercises; the last should integrate the results of the former) to estimate the capability of the health system of a nation and to detect errors in a general infectious agent outbreak protocol.
- Stockpile antiviral drugs and new adjuvants/vaccines.

Pre-pandemic period (WHO action—response)

- Identify the mode of pathogen transmission. Apply the correct preventive measures. Determine the symptoms of the disease with pandemic potential, and establish a protocol to detect new cases. Active vigilance for relevant clinical syndromes inside the area where the disease is detected.
- Identify the infectious agent. The population should be informed about the risk in a direct and simple method.
- Adopt the necessary support measures and, if possible, treatment measures. Research on a new treatment should be started as soon as the agent is identified. Conduct new clinical trials trying to find a potential new therapy or choosing the best option among current interventions.
- Development of a vaccine should be conducted at the same time as the research on new therapeutic options. Search for people that can be naturally immune to the disease, and try to find why they have that immunity.
- Distribute the treatment and vaccine, if possible, to those people with the disease and their contacts.
- Exercises from the previous period must be intensified.

Pandemic period (WHO action—response)

- Maintain the preventive measures. Public health may demand that boundaries between countries may be closed.
- Intensify research response started in the previous period.
- Disclose information about treatment and vaccination to the population.
- Intensify the treatment/vaccination campaigns. A drug or vaccine that can be self-administered will be the best option; if that is not possible, implement points for mass vaccination.

Transition phase

- Maintain the preventive measures. Restrictions on crossing boundaries can be lifted.
- Maintain the treatment/vaccination campaigns.
- Maintain the research response.
- At the end of this period, the pandemic is declared over, and a new inter-pandemic period starts.

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Chapter 14

Encephalitis

See also Chapters 28, 29, 64, 107.

Introduction

Encephalitis is a rare, but devastating, disease in children. It is defined by the presence of an inflammatory process of the brain, in association with clinical evidence of neurological dysfunction. In children, it is most commonly caused by infection, usually viral, but may also have metabolic, toxin/drug-mediated, autoimmune vasculitic, malignant, or genetic origins. Encephalitis in children may manifest as either acute encephalitis (direct invasion of the CNS) or post-infectious encephalitis (post-infectious immune-mediated demyelination). The diagnosis of encephalitis is usually confirmed from a combination of clinical presentation and brain imaging; it is very rarely proved by histology which requires brain biopsy.

Meningo-encephalitis describes the presence of clinical encephalitis with inflammatory changes in the CSF, implying coexisting inflammation of the covering meninges. Table 14.1 gives the differential diagnosis of encephalitis in a child.

Pathophysiology

Infection-associated encephalitis can be caused by several mechanisms:

- Organisms can enter by the haematogenous route, resulting in diffuse encephalitis, e.g. HSV/measles/influenza/*Listeria*/Lyme disease
- Viruses and selected bacteria can enter by neuronal tracts, resulting in focal encephalitis, e.g. temporal localization of HSV encephalitis due to retrograde spread of the virus from a site of latency in the trigeminal ganglion
- Immune-mediated encephalitis occurs where the host response to the infection causes 2° inflammatory changes in the CNS, most often within the white matter of the brain (e.g. after *Mycoplasma* or varicella-zoster infection)
- Slow virus brain infections may lead to low-grade inflammatory neurotoxic damage, which can take years to evolve to clinical significance. This may occur with HIV encephalopathy or subacute sclerosing panencephalitis (SSPE) with mutant measles virus, manifesting clinically up to 8–10 years after the 1° infection.

Table 14.1 Differential diagnosis of encephalitis in a child

CNS infections	Meningitis (viral/bacterial) Tuberculous meningitis Brain abscess Cerebral malaria
Para-infectious	Toxic shock syndrome Haemophagocytic lymphohistiocytic syndrome Reye syndrome Haemorrhagic shock and encephalopathy
Metabolic	• Fluid, electrolyte, acid–base disorders • Inherited diseases: • Amino acid and organic acid disorders • Urea cycle disorders • Lactic acidosis
Hypoxic–ischaemic	Vascular collapse, shock Cardiorespiratory arrest Near-miss sudden infant death
Vascular	Stroke (embolic/thrombotic) Venous thrombosis Inflammatory vasculitides (SLE, PAN, etc.)
Toxic injury	Endogenous (diabetes, uraemia, liver failure, haemolytic–uraemic syndrome) Exogenous (drugs, ingested poisons)
Seizure disorder	Status epilepticus
Immune-mediated	Anti-NMDA receptor antibody (may be post-infectious, idiopathic, or paraneoplastic) Hashimoto's encephalitis (associated with autoimmune thyroiditis) Behçet's syndrome
Raised intracranial pressure	Tumours and other malignancies Haematomas Acute hydrocephalus Lead poisoning

NMDA, *N*-methyl *D*-aspartate; PAN, polyarteritis nodosa; SLE, systemic lupus erythematosus.

Pathological findings

- Virus-induced cytolysis results in focal or generalized loss of neurons. Perivascular and parenchymal inflammation of the cortical grey matter, adjacent grey–white junction, basal ganglia, or brainstem is characteristic.
- Some viruses, including CMV and adenoviruses, produce characteristic inclusions in a small number of infected cells.

- Inflammation can cause a localized vasculitis that leads to haemorrhage or necrosis; this can occur with HSV infection and, in some cases, with influenza. Some agents cause direct endothelial damage.
- In immunodeficient patients, the natural history is frequently chronic, and pathological findings include cerebral atrophy, neuronal loss, and demyelination.
- Table 14.2 gives the commoner causes of encephalitis in children; however, in up to a third of cases, the aetiological agent is not identified.

Table 14.2 Infectious causes of encephalitis

Viruses	Herpesviruses (HSV, VZV, CMV, EBV, HHV-6)
	Enteroviruses (including polio)
	Parechovirus
	Adenoviruses
	Influenza viruses
	Mumps virus
	Measles
	Rubella
	Rabies virus
	Lymphocytic choriomeningitis virus
	HIV
	Arboviruses (e.g. central European tick-borne encephalitis virus, West Nile virus, Japanese B, dengue, bunyaviruses; see Fig. 14.1)
Bacterial and other	GBS (neonatal)
	L. monocytogenes
	Mycoplasma pneumoniae
	Borrelia burgdorferi
	Bordetella pertussis (toxin-mediated)
	Bartonella henselae (toxin-mediated)
	Shigella spp. (toxin-mediated)
	Salmonella spp. (toxin-mediated)
	Campylobacter jejuni (toxin-mediated)
	M. tuberculosis
	Toxoplasma gondii
	Rickettsia rickettsii

Incidence and aetiology

- Encephalitis is a rare disease, with an estimated incidence of only 4/100 000 in the UK. Incidence varies greatly in different parts of the world, depending on the season of the year and the geographical restriction of different organisms.
- In a recent study of all age-reported encephalitis cases in England and Wales, infants aged <3 months accounted for 27% of cases but had the highest incidence (329/100 000). Enteroviruses were responsible for 52% of all cases (92% in <3 month olds), followed by HSV (29%) and VZV (13%).
- Manifestations of encephalitis depend on the host and the infecting organism; certain infections occur in both immunocompetent and immunocompromised hosts, but others only in the immunocompromised.
- Why only a very small minority of individuals develop encephalitis with common infections is not well understood, but host susceptibility factors are beginning to be identified. This has been demonstrated for rare individuals who have recurrent HSV encephalitis where an autosomal recessive deficiency in the intracellular protein UNC-93B results in impaired cellular interferon-α/β and γ antiviral responses, leading to recurrent HSV encephalitis.

Immunocompetent hosts

- Rates of epidemic encephalitis have fallen due to improved living conditions, vector control, and vaccines. Prior to MMR vaccination, mumps was the commonest cause of meningo-encephalitis in the UK. 1° varicella-zoster infection can be associated with generalized encephalitis or a post-infectious encephalitis, which usually manifests as cerebellitis. In some parts of the world, polio remains an important cause of encephalitis. Worldwide, the flavivirus Japanese B is one of the commonest causes of encephalitis, occurring most often in Asia. See Fig. 14.1 for the worldwide distribution of the many arboviruses which may cause encephalitis.
- Enterovirus infections are common, often in summer and autumn; symptoms may vary from none to meningitis or meningo-encephalitis. Most children make a full recovery, but some, especially young infants with parechovirus infection, may have long-term brain damage. Outbreaks of ECHO virus cause severe encephalitis in young children in the Far East.
- HSV is the leading cause of sporadic encephalitis in all ages (~2 cases per million population per year), and neonatal HSV encephalitis occurs in 2–3 per 10 000 live births in the US (less common in the UK). HSV encephalitis in older children and adults is neuronally spread and usually focused in the temporal lobes. In the neonate, the infection is haematogenously spread; the viral inoculum is much greater, and viral cytopathic damage seen throughout the brain substance. Relapse after HSV encephalitis can occur in up to a quarter of patients.
- Acute necrotizing encephalopathy—this was first described in Japanese children and is usually associated with influenza infection. Influenza

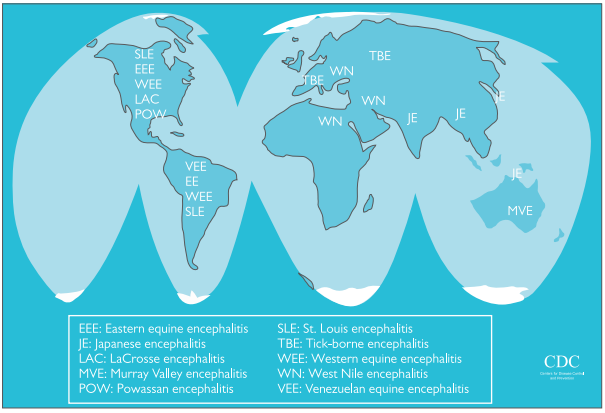

Fig. 14.1 Worldwide distribution of the major arboviruses that cause encephalitis.
(Reproduced from the Centre for Disease Control and Prevention, Atlanta USA, <http://www.cdc.gov/ncidod/dvbid/arbor/worldist.htm>)

virus is present in the respiratory tract, but not the CNS, where there is a severe pro-inflammatory response leading to brain necrosis. The condition may also be associated with a severe systemic inflammatory response with multi-organ failure. There is high mortality (25%), and most children have major neurological sequelae.

- Toxic encephalopathy (secondary to infectious agents)—a number of infections may have an encephalitic manifestation in some hosts, which is not due to the organism itself, but to toxin-mediated effects. Well-known examples include *Bordetella pertussis* and *Shigella* spp. (Table 14.2).

Post-infectious encephalitis

Acute demyelinating encephalomyelitis (ADEM) is the commonest demyelinating condition seen in children; it may complicate common childhood infections (e.g. HHV-6 infection, VZV, adenovirus, measles, influenza, *Mycoplasma*). It usually occurs some time after the prodromal infection (1–3 weeks) and is part of the spectrum of acute disseminated encephalomyelitis. There is a clinical continuum of such post-infectious inflammatory processes from the more diffuse to the more specific which affect the central and peripheral nervous systems, including: optic neuritis, transverse myelitis, acute cerebellar ataxia, Guillain–Barré syndrome, Miller–Fisher syndrome, and encephalomyeloradiculoneuropathy.

Other post-infectious encephalitides

- Anti-NMDA (*N*-methyl *D*-aspartate) receptor antibody encephalitis—this may occur as a post-infectious syndrome, with cross-reactive antibody production, leading to a secondary worsening of encephalitis,

often with a severe movement disorder. This is commoner in children than adults. Anti-NMDA receptor antibody encephalitis is now well recognized to occur post-HSV encephalitis, causing a biphasic illness with prolonged severe symptoms. Treatment with plasma exchange and immune modulation is required.

- Sydenham's chorea—following GAS infection, cross-reactive antibodies react with brain and basal ganglia tissue to produce this classic manifestation of rheumatic fever.
- PANDAS—paediatric autoimmune neuro-psychiatric disorders associated with streptococcal infection. Following GAS infection, a number of different syndromes have been described, including: obsessive–compulsive disorder; tics; Tourette's syndrome; and dyskinetic syndromes. These have been associated with anti-basal ganglia antibodies and MRI changes in the basal ganglia.
- Encephalitis lethargica—may occur post-viral infection, due to autoimmunity to deep grey matter neurons, manifesting as lethargy, parkinsonism, dyskinaesias, and neuro-psychiatric symptoms.

Immunocompromised hosts

- Congenital infections in the fetus with a poorly developed immune system, e.g. with members of the herpes family (CMV, VZV), rubella virus, syphilis, or *T. gondii*, may cause severe structural brain damage, and neurological symptoms present at birth.
- Infants and children with congenital immune deficiencies may present with encephalitis; this should always be considered in the differential diagnosis, e.g. infants with agammaglobulinaemia may develop chronic enteroviral encephalitis.
- HIV crosses the blood–brain barrier and establishes a slow neurotoxic inflammatory state. Around 5–10% of infants with HIV present with encephalopathy in the first year of life; untreated, this is associated with a very poor survival prognosis and often occurs with concomitant CMV infection. These infants present with motor signs, microcephaly, and global developmental delay; antiretroviral treatment prevents further deterioration. In older children or adults, CNS HIV may manifest as dementia, with vasculitis, neuronal loss, and brain atrophy. Individuals with advanced HIV disease and severe immunosuppression are also at risk of encephalitis from opportunistic infections (e.g. toxoplasmosis, VZV, CMV). They may also develop progressive multifocal leucoencephalopathy (PML) caused by polyoma virus infection (JC virus).
- Children who are immunosuppressed for iatrogenic reasons are also at risk of encephalitis; examples include: reactivation/infection with herpesviruses (CMV, HHV-6, VZV, EBV); JC virus; and enteroviruses.
- Hyperpyrexic (haemorrhagic) shock with encephalopathy occurs in infants <1 year of age. Reye's syndrome is associated with antecedent viral infections, including chickenpox and influenza.

Clinical features

The symptoms and severity of encephalitis depend on the age of the patient at the time of infection, the underlying aetiology, the type of virus, and the anatomical area(s) of the CNS affected.

- Onset is usually acute, often preceded by a non-specific, acute febrile illness.
- In some cases, onset may be subacute with altered behaviour, memory loss, personality change, abnormal movements, etc.
- Presenting symptoms in older children are headache and malaise; infants are typically irritable and lethargic.
- Early symptoms: fever, meningeal irritation (nausea, vomiting, neck pain and rigidity), and photophobia.
- Late symptoms: altered level of consciousness (lethargy to confusion to coma), generalized or focal CNS abnormalities (tremor, seizures, loss of bowel or bladder control), or unprovoked emotional outbursts.

Investigations and diagnosis

Important history for a suspected case of encephalitis

- Recent illness.
- Exposure to ill contacts.
- Place of residence (rural, urban).
- Animal exposure.
- Tick or mosquito bite.
- Recent travel or outdoor activities.
- Medications (taken by patients or other family members).
- Evidence of immunocompromise in the host.

Lumbar puncture and cerebrospinal fluid tests

- CSF abnormalities do not necessarily correlate with clinical severity.
- Measure the opening pressure, red cells, white cells, glucose, and protein. These may be normal, or the protein/WCC may be slightly elevated. Red cells may be elevated in cytopathic infection such as HSV encephalitis. A mononuclear predominance is commonest.
- Routine microscopy, rapid antigen, and culture for bacteria, *Mycobacterium*, and fungi.
- PCR is the most sensitive method to diagnose viral causes. HSV PCR may be falsely negative in the first 48–72 hours, and sensitivity will also be reduced after treatment with aciclovir. Bacteria-specific PCRs, or the 16S ribosomal PCR, may be used to try to detect bacterial infections where antibiotic treatment has already been started.
- CSF serology and PCR can be used to detect syphilis or Lyme disease.
- If SSPE is suspected, then paired serum and CSF measles antibody titres must be measured.
- CSF oligoclonal bands may be requested if demyelination is suspected.

Brain imaging

- MRI is the most useful imaging modality, showing brain oedema and inflammation in the cerebral cortex, grey–white matter junction, or basal ganglia. Make sure that all appropriate imaging sequences are undertaken, and with contrast where necessary. Always review brain MRIs with a neuroradiologist.
- Repeat brain MRI is important to demonstrate evolution of the inflammatory process; very early imaging within 24–48 hours of presentation may not demonstrate significant abnormality.
- Where post-infectious encephalitis is associated with a focus of demyelination in the white matter, e.g. in the basal ganglia or spinal cord, gadolinium contrast may improve the sensitivity of MRI in detecting vasculitis.
- CT should be used to evaluate patients with encephalitis if MRI is unavailable. This is important in the acute setting to exclude other forms of CNS disease, e.g. tumour, effusion, hydrocephalus, abscess, etc.

Electroencephalography

- A useful complementary test.
- Identifies patients with non-convulsive seizure activity who are confused, obtunded, or comatose.
- In HSV, electroencephalography (EEG) may show focal unilateral or bilateral periodic discharges localized in the temporal lobes.

Blood tests and other specimens

- Standard laboratory tests and paired sera for serological tests for any suspected virus are important.
- Blood, urine, nasopharyngeal aspirate (NPA)/throat swabs, eye swabs (if inflamed), and stool/rectal swabs for culture of viruses and bacteria should always be collected. Skin lesions may be biopsied, and blister lesions should also be swabbed for bacteria and viruses.
- Anti-streptolysin O titre if streptococcal infection suspected.

Brain biopsy

- Although this is the definitive test for the diagnosis of encephalitis, it is very rarely done.

Management

Early treatment of encephalitis can reduce mortality and sequelae.

Supportive treatment

- This is the mainstay of management.
- Neuro-protective measures, including: airway protection; lowering temperature; optimizing homeostasis; and interventions to reduce brain swelling.
- Treat seizures, SIADH, disseminated intravascular coagulation (DIC), and arrhythmias.

Antimicrobials

- Appropriate *high-dose* IV aciclovir should be initiated in all patients with suspected encephalitis, pending results of diagnostic studies.
- Until a bacterial cause of CNS inflammation is excluded, parenteral broad-spectrum antibiotics with excellent CNS penetration should be given, usually ceftriaxone.
- Ganciclovir or foscarnet may be given for CMV, HHV-6, or EBV encephalitis.
- Oseltamivir and/or zanamivir may be given for influenza encephalitis.
- Always consider—could this be TB?
- Antifungals may be used, especially in immunocompromised patients.
- Antiprotozoals may also be used, based on diagnostic findings and suspicion.

Steroids and other immune modulator therapies (e.g. intravenous immunoglobulin)

- Their role is controversial; many reports suggest that they may be effective at improving neurological outcome, especially in cases of post-infectious encephalomyelitis. An RCT of IVIG in children is under way in the UK.

Vaccines

Vaccines are available for measles, mumps, rubella, VZV, rabies, Japanese encephalitis virus, tick-borne encephalitis (TBE), and influenza. Rarely, post-vaccine encephalitis may occur with live vaccines (e.g. Japanese encephalitis virus).

Outcome

Severe viral encephalitis can lead to respiratory arrest, coma, and death. The overall mortality rate is 3–4%. Children <1 year have fatality rates of up to 40–50%, and neonates with disseminated viral infection have a very poor prognosis. There is an overall 7–10% risk of morbidity and marked neurodevelopmental impairment. However, the outcome depends on the original infecting organism and is much more severe for cytopathic infections, such as HSV, compared to the enteroviruses.

Further research

Further research into:

- Host susceptibility and the immune response will help us to identify and protect specific at-risk hosts
- Antiviral treatments and immune modulation will help us to reduce tissue damage and long-term sequelae
- Vaccination will help to protect more infants and children from encephalitic infections.

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Chapter 15

Enlarged lymph nodes

See also Chapters 25, 38, 44, 56, 65, 90, 104, 105, 112.

Introduction

- Lymph node (LN) size depends on the child's age, the location of the LN, and antecedent immunological events.
- Lymphoid mass steadily increases after birth until between 8 and 12 years of age, and undergoes progressive atrophy during puberty.
- In healthy children, including neonates, mobile LNs, usually measuring <1cm in diameter, are often palpable in the cervical and axillary regions and do not usually require investigation in the absence of other signs or symptoms.
- Inguinal LNs measuring up to 1.5cm may also be normal.
- In contrast, progressively enlarging LNs associated with other systemic or local features require investigation.
- Palpable supraclavicular, epitrochlear, and popliteal LNs should always be considered to be abnormal and investigated.
- The differential diagnosis of LN enlargement is extensive and includes infectious and non-infectious causes.
- The possibility of malignancy must always be considered.
- Treatment with glucocorticoids must be avoided before a definite diagnosis is made.

Causative organisms

- The range of infectious agents causing LN enlargement are usefully considered according to the pattern of LN involvement (Fig. 15.1).
- The causative organisms and differential diagnoses to be considered according to the predominant pattern of LN involvement are outlined in:
  - Table 15.1 (generalized)
  - Table 15.2 (cervical)
  - Table 15.3 (abdominal or mediastinal/hilar).
- The common causes of LN enlargement change with age, as outlined in Table 15.4.
- Miscellaneous eponymous syndromes associated with lymphadenopathy are outlined in Table 15.5.

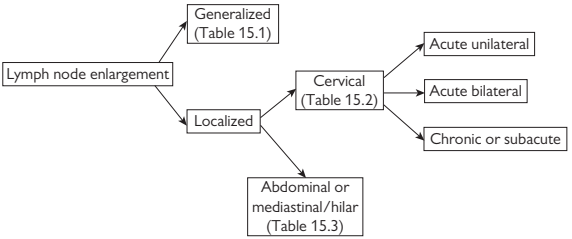

Fig. 15.1 Diagnostic approach to lymph node enlargement in children.

Table 15.1 The differential diagnosis of generalized lymphadenopathy in children

Viral	EBV, CMV, and HHV-6
	Parvovirus B19
	Measles, rubella, adenovirus
	Enteroviruses, hepatitis A and hepatitis B viruses
	VZV
	HIV
	Dengue fever
	Chikungunya virus
	West Nile virus
	Lassa and Ebola viruses
Bacterial	Cat scratch disease (*Bartonella henselae, Bartonella bacilliformis*)
	Enteric pathogens (*Salmonella typhi, Yersinia enterocolitica*)
	Respiratory pathogens (*Mycoplasma pneumoniae, Legionella pneumophila*)
	Scarlet fever (*Streptococcus pyogenes*)
	Spirochaetes—Lyme disease (*Borrelia burgdorferi*), leptospirosis (*Leptospira* spp.), congenital or 2° syphilis (*Treponema pallidum*)
	Rickettsia—many including scrub typhus (*Orientia tsutsugamushi*) and ehrlichial diseases (*Ehrlichia sennetsu*)—rare
	Brucellosis (*Brucella melitensis*)—rare
	Tularaemia (*Francisella tularensis*)—rare
Mycobacteria	TB (*Mycobacterium tuberculosis*)
Fungal	Histoplasmosis, coccidiomycosis, paracoccidiomycosis—rare
Parasitic	Toxoplasmosis
	Trypanosomiasis—rare
	Visceral leishmaniasis (kala-azar)—rare
	Schistosomiasis and filariasis

(*Continued*)

Table 15.1 (*Contd.*)

Non-infectious causes	Malignancy (lymphomas, metastases)
	Haemophagocytic lymphohistiocytosis
	1° immunodeficiencies (CGD, Wiskott–Aldrich syndrome, Chediak–Higashi, hyper-IgE syndrome, common variable immunodeficiency, X-linked lymphoproliferative syndrome)
	Rheumatological disorders (systemic-onset JIA, SLE)
	Drug reactions (multiple, e.g. phenytoin)
	Typhoid immunization
	Sarcoidosis
	Chronic atopic eczema
	Miscellaneous (Table 15.5): Rosai–Dorfman disease (sinus histiocytosis with massive lymphadenopathy), Kikuchi–Fujimoto disease (histiocytic necrotizing lymphadenitis), multicentric Castleman's disease

Table 15.2 The differential diagnosis of cervical lymphadenopathy in children according to the mode of initial presentation

Acute unilateral	Acute bilateral	Chronic (or subacute)
S. aureus *S. pyogenes* (GAS) *Streptococcus agalactiae* (GBS) Anaerobes (e.g. *Fusobacterium* and *Peptostreptococcus* spp.) Also unusual organisms: *Francisella tularensis, Pasteurella multocida, Yersinia* spp., *Streptococcus pneumoniae*, α-haemolytic streptococci, CoNS, *Legionella, Nocardia brasiliensis, Histoplasma, Coccidioides*	EBV, CMV HSV Adenovirus Enteroviruses HHV-6, -7, and -8 (rarely) Influenza, parainfluenza Measles Rubella Parvovirus B19 *M. pneumoniae* *Corynebacterium diphtheriae*	NTM *B. henselae* (cat scratch disease) *T. gondii* *M. tuberculosis* Actinomycetes (*Actinomyces israelii, Nocardia* spp.) BCG vaccination
Non-infectious cervical lymphadenopathy		
Malignancy Kawasaki disease Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) Sarcoidosis Miscellaneous (Table 15.5): Rosai–Dorfman disease (sinus histiocytosis with massive lymphadenopathy), Kikuchi–Fujimoto disease (histiocytic necrotizing lymphadenitis), Kimura's disease		
Other neck masses		
Salivary gland and thyroid masses Head and neck malignancy Congenital abnormalities (thyroglossal cysts, cystic hygroma, etc.)		

Table 15.3 The differential diagnoses of mediastinal and abdominal lymphadenopathy in children

	Mediastinal and hilar	Abdominal and retroperitoneal
Viral	Viral respiratory tract pathogens	Virus-associated gastroenteritis
	Many generalized viral infections (Table 15.1) can present predominantly with localized lymphadenopathy (e.g. EBV, HIV)	
Bacterial	Suppurative lung disease—bronchiectasis, lung abscesses	Bacterial gastroenteritis, e.g. *Salmonella, Shigella, Yersinia enterocolitica, B. henselae*
	M. pneumoniae	
	Melioidosis	Localized abdominal infections, e.g. appendicitis
	B. henselae	
	Actinomycetes	
Mycobacterial	*M. tuberculosis*	*Mycobacterium bovis*
	NTM	*M. tuberculosis*
Fungal	*Histoplasma, Blastomyces, Coccidioides, Paracoccidioides*	
	Cryptococcus	
Parasitic	Toxoplasmosis	Parasitic infections of the GI tract, e.g. *Entamoeba histolytica*
Non-infectious causes	Malignancy	Crohn's disease
	1° immunodeficiencies (e.g. CGD)	Coeliac disease
	Sarcoidosis	Familial Mediterranean fever

Table 15.4 Age-specific causes of lymphadenopathy in children

Age group	Causative organism
Neonates	*S. aureus*
	S. agalactiae (GBS)
Infants	*S. aureus*
	S. pyogenes (GAS)
	Consider Kawasaki disease
1–4 years	*S. aureus*
	S. pyogenes (GAS)
	NTM
	Kawasaki disease
5–15 years	Anaerobic bacteria
	Toxoplasmosis
	Cat scratch disease
	TB
	Malignancy

Table 15.5 Miscellaneous eponymous syndromes associated with lymphadenopathy

Oculoglandular syndrome of Parinaud	Unilateral chronic ulceration of the conjunctiva and ipsilateral cervical lymphadenopathy. Most commonly caused by *B. henselae* in childhood
Rosai–Dorfman disease (sinus histiocytosis with massive lymphadenopathy)	Progressive painless bilateral symmetric or asymmetric cervical lymphadenopathy. Other LNs and extra-nodal sites may be involved. Associated with fever, anaemia, leucocytosis, raised ESR, and hypergammaglobulinaemia. Occurs in first two decades of life. Diagnosed on biopsy. Generally resolves spontaneously
Kikuchi–Fujimoto disease (histiocytic necrotizing lymphadenitis)	Unilateral, usually matted, tender cervical lymphadenopathy associated with fever, leucopenia, and a raised ESR. Systemic features include weight loss, night sweats, malaise, and joint pains. Diagnosed on biopsy, which is also required to exclude malignancy. Generally resolves spontaneously, although has been associated with SLE
Kimura's disease	Unilateral chronic cervical LN enlargement, occurring most commonly in ♂ of Asian origin. Associated with overlying subcutaneous nodules. Benign, although may be disfiguring
Castleman's disease (giant lymph node hyperplasia)	Lymphoproliferative disorder which may be localized to a single LN and can be treated with local excision. A disseminated form (multicentric Castleman's disease), particularly occurring in HIV-infected individuals, is strongly associated with HHV-8 infection. Patients have fever, myalgia, and weight loss associated with diffuse lymphadenopathy and hepatosplenomegaly, and a generalized inflammatory response
Gianotti–Crosti syndrome (papular acrodermatitis)	Younger children, fever, widespread lymphadenopathy, hepatomegaly, widespread papules over limbs, face, palms, and soles, usually resolving in around 1 month—occurs with acute hepatitis B and other viral infections

Prevalence and epidemiology

- LNs are palpable in between 38% and 45% of otherwise healthy children and are most commonly palpable between 3 and 5 years of age.
- Acute unilateral cervical lymphadenitis is caused by streptococcal or staphylococcal infection in 40–80% of cases.
- Up to 95% of cases of mycobacterial lymphadenitis are caused by NTM, and NTM is the commonest cause of a chronic indurated cervical abscess.
- Estimated incidence of NTM lymphadenitis is 2–3 cases/100 000 children up to the age of 4 years, although the distribution of NTM appears to be geographically and environmentally variable and may be lower in areas using neonatal universal BCG.
- Chronic posterior cervical lymphadenitis is the commonest form of acquired toxoplasmosis and is the sole presenting symptom in 50% of cases.

- Of children requiring a LN biopsy, 52% will have benign reactive lymphadenopathy, 32% granulomatous disease, 13% neoplasia, and 3% chronic lymphadenitis.
- Using PCR, the aetiology can be identified in 82% of culture- or serology-negative cases: *Mycobacterium* spp., followed by *Bartonella* and *Legionella* spp., were identified in 62%, 10%, and 10%, respectively.
- Prevalence of malignancy in adenopathy biopsies ranges from 13% to 27%.

Clinical presentation and differential diagnosis

- A detailed history and thorough clinical examination are critical in directing initial investigations toward the most probable and important causes.

History

- Age of the child (Table 15.4):
  - *S. aureus*, GAS, and NTM are commoner in children between 1 and 4 years
  - Toxoplasmosis, cat scratch disease, and TB are commoner in older children
  - Lymphadenopathy 2° to neoplasia increases in the adolescent age group.
- Rate of LN enlargement (acute, subacute, chronic).
- Site (Fig. 15.1).
- Associated local symptoms:
  - Pain, pharyngitis, cough (e.g. acute bacterial lymphadenitis).
- Skin changes (e.g. erythema—acute bacterial lymphadenitis; violaceous colour—NTM). Associated systemic features:
  - Fever (infectious and non-infectious causes)
  - Ear, nose, and throat (e.g. scarlet fever, measles, and other viruses)
  - Respiratory (e.g. TB, *Mycoplasma, Legionella*, fungal infections, local compression of structures associated with mediastinal LN enlargement)
  - GI (e.g. infectious gastroenteritis)
  - Musculoskeletal (e.g. arthritis—Lyme disease or rheumatological conditions; myalgia—leptospirosis)
  - Neurological—headaches, meningism (e.g. Lyme disease, leptospirosis, rickettsial disease)
  - Rash (e.g. measles and other viruses, scarlet fever, spirochaetes, Lyme disease, leptospirosis, 2° syphilis), rickettsial disease (e.g. scrub typhus), eczema, rheumatological conditions
  - Local lesions (e.g. local skin infection with inflamed draining LNs, *Bartonella*, tularaemia, scrub typhus, trypanosomiasis, leishmaniasis)
  - Conjunctivitis (e.g. measles, adenovirus, oculoglandular syndrome of Parinaud , Kawasaki disease)
  - Mouth—tooth decay (anaerobes), ulcers (periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA), enterovirus, or HSV)
  - Weight loss, night sweats (HIV, TB, malignancy, etc.).

- Immunization status (measles, rubella, diphtheria, hepatitis A and B, BCG).
- Medications (e.g. phenytoin, carbamazepine).
- Contacts (viral respiratory infections, EBV, CMV, GAS, TB).
- Travel history:
  - TB-endemic areas
  - *Brucella* (worldwide but predominant in the Mediterranean, Middle East, Indian subcontinent, parts of Central and South America, Africa)
  - Tularaemia (worldwide, predominantly in the northern hemisphere, North America, but cases also reported in Europe)
  - Melioidosis (South East Asia; also reported in Northern Australia, India, Central America)
  - *Rickettsia* (many geographical distributions, according to species, e.g. scrub typhus—South East Asia and Oceania)
  - Fungi (e.g. *Histoplasma*—many parts of world outside Europe; *Coccidioides*—North America, extending into Central and South America)
  - Trypanosomiasis (sub-Saharan Africa, Central and South America)
  - Leishmaniasis (Central and South America, Southern Europe, North and East Africa, Middle East, Indian subcontinent)
  - Schistosomiasis (predominantly sub-Saharan Africa, also areas of South America, Middle East, South East Asia)
  - Filariasis (worldwide tropical distribution)
  - Dengue fever (worldwide tropical distribution).
- Contact with domestic and non-domestic animals—ask about unusual pets! (*Bartonella*, tularaemia, *Brucella, Rickettsia, Mycobacterium marinum*).
- Ingestion of unpasteurized milk (e.g. *Brucella, Mycobacterium bovis*).
- Tick bites (Lyme disease, *Rickettsia*, tularaemia).
- Risk factors for HIV (link to high-incidence country, maternal health), hepatitis B (maternal health, risk factors for horizontal transmission), and TB (family and other contacts, travel, and immigration).
- High-risk behaviour (sexually transmitted infections, STIs).
- History suggestive of 1° or 2° immunodeficiency (e.g. recurrent abscesses and infections).

Examination

Standardized description of the LNs should include:

- Size, location
- Single or multiple
- Consistency (soft, firm, rubbery, fluctuant)
- Attachment (superficial or deep)
- Skin changes (local abrasions and overlying skin changes)
- Tenderness.
- Spontaneous drainage and/or formation of a fistulous tract.

Full systemic examination guided by findings from the history but not forgetting:

- Examination of other LN groups—head and neck, supraclavicular, axillary, epitrochlear, inguinal, popliteal
- Identification of splenomegaly and hepatomegaly (EBV, CMV, brucellosis, HIV, neoplastic or rheumatologic disease)

- Examination for infection in tissues drained by nodes (remember the mouth, teeth, and gums)
- Eyes—conjunctivitis (e.g. Kawasaki disease, leptospirosis, oculoglandular syndrome)
- Skin—viral exanthema, localized lesions (cat scratch disease, tuleraemia, HSV, *S. aureus*, or GAS)
- Documentation of fever and weight loss.

Clinical syndromes and associated causes

Generalized lymphadenopathy

- Defined as enlargement of >2 non-contiguous LN groups.
- Most often associated with systemic viral illness (Table 15.1).
- HIV is an important differential diagnosis.
- Malignancy should also be considered because of the dangers of delay.
- In a newborn, generalized lymphadenopathy associated with hepatosplenomegaly is likely to indicate a congenital infection (HIV, rubella, CMV, *T. gondii, T. pallidum*)

Localized lymphadenopathy

Most causes of generalized lymphadenopathy may present with predominantly localized disease.

Cervical lymph node enlargement

- Most commonly represents a transient reactive response to a benign local or generalized infection, but occasionally it might be a sign of a more serious disease (e.g. malignancy).
- A child presenting with cervical lymphadenopathy will generally fall into one of three categories (Table 15.2), distinguished on initial history and physical examination:
  - Acute unilateral (pyogenic) cervical lymphadenitis
  - Acute bilateral cervical lymphadenopathy
  - Chronic or subacute cervical lymphadenopathy.

Acute unilateral cervical lymphadenopathy

- A child with a warm, tender, enlarged (>2–3cm) LN, which may be fluctuant and associated with overlying erythema and a fever, is likely to have an acute pyogenic lymphadenitis, although other neck masses, such as cystic hygroma, may also become infected.
- Cervical lymphadenitis represents over 90% of acute lymphadenitis in childhood, although lymphadenitis at other sites, such as in the axillary or inguinal regions, should usually be approached in the same way.
- *S. aureus* and *S. pyogenes* account for up to 80% of cases (Table 15.2).
- GBS is a further important cause in the neonatal period and is likely to be associated with systemic features of sepsis.
- Oral anaerobes must also be considered in older children, particularly in the presence of dental caries/periodontal disease.
- Kawasaki disease is an important differential diagnosis to consider in a child with acute cervical lymphadenopathy.

Acute bilateral cervical lymphadenopathy

- A common response to acute viral pharyngitis and systemic viral infections in children and does not generally require detailed investigation.
- The LNs are usually small and multiple. They may or may not be tender and are not associated with warmth or erythema.
- Likely infectious agents (Table 15.2) may be indicated by their associated symptoms and signs:
  - Splenomegaly/hepatomegaly (EBV/CMV)
  - Gingivostomatitis (HSV)
  - Pharyngitis/conjunctivitis (adenoviruses, measles, Kawasaki disease)
  - Rash (enteroviruses, CMV, HHV-6, rubella, measles, parvovirus, Kawasaki disease)
  - Respiratory symptoms (*Mycoplasma*).

Chronic or subacute cervical lymphadenopathy

- A clinical presentation that is inconsistent with an acute lymphadenitis or a failure to respond to antibiotic therapy should prompt a search for alternative infectious and non-infectious causes.
- Typically, the LNs are painless or minimally tender and are not associated with an increase in skin temperature.
- NTM, cat scratch disease, and toxoplasmosis are the commonest infectious causes (Table 15.2).
- Most children with NTM infection present with:
  - A firm, painless, discrete mass or masses
  - 'Cold' abscess formation
  - The overlying skin can develop a characteristic violet colour
  - Spontaneous drainage with sinus tract formation occurs in around 10%.
- *M. tuberculosis* may manifest with a suppurative LN identical to that of NTM—remember that supraclavicular LN in TB is 2° to a pulmonary focus.
- Suppurative adenopathy occurs in between 10% and 35% of patients with cat scratch disease in axilla, cervical, or epitrochlear nodes.
- Congenital lesions (thyroglossal duct cyst, cystic hygroma, haemangioma, etc):
  - Present at birth or are identified soon after
  - Painless, diffuse, soft, and compressible
  - Transilluminate, usually red or blue in colour
  - Cystic malformations may become infected.
- PFAPA may be considered in a child presenting with recurrent bilateral cervical lymphadenopathy, periodic fever, aphthous stomatitis, and pharyngitis. Not all features are required, and the diagnosis is made clinically.

Axillary lymphadenopathy

- Often represents a response to a pyogenic infection of the upper extremity.
- Cat scratch disease is a particular concern.
- Regional cutaneous TB (scrofuloderma) can be associated with the node enlargement.
- Granulomatous lymphadenopathy is the commonest complication of BCG vaccination.

Abdominal and mediastinal lymphadenopathy

- Many of the causes of generalized lymphadenopathy can present with LN enlargement,which is predominantly localized to the mediastinal/hilar LNs or the abdominal/mesenteric/retroperitoneal LNs.
- Local infections of the respiratory or GI tracts may result in enlargement of the draining LNs. In this case the cause is likely to be identified from the associated symptoms and signs prompting relevant investigations (e.g. stool sample).
- Consider an underlying immune system defect in children who are diagnosed with infection caused by actinomycetes, *Histoplasma, Cryptococcus*, and *Coccidioides*, or disseminated NTM disease.

Inguinal lymphadenopathy

- Results from superficial or deep infection of the lower extremity.
- *S. aureus* and *S. pyogenes* are most commonly found.
- *B. henselae, Yersinia enterocolitica, Salmonella*, and *Francisella tularensis* can also infect the nodes.
- Can be associated with fever, limp, abdominal or hip pain, and spasm of the psoas muscle.

Malignancy

- Malignancy (especially lymphomas in teenagers) needs to be considered in all children presenting with localized LN enlargement. Specifically:
  - The adenopathy is usually non-tender, firm, and rubbery, with no warmth or erythema of the overlying skin (although the possibility of 2° infection should not be forgotten)
  - The nodes can become fixed, hard, and bulky and grow rapidly
  - Supraclavicular LN enlargement is uncommon following infection. The left supraclavicular node—Virchow's node—drains lymphatics from the thorax and abdomen. However, other LN groups are often involved, and an absence of supraclavicular lymphadenopathy should not be considered reassuring.

Investigations

- Most cases of lymphadenopathy in children are benign, usually associated with viral illness, and do not generally require any investigation.
- Laboratory tests, imaging, and biopsy may be indicated if a serious underlying disease is suspected.

A list of investigations is given below, some of which may be useful if there is a *compatible history and clinical examination*. However, the ordering of investigations indiscriminately, without reasonable clinical suspicion, is certainly not recommended.

- Throat/nasal swab/NPA or blood sample for virus identification.
- FBC ± blood film.
- Inflammatory markers (CRP, ESR).
- Liver enzymes, lactic dehydrogenase (LDH) (malignancy), and ferritin (systemic-onset JIA, haemophagocytic lymphohistiocytosis).

- Blood, throat, skin, LN cultures.
- CSF examination in infants with GBS infection.
- Serology (acute ± convalescent), including: EBV, CMV, HHV-6, HIV, measles, parvovirus, GAS, *Mycoplasma, Borrelia*, syphilis (VDRL), *Leptospira, Brucella, Bartonella*, histoplasmosis, and coccidiomycosis.
- Stool sample for virus, bacteria, ova, cysts, and parasites.
- Tuberculin skin (Mantoux) test ± further investigations for TB.
- Immunological tests (e.g. neutrophil function)—expert advice useful.

Imaging

Ultrasound scan

- To confirm the origin of swelling.
- To identify abscess formation.
- To guide core-needle biopsy or aspiration, if needed.

Chest X-ray

- A normal CXR does not exclude significant hilar lymphadenopathy, which may require a CT scan.

Computerized tomography or magnetic resonance imaging

- To identify other sites of lymphadenopathy.
- To identify LNs with a malignant appearance.
- To delineate the solid, viable part of the LN for biopsy.

Pathology

- Biopsy may be required for definitive diagnosis and to exclude malignancy.
- Fine-needle aspiration (FNA) is a very useful, quick investigation in older children, with a very low complication rate. Excision biopsy ensures that adequate representative tissue is obtained. This is also the definitive treatment for localized NTM disease.
- Tissue should always be sent for both:
  - Histopathological examination (including microbiological stains)
  - Bacterial (including anaerobic), mycobacterial, and fungal culture
  - *It is extraordinary how often this still does not happen!*
- Discussion with microbiology and histopathology (and the surgeon) is strongly encouraged prior to obtaining samples to ensure they are processed appropriately to maximize the chances of identifying organisms, for which prolonged culture may be required (e.g. *Mycobacterium* or *Brucella*) or which have fastidious growth requirements (*F. tularensis*), and to ensure appropriate stains are carried out to identify infectious agents. Samples may also be stored for future analysis by PCR or other techniques.

Management and treatment

Generalized lymphadenopathy

- The treatment is largely governed by the underlying cause.
- Most cases require no treatment.

Localized lymphadenopathy

- Treatment of bilateral cervical lymphadenitis depends on the underlying cause.
- Most cases are self-limited and require no specific treatment other than observation.
- Treatment will largely be symptomatic/supportive in the child with normal immune function.
- In the majority of children with acute pyogenic lymphadenitis, empirical antibiotic therapy will be warranted and should provide adequate coverage for both *S. aureus* and *S. pyogenes*, pending culture and sensitivity results. Choice of agent:
  - Co-amoxiclav, first- or second-generation cephalosporin (± metronidazole if anaerobes suspected)—beware rash with amoxicillin and EBV infection
  - Clindamycin is an alternative single-agent treatment
  - Oral flucloxacillin is not generally recommended, as it is poorly tolerated, the liquid preparation tastes unpleasant, and it requires administration every 6h.
- Route of administration:
  - In a well child with few systemic features, initial oral therapy may be appropriate with close monitoring
  - In a child who is systemically unwell or is unable to tolerate oral therapy, IV antibiotics are warranted.
- Duration of therapy should be 7 days—this may be extended, depending on the associated clinical features.
- Failure to respond to initial therapy may indicate:
  - Abscess formation
  - The presence of a less common organism requiring alternative treatment, following identification by biopsy or FNA
  - The presence of a resistant organism—is community-acquired MRSA likely?
  - Failure to take or tolerate the prescribed oral medication.
- Children <1 year of age and those in whom the LN has been present for >48h are more likely to require surgical intervention.
- Failure of the lymphadenopathy to regress after 4–6 weeks may be an indication for a diagnostic biopsy.
- Indications for early excision biopsy:
  - LN larger than 3cm. Unusual location, e.g. supraclavicular area
  - Previous history of malignancy
  - Associated symptoms (weight loss, night sweats, hepatosplenomegaly, abnormal radiological findings).
- NTM lymphadenitis is often treated with surgical excision which is diagnostic and can be curative, and is therefore considered to be the gold standard by many, although the condition may be self-limiting. Isolated TB lymphadenitis should be treated for 2 months with isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 4 months of isoniazid and rifampicin.

Future research

- There are no strongly evidence-based clinical algorithms and protocols for referral or management of children with enlarged superficial LNs.
- Introduction of coordinated problem-based referral and management pathways is warranted.
- Further development and evaluation of rapid diagnostic tests for persistent culture and serology-negative cases are needed.
- Prospective trials of treatment for NTM are needed.

Further reading

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Chaper 16

Ocular infections

See also Chapters 11, 38, 44, 46, 48, 57, 58, 62, 68, 104, 107, 110.

Introduction

Ocular infections in children require rapid review and diagnosis, because they are potentially sight-threatening. Prognosis depends on the extent and site of infection (Fig. 16.1). In most cases, a prompt review by an ophthalmologist is required. This chapter discusses keratitis, endophthalmitis, uveitis, retinitis, and intraorbital infection.

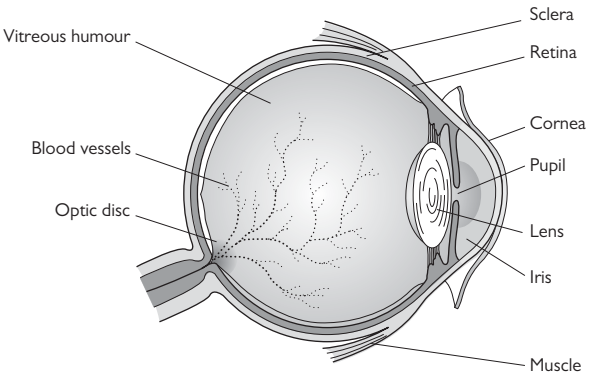

Fig. 16.1 The various anatomical sites in the eye where infection may occur.

Keratitis

- *Definition*—inflammation of the cornea.
- Potentially affects vision, therefore requires urgent ophthalmology review, particularly if associated with corneal ulceration.
- Unlike conjunctivitis, it is characterized by variable loss of vision at presentation.
- Photophobia and reflex blepharospasm make examination difficult, particularly in younger children.
- Corneal scrapings may be used to identify the causative organism.

Causative organisms

Bacterial

- Commonest.
- Usually caused by direct inoculation, i.e. trauma, contact lens use.
- Dry eyes predispose to bacterial infection.
- Endophthalmitis/corneal perforation results if treatment is delayed.

Neonates

- *N. gonorrhoeae*.

Child

- *S. aureus*.
- *S. pneumoniae*.
- *P. aeruginosa*—usually associated with contact lens use.
- *Klebsiella pneumoniae*.
- *Bacillus cereus*, atypical *Mycobacterium* less commonly.
- *C. trachomatis*—extremely common in developing countries and can follow follicular conjunctivitis.

Presentation

- Extremely painful.
- Hyperaemia.
- Chemosis, conjunctival injection, focal haziness, corneal opacification.
- Associated purulent conjunctivitis.
- Corneal ulcers.
- Hypopyon—pus in the anterior chamber of the eye, usually collects at the bottom of the chamber and may be seen as a fluid level.

Investigations

- Corneal scrapings for culture and microscopy after topical anaesthesia under sterile technique.
- May be helpful to culture material from conjunctiva, eyelids, contact lenses.
- Giemsa, Gram, and silver staining required from scrapings.

Differential diagnosis

- Foreign body.
- Corneal abrasions.

Treatment

- Small ulcers—topical antimicrobials, usually chloramphenicol, fusidic acid, or gentamicin, depending on the organism suspected.
- Frequency depends on the severity of infection; usually begin with drops 2-hourly, and tailor accordingly.
- Topical ciprofloxacin or gentamicin, or polymyxin B if *P. aeruginosa* infection is suspected.

Viral

- HSV types 1/2—either herpetic conjunctivitis or perinatally acquired. Usually unilateral. Infection involves deeper stromal structures and thought to be 2° to a heightened inflammatory response, leading to blindness. Acute disease is usually self-limited. Recurrences are common

(up to 80%) and can lead to a wider area of injury. Use of topical steroid drops can exacerbate the infection.
- VZV—with disseminated disease, particularly in immunocompromised patients.
- Adenovirus—highly contagious, particularly subgroup D types 8, 19, and 37 which cause epidemic keratoconjunctivitis.
- Molluscum contagiosum, measles, and EBV are rarer causes.

Presentation
- HSV and VZV:
  - Decreased corneal sensation
  - Characteristic dendritic ulcers on fluorescein staining
  - Stromal disease may progress to necrotizing inflammation
  - VZV may cause a nummular keratitis—with fine granular infiltrates in the anterior corneal stroma.
- Adenovirus:
  - Begins unilaterally, pink hyperaemia
  - Clear watery discharge and photophobia
  - Diffuse punctate keratitis on fluorescein staining
  - Spread to other eye common
  - Acute keratitis lasts 2–3 weeks, followed by subepithelial infiltrates
  - Associated with preauricular lymphadenopathy.

Investigations
- Corneal scrapings should be collected into viral transport media by sterile technique.
- Should have same-day inoculation for cell culture.
- PCR is useful for rapid diagnosis, e.g. HSV, VZV.
- Immunochromatographic assay (ICGA) kit for rapid HSV diagnosis.

Treatment
- HSV:
  - Topical aciclovir five times daily. Continue for at least 3 days post-healing, usually for 10–14 days
  - Oral aciclovir or valaciclovir for 7–14 days has adequate corneal penetration and may be preferable in paediatric patients. Oral agents may be used for up to 12 months to prevent recurrence at prophylactic doses.
  - Monoclonal antibodies and gene therapy under investigation.
- VZV:
  - Topical antimicrobials to prevent 2° infection
  - Systemic aciclovir in severe disease or immunocompromise for 7–14 days or until lesions have healed
  - In severe keratitis, topical corticosteroids may be used in conjunction with what has been discussed.
- Adenovirus:
  - Artificial tears, cycloplegics.

Fungal
- Rare; risks include underlying immunocompromise, corneal trauma.
- *Candida* commonest; filamentous fungi, e.g. *Fusarium, Aspergillus*, less so in children.

Presentation and differential
- Slowly enlarging corneal ulcers with feathery margins.
- Central corneal opacification.
- Candida associated with yellowish white micro-abscesses.

Investigations
- Corneal scrapings for extended culture.
- Silver staining or calcoflour white staining may be required for microscopy.

Treatment
- Topical fluconazole 1% IV solution, miconazole 10mg/mL or amphotericin (0.15–1%).
- May be used in conjunction with systemic therapy if severe.

Endophthalmitis

- *Definition*—infection of intraocular fluid and/or intraocular structures.
- *Emergency*, vision-threatening, therefore requires prompt recognition.
- Requires urgent review by ophthalmology.
- Most commonly caused by penetrating trauma or associated systemic infection.
- Culture/smear of aqueous, vitreous fluids and conjunctiva required to identify the organism.

Causative organisms

Trauma/post-operative infection

Acute (within 48–72h)
- CoNS.
- *S. aureus*.
- Streptococci.
- *Pseudomonas*.
- *B. cereus*—characterized by abrupt onset of symptoms 12–24h after eye injury and a ring corneal infiltrate. Most eyes lose all vision, even with prompt treatment.
- *Candida*, usually *C. parapsilosis*.
- *Aspergillus*, rarely *Fusarium* spp.

Delayed
- CoNS.
- *Propionibacterium acnes*.
- *Candida*.
- *Aspergillus*.

Endogenous (haematogenous)
- *Streptococcus*, most commonly *S. pneumoniae*.
- *Staphylococcus*.
- *Candida*, most commonly *C. albicans* as more virulent.
- *N. meningitidis*.
- *B. cereus*.
- Enteric Gram-negative bacilli.

Presentation

Depends on infecting organism, bacterial load, virulence, and host defence mechanisms:

- Eye pain, redness, lid swelling
- Decreased visual acuity
- Photophobia
- Conjunctival oedema
- Blepharospasm
- Hypopyon
- Fundoscopy shows:
  - Chorioretinitis
  - Vasculitis
  - Retinal haemorrhage and vitreous cellular reactions, resembling cotton wool balls, are characteristic of *Candida*.

Differential diagnosis

- Post-traumatic inflammatory response.
- Drug reactions, most notably with rifabutin, cidofovir.
- Tumours, e.g. retinoblastoma, lymphoma.

Investigations

- Culture of aqueous, vitreous, and conjunctiva must be obtained under general anaesthesia.
- Extended cultures may be required.
- Gram, Giemsa, and silver staining for microscopy.
- Endogenous endophthalmitis requires systemic review and culture of urine, blood, and CSF.

Treatment

Trauma or post-operative infection

- Vitrectomy, then intravitreal and/or intracameral, regular periocular, and topical antibiotics.
- Although systemic antibiotic penetration into the vitrea is poor, it requires consideration.
- If no or poor response within 3 days, a repeat vitrectomy may be required.
- Organism seen on smears should guide initial therapy—often broad-spectrum antibiotics commenced initially.
- Intravitreal agents are used after diagnostic tap.

Bacterial

- Intravitreal ceftazidime and vancomycin at separate locations with separate syringes.
- Vancomycin with either amikacin, gentamicin, or tobramycin. Repeat doses of aminoglycosides may cause macular infarction.

Fungal

- Choice of the antifungals depends on the organism suspected; commence with amphotericin. Switch to voriconazole, if sensitive, once sensitivities/organism known, as less toxic.
- Prognosis better if treated early.
- May require repeat intravitreal injection.

Corticosteroids may be used, in addition to what has been described, as fibrovascular proliferation and possible retinal detachment may complicate infection.

Endogenous infection

- Systemic antimicrobial therapy will be required, depending on systemic disease and organism isolated.
- Intravitreal antimicrobials/antifungals will be required, together with systemic antibiotics. Repeat doses if optic nerve/macula involvement or severe vitritis present.
- Prognosis is better if systemic antifungals are commenced early if fungal disease suspected

Complications

- Corneal oedema and glaucoma.
- Retinal detachment
- Panophthalmitis.
- Orbital abscess.
- Cavernous sinus thrombosis.

Uveitis, retinitis, and optic neuritis

Definition—inflammation of the internal structures of the eye.

Uveitis

- This is the inflammation of iris (anterior), ciliary body, and choroid (posterior).
- Acute inflammation—usually lasts 2–6 weeks, with chronic inflammation being more insidious.
- More commonly caused by autoimmune disease than infection.
- Organisms associated:
  - HSV as part of disseminated HSV infection, commoner in neonates
  - VZV
  - Rubella
  - HIV
  - *M. tuberculosis*, often associated with HIV infection
  - Atypical mycobacteria, most commonly *Mycobacterium abscessus/chelonae* associated with steroids/biomaterials
  - *B. burgdorferi*
  - *T. gondii*
  - *B. henselae*
  - *T. pallidum*
  - *Histoplasma*—rarely found in children.

Presentation

- Insidious irritation in one or both eyes.
- Dilatation of vessels at the corneal–conjunctival junction (limbal flush).
- Blurred vision.
- Photophobia.
- May present with cataracts/vitreous haze.

- Slit-lamp examination shows haziness and precipitates.
- Miliary tubercles or tuberculoma found in ocular TB.

Differential diagnosis
- Traumatic iritis.
- Juvenile rheumatoid arthritis.
- Behçet's syndrome.
- Ankylosing spondylitis.
- Sarcoidosis.

Diagnosis
- Careful history, including travel, pets, contacts, immune status, medication, diet, family history of autoimmune disease.
- Tests include: chest radiograph, FBC, ESR, CRP, ANA, rheumatoid factor, angiotensin-converting enzyme (ACE), HLA-B27, serology (for HSV, rubella, HIV, *Toxoplasma, Bartonella, Borrelia*), TB enzyme-linked immunospot (ELISPOT) and Mantoux, PCR of ocular fluid for HSV, *Toxoplasma*.

Treatment
- Ophthalmology review.
- Treat systemic disease.
- Topical corticosteroids in anterior uveitis, prednisolone 1% 2-hourly tapered according to response.
- Intermediate uveitis treated with periocular methylprednisolone injections.
- Chronic uveitis may be treated with methotrexate or ciclosporin, under expert review.

Complications
- Cataracts.
- Deposition of cellular debris on the iris.
- Raised intraocular pressure.
- Decreased visual acuity.

Retinitis

- Defined as inflammation of the retina or choroid, or both.
- May be unilateral or bilateral and may be a manifestation of systemic disease.
- When the macula is involved, blindness may result.

Organisms
- HSV, VZV, CMV—all are acquired perinatally (or later in life), depending on the immune status. Infect epithelial cells and cause neurotropism. Usually presents as haemorrhagic retinitis, with yellow patches, or a blanched retina with areas of haemorrhage (Fig. 16.2).
- Rubella—congenital infection.
- *T. gondii*—infection is usually congenital or due to congenital reactivation. Presents as a retinochoroiditis, with focal necrosis and additional anterior chamber inflammation. Chorioretinal pigment clumping causes deposition around the peripheral zone of inflammation. Often associated with CNS calcification.

- *B. henselae*—indirect ophthalmoscopy typically shows a macular star or stellate retinopathy.
- *Toxocara canis*—pica or exposure to dog excrement, resulting in ocular larva migrans. Inflammation occurs after larval death with eosinophilic and mononuclear cell infiltration. Indirect ophthalmoscopy shows a granulomatous mass associated with vitritis.
- *T. pallidum*—presents with both an interstitial keratitis and retinitis.
- HIV—retinopathy typically associated with haemorrhagic vasculitis.
- TB—may be associated with intraocular granuloma formation.7

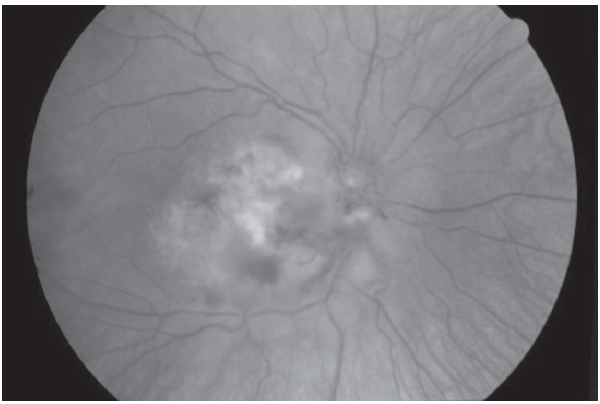

Fig. 16.2 Cytomegalovirus retinitis showing granular retinitis with perivascular sheathing.
(Reproduced from National Eye Institute, National Institutes of Health.)

Presentation

May be indolent or fulminant:

- Decreased visual acuity
- Photophobia
- Diminished red reflex
- Ocular floaters
- Photopsia
- Ophthalmoscopy shows patchy areas of white or haemorrhage on the retina with vitreous haze

Differential diagnosis

- Retinal haemorrhage post-trauma.
- SLE.
- HIV retinopathy.
- Aicardi's syndrome.
- Retinoblastoma.

Investigations

- CXR, FBC, ESR, CRP, ANA, rheumatoid factor, ACE, HLA-B27, serology (for HSV, rubella, HIV, VDRL, *Toxocara, Toxoplasma, Bartonella, Borrelia*), PCR of ocular fluid for HSV, *Toxoplasma*.

Treatment

- HSV/VZV:
  - IV aciclovir for 5–10 days which reduces the risk of infection in the second eye by 50%
  - Followed by oral aciclovir or valaciclovir for 4–6 weeks.
- CMV:
  - Ganciclovir or foscarnet or cidofovir IV as induction therapy for 2–3 weeks
  - Followed by long-term maintenance therapy for months. Ganciclovir can be implanted as a sustained-release system to last 4–6 months.
- Rubella—supportive treatment.
- Syphilis—treat as tertiary syphilis, benzylpenicillin every 4–6 hours for 14 days.
- Toxoplasmosis:
  - Congenital toxoplasmosis should be treated with pyrimethamine twice daily for 2 days, then once daily for 6 months, then three times a week for 6 months and sulfadiazine (twice daily for 12 months), with calcium folinate (three times a week) for a year. Corticosteroids may be added under expert advice
  - Older children are generally not treated, unless immuno-compromised or the lesions are close to the optic nerve or macula.
- *Toxacara*:
  - Usually not treated, unless associated with visceral larva migrans, which requires ivermectin, albendazole, or tiabendazole.

Orbital infections

Preseptal cellulitis

- Preseptal cellulitis differs from orbital cellulitis in that it is confined to the soft tissues that are anterior to the orbital septum. Neither involve the orbit.
- Infection of the eyelid and periorbital soft tissues is characterized by acute eyelid erythema and oedema.
- Results from local spread of adjacent upper respiratory tract infection (URTI), external ocular infection, or following trauma to the eyelids.
- ~80% of preseptal infections occur in children <10 years of age, most <5 years. Patients with preseptal cellulitis tend to be younger than patients with orbital cellulitis.

Causative organisms

Bacterial

- *S. pneumoniae, S. aureus*, GAS, *H. influenzae* (type b, more commonly in pre-vaccination era).
- Anaerobes.

- Infrequently, *Acinetobacter* spp., *Nocardia brasiliensis, Bacillus anthracis, P. aeruginosa, Proteus* spp., *Pasteurella multocida, M. tuberculosis*, depending on exposure.

Presentation
- Pain.
- Conjunctivitis.
- Periorbital erythema and oedema (sometimes so severe that patients cannot voluntarily open the eye).
- Sinus tenderness, rhinorrhoea, lymphadenopathy, and other hallmarks of URTIs may be present.

Differential diagnosis
- Nephrotic syndrome.
- Allergic reaction.
- Conjunctivitis.
- Contact dermatitis.

Investigations
- CRP and WCC are usually elevated; blood culture is usually negative.
- Samples of conjunctival discharge, eyelid lesions, and lacrimal sac material should be sent for culture.

Treatment
- Mild preseptal cellulitis—oral co-amoxiclav or clindamycin. Clindamycin offers good soft tissue penetration.
- In more severe preseptal cellulitis or if the child fails to respond within 48–72 hours, consider IV antibiotics. Usually IV co-amoxiclav or cefuroxime for 24–48 hours, followed by oral antibiotics.
- Clinical improvement should be seen within 24–48 hours. If the patient worsens, then consider an underlying orbital process or resistant organisms.

Complications
- Orbital cellulitis.
- Spread along tissue planes to cause subperiosteal abscess, orbital abscess, or cavernous sinus thrombosis.
- Intracranial infection—high-risk features include age >7 years, subperiosteal abscess, headache, and fever persisting despite IV antibiotics.
- Patients who are immunocompromised have a higher likelihood of developing fungal infections and/or orbital extension.

Orbital cellulitis

- Infection of the soft tissues of the orbit, posterior to the orbital septum.
- Involve ophthalmology and ear, nose, and throat (ENT) early.
- Median age of children hospitalized with orbital cellulitis is 7–12 years.
- Caused by extension of an infection from the periorbital structures, most commonly from the paranasal sinuses, direct inoculation of the orbit from trauma, or haematogenous spread from bacteraemia.

Causative organisms

Bacterial

- *Streptococcus* spp.
- *S. aureus*.
- Hib, more commonly in pre-vaccination era.
- *Pseudomonas*.
- *Klebsiella*.
- *Enterococcus*.

Polymicrobial infections with aerobic and anaerobic bacteria are commoner in patients aged ≥16 years.

Fungal

- *Mucor* and *Aspergillus* commonest, usually associated with immunocompromise.
- TB.

Presentation

- Conjunctival chemosis.
- Lid oedema.
- Rhinorrhoea, purulent nasal discharge may be present.
- Orbital pain and tenderness are present early.
- Vision may be normal early, but it may become difficult to evaluate in very ill children with marked oedema.
- Dark red discoloration of the eyelids, chemosis, hyperaemia of the conjunctiva.
- Proptosis and ophthalmoplegia develop, as infection progresses.
- Late signs are increased orbital pressure, reduced corneal sensation.

Differential diagnosis

- Thyroid exophthalmos.
- Idiopathic inflammation—sarcoidosis, orbital myositis, orbital pseudotumour, Wegener's granulomatosis.
- Neoplasm with inflammation—lymphoma, histiocytosis X, leukaemia, retinoblastoma, neuroblastoma, rhabdomyosarcoma.

Investigations

- FBC—leucocytosis common, blood cultures prior to the administration of any antibiotics, although they are unlikely to reveal the responsible organism. Swab purulent material from the nose for Gram stain, and culture on both aerobic and anaerobic media.
- Needle aspiration of the orbit is contraindicated.
- LP if any signs of meningism.
- CT with contrast or MRI (MRI better if cavernous sinus thrombosis suspected).
- If ethmoidectomy performed, urgent microscopy; request extended aerobic and anaerobic culture.
- Continuing deterioration on antibiotic therapy suggests abscess formation, and repeat imaging will be required.

Treatment

- IV antibiotics—ceftriaxone IV and metronidazole, or high-dose co-amoxiclav. Clindamycin may be added. Vancomycin if MRSA suspected.
- Ophthalmology and ENT review.
- Sinus surgery may be required.
- Consider orbital surgery in every case of subperiosteal or intraorbital abscess, particularly if: vision affected, an afferent pupillary defect develops, proptosis progresses despite appropriate antibiotic therapy, or the size of the abscess does not reduce on CT scan within 48–72 hours after appropriate antibiotics have been administered.
- In cases of fungal infection, surgical debridement of the orbit is indicated, together with high-dose antifungal treatment, usually amphotericin/AmBisome® IV.
- Neurosurgical involvement if cerebral abscess on imaging.
- Switch to oral treatment only in uncomplicated orbital cellulitis, once afebrile and substantial clinical improvement.

Complications

- Subperiorbital or orbital abscess.
- Permanent vision loss from corneal damage.
- Meningitis.
- Cavernous sinus thrombosis.
- Intracranial, epidural, or subdural abscess formation.

Table 16.1 presents a comparison of the two types of cellulitis.

Table 16.1 Preseptal versus orbital cellulitis

	Preseptal	Orbital
Proptosis	Absent	Present
Ocular motility	Normal	Painful and restricted
Visual acuity	Normal	Reduced in severe cases
Colour vision	Normal	Reduced in severe cases
Relative afferent papillary defect	Normal	Present in severe cases

Reproduced from Denniston A, Murray P (2006). *Oxford Handbook of Ophthalmology*, with permission from Oxford University Press.

Further reading

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Chapter 17

Immunocompromised children with infection

See also Chapters 2, 3, 4, 19, 23, 24.

Introduction

- Due to substantial medical advances, including chemotherapy and human stem cell transplantation (HSCT), there are an increasing number of children who are alive with 1° or 2° immunodeficiencies. At the same time, the improvement of diagnostic techniques, such as flow cytometry and molecular biology, allows for a better understanding of an immunodeficient patient, which, in turn, helps to individualize and optimize supportive care.
- Immunocompromised children are at an increased risk for infection and can be categorized, according to the underlying immunodeficiency (Box 17.1). The main categories include 1° immunodeficiencies, and acquired or 2° immunodeficiencies. 2° immunodeficiencies, in particular treatment for cancer, are often associated with alteration of the mucosal and skin barriers or of the normal microbial flora, both of which further increase the risk for infection.

Causative organisms

- The underlying immunodeficiency largely influences the patient´s vulnerability to a specific pathogen (Tables 17.1 and 17.2). Importantly, organisms considered to be avirulent in an immunocompetent host may cause severe disease in an immunocompromised patient. In general, the isolation and identification of the causative pathogen should be attempted, and the knowledge of the underlying immunodeficiency will help to optimally target investigations and empiric therapy.
- Children with defects in the B-cell arm of the immune system fail to exhibit appropriate antibody responses, which predisposes to infections with encapsulated organisms such as *S. pneumoniae, H. influenzae*, and *N. meningitidis*. However, rotavirus, enteroviruses, JC virus, and *Giardia* can also cause severe and persistent infection in these patients. *S. pneumoniae, H. influenzae, N. meningitidis*, as well as *Salmonella*, are also common pathogens in children with defective opsonization such as in patients with congenital asplenia, splenic dysfunction due to haemoglobinopathies, or those after splenectomy. Children with cell-mediated deficiency are especially susceptible to viral, fungal, and protozoan infections, as it is the case in children untreated for HIV. In children with a combined B-cell and T-cell defect, the disease spectrum depends on the extent of the defect. Functional defects and/or decreased numbers of granulocytes predispose to bacterial and

Box 17.1 Classification of 1° immunodeficiency diseases

Combined immunodeficiencies such as:

- T–B^+ severe combined immunodeficiency (SCID) such as JAK3, IL-7Rα, or CD45 deficiency
- T–B^- SCID such as RAG 1 or RAG 2 deficiency
- Combined immunodeficiencies, generally less profound than SCID, such as deficiency of CD40, CD40 ligand, CD8, MHC class I or II
- Combined immunodeficiencies with associated or syndromic features such as Wiskott–Aldrich syndrome, ataxia–telangiectasia, or Nijmegen breakage syndrome.

Predominantly antibody deficiencies such as:

- Severe reduction in all serum immunoglobulin isotypes, with profoundly decreased or absent B cells, such as BTK deficiency, myelodysplasia with hypogammaglobulinaemia
- Severe reduction in at least two serum immunoglobulin isotypes, with normal or low number of B cells, such as common variable immunodeficiency disorders or ICOS deficiency
- Severe reduction in serum IgG and IgA, with normal/elevated IgM and normal numbers of B cells, such as CD40L or CD40 deficiency.

Diseases of immune dysregulation such as:

- Familial haemophagocytic lymphohistiocytosis (FHL) syndromes (such as perforin deficiency or Griscelli syndrome, type 2)
- Lymphoproliferative syndromes such as XLP1, ITK deficiency
- Genetic defects of regulatory T cells such as STAT5b deficiency
- Autoimmune lymphoproliferative syndrome (ALPS) such as ALPS-FAS, ALPS-FAS LG
- Immune dysregulation with colitis such as IL-10 deficiency.

Congenital defects of phagocyte number, function, or both such as:

- Defects of neutrophil function such as severe congenital neutropenia 1 (ELANE deficiency) or SCN3 (Kostmann)
- Defects of motility such as leucocyte adhesion deficiency types 1–3 (LAD1–3)
- Defects of respiratory burst such as X-linked or autosomal recessive chronic granulomatous disease (CGD).

Defects in innate immunity such as:

- Predisposition to severe viral infection such as STAT2 deficiency
- Predisposition to invasive fungal diseases such as CARD9 deficiency
- Chronic mucocutaneous candidiasis (CMC) such as IL-17RA deficiency.

Complement deficiencies such as:

- C1q, C1r, C1s, C2, C3, C4, C5, C6, C7, and C8 deficiencies.

Source data from Al-Herz, *Frontiers Immunol* 2014, **5**, article 162.

Table 17.1 Commonest cause of infection in immunocompromised children

Bacteria	Viruses
Escherichia coli	Varicella-zoster virus
Pseudomonas aeruginosa	Cytomegalovirus
Klebsiella spp.	Herpes simplex virus
Enterobacter spp.	Epstein–Barr virus
Haemophilus influenzae	Human herpesvirus 6
Staphylococcus aureus	Respiratory and enteric viruses
Staphylococcus coagulase-negative	Adenoviruses
Streptococcus pneumoniae	
Neisseria meningitidis	
Corynebacterium spp.	
Viridans streptococci	
Listeria monocytogenes	
Enterococcus faecalis	
Clostridium spp.	
Burkholderia cepacia	
Mycobacterium spp.	
Nocardia spp.	
Fungi	**Protozoa**
Candida spp.	*Toxoplasma gondii*
Aspergillus spp.	*Cryptosporidium parvum*
Cryptococcus neoformans	
Mucormycetes	
Pneumocystis jirovecii	

fungal infections, in particular deep and organ abscesses. Pneumococci and staphylococci are characteristic pathogens in defects in cellular innate immunity. Further pathogen-specific 1° immunodeficiency disorders (PIDs) are HSV encephalitis in type I IFN signalling defects, and mycobacterial infections in defects in IL-12/IFN-γ signalling.

- In children undergoing treatment for an underlying malignancy, neutropenia, usually defined as an absolute neutrophil count (ANC) of <500/microlitre, is the single most important risk factor for infection. Whereas Gram-positive bacteria (including CoNS, *S. aureus*, and *S. pneumoniae*) are the commonest isolated pathogens in the neutropenic cancer patient, Gram-negative organisms, such as *P. aeruginosa, E. coli*, and *Klebsiella*, often cause fulminant and life-threatening infections. Patients with prolonged neutropenia, defined by an ANC of ≤500/microlitre for at least 10 days, are at an increased

risk for invasive fungal infections (IFIs), in particular due to *Candida* spp. and *Aspergillus* spp., less often due to mucormycetes.

- The risk of infections following HSCT depends on the time period after transplantation, which can be divided into the pre-engraftment period (0–30 days after transplantation), the post-engraftment period (30–100 days), or late post-transplantation (>100 days) (Fig. 17.1).
- The pre-engraftment period is mainly characterized by mucositis and neutropenia, which predispose the patient to infections with both Gram-positive and Gram-negative bacteria. Although bacteraemia is the commonest documented infection and occurs in 40–50% of all HSCT recipients, infections due to yeast and viral infections are seen during this period, in particular reactivation of herpes simplex infection in previously infected patients and nosocomial viral infections (e.g. RSV, influenza, adenovirus, rotavirus).
- In the post-engraftment period, which is characterized by impaired cellular immunity, the patient is at an increased risk for opportunistic viral and fungal pathogens, in particular CMV disease (1° infection, as well as reactivation), reactivation of *T. gondii* and fungi (*Aspergillus* spp. and *Candida* spp.).
- In the late post-transplantation period, when cellular and humoral immunity are impaired, the risk for infection is especially high in patients who receive immunosuppressive drugs for severe GVHD. In these patients, viral infections (primarily reactivation of VZV) are responsible for >40% of infections, whereas bacterial infections (particularly of the upper and lower respiratory tracts) and IFIs occur less frequently.
- Similarly to HSCT, the risk periods for infectious complications after solid organ transplantation can be divided into the early (0–30 days after transplantation), intermediate (30–180 days), and late (>180 days) post-transplantation periods. Early infections usually result as a complication of either the transplant surgery itself or the presence of indwelling catheters. Infections during the intermediate time period are usually due to immunosuppression, which tends to be at its greatest intensity during the first 6 months following transplantation. This is the time period of greatest risk for infections due to opportunistic pathogens such as CMV and *P. jirovecii*. However, anatomical abnormalities as a consequence of the transplant surgery may also be considered as a cause for recurrent infections in this time period. Infections developing late after transplantation typically result as a consequence of uncorrected anatomic abnormalities, chronic rejection, or exposure to community-acquired pathogens. Compared to the earlier period, community-acquired infections, such as VZV and EBV, usually do not cause severe disease due to the reduced immunosuppression in the late period, but 1° EBV infection may lead to uncontrolled post-transplant lymphoproliferative disorder (PTLD), including post-transplant lymphoma.
- Relatively little is known regarding the risk of infection in patients receiving new compounds such a cytokines or antibodies to cytokines. Notably, children receiving anti-tumour necrosis factor (TNF) therapy are at an increased risk for intracellular pathogens, including mycobacteria (Table 17.2). Patients receiving anti-IL-1 therapy have an increased rate of respiratory infections. Moreover, patients under anti-IL-6 treatment show a reduced early response in infections, i.e. CRP levels do not provide reliable guidance in these patients.

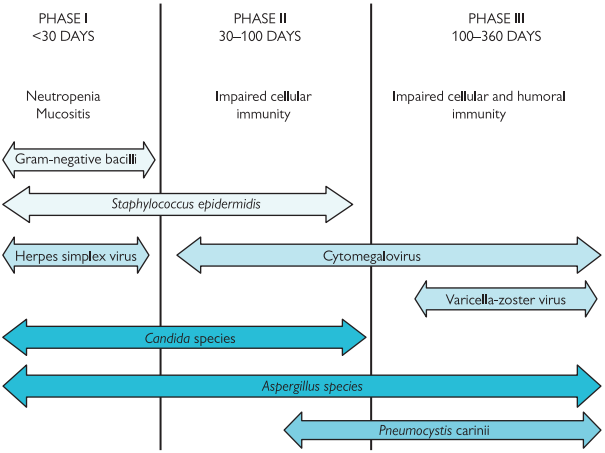

Fig. 17.1 Risk for infectious complications in children and adolescents, according to the time period after allogeneic haematopoietic stem cell transplantation.

Table 17.2 Increased risk to infection with specific pathogens due to therapy-induced alterations of different limbs of the immune system

	Phagocytes	B-cells	Cell-mediated	Natural Killer cells	Barriers
Bacteria					
Staphylococci	↑↑				↑↑
Streptococci	↑↑	↑↑			↑↑
Escherichia coli	↑↑				
Klebsiella spp	↑↑				
Enterobacter spp	↑↑				
Serratia spp	↑↑				
Pseudomonas aeroginosa	↑↑				
Haemophilus influenza type B		↑↑			
Neisseria meningitides		↑↑			
Salmonella spp		↑↑			
Campylobacter spp		↑↑			

(*Continued*)

Table 17.2 (*Contd.*)

	Phagocytes	B-cells	Cell-mediated	Natural Killer cells	Barriers
Corynebacterium spp		↑↑			↑↑
Listeria monocytogenes			↑↑		
Legionella spp			↑↑		
Mycobacterium (atypical)		↑↑	↑↑		↑↑
Mycobacterium tuberculosis			↑↑		
Viruses					
Herpes-simplex virus			↑↑	↑↑	
Varicella-zoster virus			↑↑		
Cytomegalo virus			↑↑	↑↑	
Epstein-barr virus			↑↑		
Respiratory syncytial virus			↑↑		
Adenovirus			↑↑		
Influenza			↑↑		
Fungi					
Candida spp	↑↑				↑↑
Aspergillus spp	↑↑		↑↑		↑↑
Cryptococcus neoformans			↑↑		
Histoplasma capsulatum			↑↑		
Coccidioides immitis			↑↑		
Trichosporon beigelii	↑↑				
Fusarium spp	↑↑				↑↑
Parasites					
Pneumocystis carinii		↑↑	↑↑		
Toxoplasma gondii			↑↑		
Cryptosporidia spp			↑↑		

Clinical presentation and differential diagnosis

- The clinical presentation of a patient with immunodeficiency mainly depends on the underlying defect. 1° immunodeficiencies are usually undiagnosed at the first presentation of a child and are often restricted to one arm of the immune system (e.g. agammaglobulinaemia or CGD). This is in contrast to the well-described suppression of several arms of the immune system (e.g. defects of the mucosal/skin barrier, neutropenia, lymphopenia) in children receiving chemotherapy for a malignancy or children undergoing HSCT. Whereas infectious complications are expected in the latter patient population, investigations regarding an underlying immunodeficiency should be considered in children with severe, recurrent, and unusual infections.
- 1° immunodeficiencies: in antibody deficiencies, such as X-linked agammaglobulinaemia, common variable immunodeficiency, and hyper-IgM syndrome, children are usually asymptomatic until 5–6 months of age. Once maternal passive antibodies wane, these children present with recurrent episodes of otitis media, bronchitis, pneumonia, bacteraemia, and meningitis. Whereas the significance of specific IgG subclass deficiencies regarding the risk of recurrent severe infections remains controversial, the major clinical manifestations in patients with selective IgA deficiency are mild to moderate diseases at sites of mucosal barriers and recurrent sino-pulmonary infection and gastrointestinal disease.
- In cell-mediated deficiency, clinical manifestations include rhinitis, pneumonia, otitis media, chronic diarrhoea, and mucocutaneous candidiasis. Notably, these patients may first present with persistent diarrhoea after rotavirus vaccination.
- In combined B-cell and T-cell defects, complete immunodeficiency is found in patients with severe combined immunodeficiency syndrome (SCID). Not surprisingly, these children may present within the first 6 months of life with severe infections caused by both Gram-positive and Gram-negative bacteria, fungi, or viruses. However, failure to thrive, chronic diarrhoea, mucocutaneous or systemic candidiasis, *P. jirovecii* pneumonitis, and CMV infection are also common problems in patients with SCID.
- Patients with ataxia–telangiectasia, Wiskott–Aldrich syndrome, and hyper-IgE syndrome usually have partial defects of the B- and T-cell systems. Infectious complications include late-onset recurrent sino-pulmonary infections due to both bacteria and respiratory viruses in children with ataxia–telangiectasia, recurrent episodes of *S. aureus* abscesses of the skin, lungs, and musculoskeletal system, as well as IFIs in children with hyper-IgE syndrome and infections due to *S. pneumoniae, H. influenzae*, or *P. jirovecii* in patients with Wiskott–Aldrich syndrome where thrombocytopenia and eczema may already be an indication of the diagnosis.
- Abnormalities of the phagocytic system are often associated with bacterial or fungal infections of the skin, mucosa, lung, liver, and bones.

Children with leucocyte adhesion defects may have a history of delayed cord separation and recurrent infections of the skin, oral mucosa, and genital tract; ecthyma gangrenosum and pyoderma gangrenosum also occur. Children with CGD may present with recurrent infections due to *S. aureus, Serratia marcescens, Burkholderia cepacia*, and *Aspergillus* spp., especially involving the skin, lung, liver, and bone. Depending on the respiratory activity of the phagocytes, the patients develop the first infection during the first months of life or at a later time, even after several years. In contrast, 1° congenital neutropenia (Kostmann's syndrome) most often presents during the first year of life with cellulitis, perirectal abscesses, or stomatitis caused by *S. aureus* or *P. aeruginosa*.

- In patients with defective opsonization or complement deficiency, encapsulated bacteria can cause sepsis, pneumonia, meningitis, and otitis media. Of note, defects in the terminal complement pathways may present in adolescence with meningococcal disease.
- Patients with defects in IL-12/IFN-γ signalling may have overwhelming infections with mycobacteria and *Salmonella* spp.
- Chronic mucocutaneous and systemic infections with *Candida* are indicative of defects in IL-17 formation (e.g. CARD9 deficiency).
- In patients receiving chemotherapy for an underlying malignancy, the highest risk for infection is the time when the ANC falls or is even <500/microlitre. On the other hand, the lack of neutrophils can lead to a reduced or absent inflammatory response, and fever may be the only manifestation of infection. Therefore, fever in the neutropenic patient has to be considered as an infection complication and needs to be seen as an emergency. Fever may not always be present in neutropenic sepsis, so deterioration of the clinical condition (e.g. rising tachycardia, tachypnoea, reduced perfusion) should be taken as signs of sepsis and prompt rapid treatment with empiric broad-spectrum antibiotics.
- In the transplant recipient, clinical symptoms of an infectious complication depend on the haematopoietic recovery. Notably, severe GVHD is often difficult to distinguish from infectious complications (e.g. severe and chronic diarrhoea might be caused by a viral infection and/or by GVHD).

Investigations

- In addition to the investigations prompted by the clinical presentation (e.g. imaging of the lungs in children with respiratory symptoms), investigation of a possible immunodeficiency should be considered in children with recurrent, severe, or unusual infections. Baseline investigations include full blood count and differential blood counts, assessment of lymphocyte subpopulations, immunoglobulin levels, antibody titres to vaccines, HIV status, and chest X-ray. In the case of a suspicious blood count, a bone marrow evaluation should be performed.
- Because patients with fever and neutropenia may only have subtle signs and symptoms of infection, the presence of fever warrants, in addition to the assessment of vital signs, a thorough physical examination, with careful attention to the oropharynx, lungs, perineum

and anus, skin, nail beds, and areas around intravascular catheter sites. Laboratory evaluation includes a complete blood cell count, serum electrolytes, creatinine, blood urea, and liver enzymes. Blood cultures should be obtained from each lumen of a central venous catheter. Although peripheral blood cultures might increase the yield of positive cultures, the need of performing this procedure is controversial. Other microbiological studies should be done if there are associated symptoms: nasal aspirate for virus PCR in patients with upper respiratory tract symptoms; stool for rotavirus and *Clostridium difficile* in patients with diarrhoea. Whereas routine chest X-rays are not recommended in the febrile neutropenic patient, imaging of the lungs should be performed in patients with respiratory symptoms. Notably, CT scans are more informative, compared to conventional chest X-ray. Importantly, these investigations must not delay the immediate initiation of broad-spectrum antibiotics.

- Specific investigations in transplant recipients vary, according to the type of transplantation performed, the period after transplantation, the type and amount of immunosuppression given, and the child's history to previous infectious complications (e.g. IFI).

Management and treatment

- *Therapy of suspected infection*. The most important principle of treatment in patients with suspected or proven immunodeficiency is the prompt initiation of antimicrobial treatment. The regimen has to include agents against the most likely pathogens in an established state of immunodeficiency but also has to consider the local epidemiology and pattern of resistance. In febrile neutropenic cancer patients, first-line antimicrobial therapy must cover both Gram-positive and Gram-negative pathogens, including *P. aeruginosa*. Glycopeptides only have to be included in the first-line therapy if an infection due to Gram-positive pathogens is suspected (e.g. infection of a central venous line). Febrile neutropenic patients have to be reassessed daily, and antimicrobial therapy has to be adapted, according to new findings. If fever refractory to broad-spectrum antibiotics persist for >4–5 days in neutropenic patients, empirical antifungal therapy should be initiated. The routine administration of antiviral agents is not recommended without specific evidence of viral disease.
- *Prophylaxis*. Another mainstay of infection control in immunocompromised patients is antimicrobial prophylaxis. Prophylactic measures include: (1) non-pharmacological measures, such as the avoidance of construction sites, since they constitute a risk of infections with moulds in patients with phagocyte defects or prolonged neutropenia; (2) immunomodulatory compounds, such as G-CSF, in patients with Kostmann syndrome or in selected neutropenic cancer patients; and (3) medical prophylaxis. In most patients, in particular in those with an impairment of lymphocytes, prophylaxis against pneumocystis pneumonia (PCP) using co-trimoxazole (TMP-SMX) two or three times weekly is advised.

- Prophylaxis against bacterial infections with broad-spectrum antibiotics is generally not indicated; penicillin should be given to patients with complement deficiency or asplenia. Antifungal prophylaxis is generally indicated in patients with combined immunodeficiencies and CGD, and should also be considered in high-risk cancer patients (e.g. during intensification treatment for acute myelogenous leukemia, leukaemia relapse, or allogeneic HSCT recipients).
- Replacement of antibody with IVIG is the mainstay of treatment for most of the 1° antibody deficiencies. Due to the limited evidence of increased susceptibility to severe infections in patients with deficiencies of specific IgG subclasses, IVIG is generally not recommended in these patients. Caution is indicated in patients with complete IgA deficiency, because they may develop antibodies leading to anaphylaxis.
- *Vaccination*. Live-attenuated vaccines are contraindicated in children with 1° T-cell abnormalities or in severely immunocompromised children (e.g. children receiving chemotherapy for a malignancy or HSCT recipients with GVHD receiving immunosuppressive drugs). However, influenza vaccination is strongly recommended in immunocompromised children. Importantly, children undergoing treatment for cancer and transplantation should be re-evaluated for protective routine immunization antibody titres and eventually revaccinated after completion of therapy.
- Children with defective opsonization, complement deficiency, or asplenia should receive vaccination against encapsulated bacteria such as Hib, *S. pneumoniae*, and *N. meningitidis*.
- Importantly, household contacts of immunocompromised children should receive immunization, in particular against influenza and VZV.

Follow-up and outcome

- The number of immunocompromised children is steadily increasing, and infectious complications are a major cause of morbidity and mortality in these patients. Due to better supportive care strategies, long-term survival of this population has significantly improved over the last decades. The incidence of infectious complications in patients with HIV has decreased due to effective ART. In addition, HSCT may offer cure for selected patients such as for patients with CGD. Infectious complications may also delay chemotherapy or HSCT, and thus ultimately worsen the overall prognosis. The wide use of prophylactic antibacterial and antifungal compounds has significantly decreased the risk for infections but is costly and increases the risk for resistant pathogens, and the long-term impact on the epidemiology has to be awaited.

What's new?

- Improved understanding of 1° and 2° immunodeficiencies and new antimicrobial and immunomodulatory compounds allow better supportive care.

What's next?

Studies are focusing on improving the risk stratification for infections in immunocompromised patients (e.g. by clinical algorithms or polymorphisms of different molecules of the immune system) and also validation of the value of newer diagnostic procedures in children (e.g. PCR techniques, serologic markers).

Further reading

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Chapter 18

Immunization of the immunocompromised child

Specific vaccines of relevance to immunocompromised children

The vaccines included in routine immunization schedules used in Europe are outlined in Appendix 3. For details of individual vaccines please refer to specific infection chapter. Some of these need specific consideration in immunocompromised children, including the following.

Rotavirus

Two live vaccines are available: Rotarix® (two doses) and RotaTeq® (three doses). The first dose requires administration before 15 weeks of age (the second dose before 23 weeks and 6 days), therefore before the presentation of most immunocompromising conditions.

Administration is:

- To be avoided in patients with SCID
- Safe in patients with HIV on ART
- Of uncertain efficacy and safety in infants with other immunocompromising illnesses; however, most children are likely to benefit, as natural rotavirus infection is almost unavoidable
- Advised in infants born into households with an immunocompromised inhabitant, according to the routine infant schedule.

Varicella

Two live attenuated vaccines available, administered as two doses, given 4–8 weeks apart from 12 months of age. Monovalent vaccines preferred to combination vaccines with measles, mumps, rubella, and varicella (MMRV), which have a higher varicella dose.

- Avoid in children with immunocompromise, with the possible exceptions of seronegative children:
  - With 22Q11 deletion/di George syndrome
  - With HIV if % CD4 >15.
- Where possible, give a dose 3–4 weeks before commencing immunosuppressive therapy for seronegative children.
- Use in children already on low-dose immunosuppressants is controversial and should be discussed with paediatric infectious disease clinicians.
- Efficacy potentially reduced in immunocompromised children.
- Administer to contacts of immunocompromised; the benefit/risk ratio remains positive, despite case reports of 2° transmission of the vaccine strain.

BCG

Live attenuated vaccine.

- Do not administer to immunocompromised children.
- Delay in babies born to HIV-positive mothers until the infant has had two negative HIV PCR tests, one of which is at least 6 weeks after antiretroviral therapy has stopped.

Measles, mumps, rubella

Combination of three live attenuated viruses.

- Do not administer to children on high-dose immunosuppressants and chemotherapy, and with disorders of T-cell function.
- Can be given to HIV-positive children and those with di George syndrome ≥12 months of age if CD4% ≥15.

Influenza

- Annual influenza immunization is appropriate for most immunocompromised children (two doses given 1 month apart in first season for children under 9 years; otherwise a single dose given annually).
- The live attenuated influenza vaccine (LAIV) is only licensed from 2 years of age, at-risk children younger than this should receive the inactivated vaccine.
- Inactivated influenza vaccines should be given instead of LAIV for children or adolescents on high-dose immunosuppressants or chemotherapy, or with T- or B-cell immunocompromise.
- LAIV *not* contraindicated in children ≥2 years of age with:
  - Stable HIV infection receiving ART
  - Topical/inhaled corticosteroids, low-dose systemic corticosteroids, or corticosteroids for replacement therapy, e.g. for adrenal insufficiency.
- Immunization of household contacts encouraged; however, shedding of the live attenuated virus in the weeks following immunization creates the theoretical risk of transmission to severely immunocompromised hosts; therefore, close contacts of such children should receive the inactivated influenza vaccine.

Pneumococcus

Children with broad range of immunodeficiencies and chronic illnesses are at increased risk of pneumococcal disease, especially those with haematological malignancy, HIV, and splenic dysfunction. Immunization with one of the two licensed pneumococcal glycoconjugate vaccines (10-valent PCV10 or 13-valent PCV13) is now universal in most European countries, and the resultant herd immunity is expected to reduce the disease burden due to these serotypes, even in immunocompromised children.

- Administer PCV10 or PCV13 in infancy, according to local routine immunization schedules.
- For older children, current UK recommendations are:
  - One dose of PCV13 for a child ≥2, but <5 years old if not already given (two doses for splenic dysfunction or immune system impairment)

- One dose of PCV13 for children ≥5 years old and severely immunocompromised (e.g. bone marrow transplant patients, those with haematological malignancies or primary immunodeficiencies).

Although included in some immunization guidelines for children over 2 years of age, the benefits from an additional 23-valent plain polysaccharide vaccine are uncertain, given concerns regarding immunological hyporesponsiveness with repeated immunization. Disease-specific guidance has been provided for some conditions, e.g. HIV guidelines produced by Children's HIV Association (CHIVA, <http://www.chiva.org.uk>), and these should override more general guidelines.

Meningococcus

Specific conditions at increased risk of invasive meningococcal disease (IMD) are asplenia/splenic dysfunction, complement deficiency, and eculizumab therapy.

Serogroups A, C, W, and Y

Two quadrivalent glycoconjugate MenACWY vaccines are licensed in Europe: Nimenrix® (MenACWY-TT, licensed as a single dose from 12 months of age) and Menveo® (MenACWY-CRM, licensed as a single dose from 2 years of age). These vaccines should be used in preference to plain polysaccharide vaccines for all children at increased risk of IMD.

- Although no glycoconjugate MenACWY vaccine is licensed in Europe for use in <12 months of age, some national guidelines (e.g. UK) suggest using MenACWY as a substitute for monovalent MenC vaccine in infant immunization programmes for children at increased risk of IMD.
- For children previously immunized with MenC vaccine, give a further dose of MenACWY conjugate vaccine ≥1 month later.
- Children/adolescents previously receiving a plain polysaccharide MenACWY vaccine should receive a dose of glycoconjugate MenACWY vaccine.
- Children at increased risk of IMD who are travelling to countries with a high incidence of serogroup A meningococcal infection (e.g. Saudi Arabia and sub-Saharan Africa) should be given a further dose of MenACWY conjugate vaccine, in addition to those recommended above, prior to travel.

Serogroup B

A serogroup B meningococcal vaccine (Bexsero®, 4CMenB) has been licensed in Europe for children ≥2 months old.

This vaccine is recommended for children at increased risk of IMD, according to the following schedules:

- Three doses at least 1 month apart, with a booster dose in the second year of life if <6 months of age
- Two doses at least 2 months apart, with a booster after 12–23 months if 6 months to 2 years of age
- Two doses at least 2 months apart if 2–10 years
- Two doses at least 1 month apart if 11 years or older.

Polio vaccines

- Avoid live oral polio vaccine (OPV) in all immunocompromised children and their household contacts.
- Use inactivated polio vaccines in these circumstances.

Hepatitis B vaccine

- If not included in the routine vaccine schedule, give to children at increased exposure risk (e.g. dialysis, HIV-positive family member) or with reduced hepatic capacity (e.g. chronic liver disease).
- Give as 0-, 1-, 6-month course, unless accelerated schedule required for post-exposure prophylaxis (PEP) (e.g. maternal infection), in which case a 0-, 1-, 2-, 12-month immunization course should be given.
- Check serology 6–8 weeks post-third dose.
  - If >10IU/L, but <100IU/L, offer a booster, and recheck serology after 6–8 weeks.
  - If <10IU/L after the 1° course, repeat the course and serology.
- Consider combination hepatitis A and B vaccine if over 12 months of age.

Palivizumab

Humanized monoclonal antibody against RSV F protein can protect children at increased risk from RSV infection against hospitalization and severe disease when administered monthly during the RSV season.

- Licensed for use in children:
  - Born <35 weeks' gestation who are under 6 months at the onset of the RSV season
  - Under 2 years of age and requiring treatment for bronchopulmonary dysplasia (BPD) within the last 6 months
  - Under 2 years of age with haemodynamically significant cardiovascular disease.
- Local guidance for use may differ, based on cost-effectiveness calculations. In the UK, its use is targeted at extremely low-birthweight premature infants with chronic lung disease.

Immunizing children with primary immunodeficiencies

See Chapter 17 for a discussion on 1° immunodeficiencies. For all the 1° immunodeficiencies:

- *Passive immunization* on exposure to measles, varicella, and tetanus will be required
- The importance of *immunizing immunocompetent family members* to reduce transmission should be emphasized.

Combined B-/T-cell immunodeficiency

Examples: SCID, Wiskott–Aldrich Syndrome, hyper IgM/CD40 ligand deficiency, chronic mucocutaneous candidiasis (CMC) (autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED) syndrome).

- Inactivated routine vaccines:
  - Safe; however, effectiveness is doubtful, especially for patients on immunoglobulin replacement therapy (IRT) (providing continual passive immunity).
- Live vaccines:
  - Avoid all, including rotavirus, MMR, BCG, and LAIV.
- Additional vaccines:
  - Annual inactivated influenza immunization may be beneficial.

B-cell deficiency

Examples: X-linked agammaglobulinaemia, common variable immunodeficiency, hyper IgE (Jobs) syndrome.

- Inactivated routine vaccines:
  - Safe; however, effectiveness doubtful, especially following commencement of IRT therapy.
- Live vaccines:
  - While immunization with MMR and varicella vaccine could potentially provide cellular immunity, safety is uncertain, and any immune response is unlikely if the patient is on IRT
  - Avoid BCG.
- Additional vaccines:
  - Annual inactivated influenza immunization may be beneficial.

Reduced T-cell numbers

Example: 22q11 deletion/di George syndrome.

- Inactivated routine vaccines:
  - Administer as per local routine schedule.
- Live vaccines:
  - Recent case series suggests that MMR and varicella vaccines may be given safely to patients with di George syndrome who have mild to moderate immunocompromise; these should be given at age 12–18 months if CD4 count adequate and normal mitogen response.
  - Other live vaccines (BCG, OPV, yellow fever vaccine, live influenza vaccine) should be avoided.
- Additional vaccines:
  - Pneumococcal and influenza immunizations.

Minor antibody deficiencies

Examples: IgA and IgG subclass deficiencies, ataxia telangiectasia. Some children will require regular IVIG therapy for recurrent infections, which will potentially interfere with live vaccine immunogenicity (but these should still be given).

- Inactivated routine vaccines:
  - Administer as per local routine schedule.
- Live vaccines:
  - Safe; administer as per local routine schedule.
- Additional vaccines:
  - Pneumococcal and influenza immunizations.

Phagocytic cell deficiencies

Examples: CGD, myeloperoxidase deficiency, and leucocyte adhesion deficiency.

- Inactivated routine vaccines:
  - Administer as per local routine schedule.
- Live vaccines:
  - MMR and varicella, and live attenuated influenza vaccines should be administered (varicella vaccine is advised to reduce the risk of 2° bacterial sepsis from natural infection)
  - Avoid BCG or other live bacterial vaccines such as oral typhoid.
- Additional vaccines:
  - Pneumococcal and influenza immunizations.

Complement deficiency

At increased risk of infection with encapsulated bacteria, particularly *Meningococcus*.

- Inactivated routine vaccines:
  - Administer as per local routine schedule (but ensure meningococcal immunization as per specific guidance).
- Live vaccines:
  - Safe; administer as per local routine schedule.
- Additional vaccines:
  - Immunize with MenACWY and serogroup B meningococcal vaccines
  - Pneumococcal immunizations should be administered.

Acquired immunodeficiencies

HIV infection

- Inactivated routine vaccines:
  - Administer as per local schedule
  - If highly active antiretroviral therapy (HAART) indicated, vaccination should be delayed until both viral load <50 copies/mL and CD4 % >15 for 6 months.
- Live vaccines:
  - Live attenuated influenza vaccine if ≥2 years and infection stable
  - Rotavirus vaccine safe and recommended (usual age limits apply)
  - MMR recommended, unless severe immunosuppression, i.e.:
    - —CD4 % <15 (any age), or
    - —CD4 count <750 cells/mm^3 (<12 months)
    - —CD4 count <500 cells/mm^3 (>1–5 years)
    - —CD4 count <200 cells/mm^3 (>6 years)
  - Give two doses of MMR at least 3 months apart (if under 18 months) or at least 1 month apart (if ≥18 months)

  - Give two doses of varicella vaccine 1–2 months apart in VZV seronegative children over 1 year of age and in the *absence* of severe immunosuppression (as per MMR guidance)
  - Administer MMR and varicella vaccine at least 1 month apart
  - Avoid BCG in HIV-positive children.
- Additional vaccines:
  - Annual influenza vaccine (consider live vaccine if ≥2 years)
  - All require two doses of pneumococcal glycoconjugate vaccine (PCV13 or PCV10, as used in the local schedule), given 2 months apart (if not given in infancy)
  - Consider including pertussis vaccine in adolescent booster if not included in routine immunization programme
  - Human papillomavirus (HPV) according to routine immunization practice for adolescent girls; consider also administering to adolescent boys
  - Hepatitis B vaccine.

In addition to HBV serology check, consider checking tetanus and measles antibody concentrations post-preschool and adolescent booster vaccine visits. For children immunized prior to commencing ART, consider re-immunizing after immune reconstitution on HAART.

HIV-negative children in a household with an HIV-positive member

- Routine immunizations, as per national guidelines.
- MMR and BCG should be given.
- Varicella immunization for children >1 year, if not already immune.

Immunosuppressive medication

Immunosuppressants

The following medicines/doses are considered 'high-dose':

- Glucocorticoids: high-dose glucocorticoid—pulse therapy or >2mg/kg/day or >20mg per day for 2 weeks.
- Non-biological immunosuppressants (also known as disease-modifying anti-rheumatic drugs, DMARDs):
  - Methotrexate >15mg/m^2/week
  - Ciclosporin >2.5mg/kg/day
  - Azathioprine 1–3mg/kg/day
  - Cyclophosphamide 0.5–2.0mg/kg/day orally
  - Leflunomide 0.25–0.5mg/kg/day
  - 6-mercaptopurine >1.5mg/kg/day
  - Sulfasalazine is not immunosuppresive.
- Biological agents (e.g. infliximab, rituximab, abatacept, tocilizumab, eculizumab, etc.)—at any dose within the last 6 months.

Recommendations

The European League Against Rheumatism (EULAR) guidance on immunization of children on immunosuppressive treatment broadly recommends:

- Inactivated routine vaccines:
  - Administer as per local schedule
  - If child's immunization not up-to-date, 'catch-up' immunizations should ideally be given before commencing immunosuppressants
- Live vaccines:
  - If possible, check varicella-zoster IgG status prior to treatment initiation, and administer the varicella vaccine to seronegative patients 3–4 weeks prior to starting treatment
  - Booster doses for varicella vaccine and MMR can be considered in patients on low-dose steroids or methotrexate <15mg/m^2/week
  - In addition, the Infectious Diseases Society of America (IDSA) guidelines suggest to consider 1° varicella vaccine for chronic inflammatory disease with long-term, low-level immunosuppression
- Additional vaccines:
  - Influenza and pneumococcal vaccines
- Siblings should receive MMR, as per usual schedule, and varicella vaccine if non-immune and >1 year old.

Patients on rituximab

- Inactivated routine vaccines:
  - Safe, but response to inactivated vaccines impaired
  - Aim to administer >4 weeks prior to commencing treatment (or if already on rituximab >4 weeks prior to the next dose).
- Live vaccines:
  - Avoid all live vaccines for 6 months after treatment.
- Additional vaccines:
  - Give inactivated influenza vaccine in autumn, regardless of the timing of rituximab or the lymphocyte count
  - Patients who have not already had pneumococcal immunization should ideally commence immunization 3 months before commencing the first course of rituximab with two doses of glycoconjugate pneumococcal vaccine (PCV10 or PCV13)
  - There is no evidence that a dose of pneumococcal plain polysaccharide vaccine confers additional benefit in these patients
  - Administer tetanus immunoglobulin to any patient receiving rituximab within the last 6 months with a contaminated wound
  - Once IgG concentration in the normal range, check specific antibodies (e.g. tetanus, Hib, serotype-specific pneumococcal antibodies, measles); if low, re-immunize and check levels.

Patients on eculizumab

Specifically at increased risk of meningococcal disease, given the central role of C5 (bound by eculizumab) in the complement cascade:

- Additional meningococcal immunization.

Chemotherapy for malignancy

- Inactivated routine vaccines:
  - Safe but should not be administered during induction or consolidation therapy.
- Live vaccines:
  - Avoid in patients actively receiving treatment, and for 6 months following cessation of treatment.
- Additional vaccines:
  - Pneumococcal vaccine
  - Inactivated influenza vaccination should be offered from the age of 6 months, during maintenance chemotherapy, and if autumn occurs in the first 6 months following completion of chemotherapy
  - At 6 months following completion of chemotherapy, administer a booster dose of all routine vaccines (or alternatively check serology, and administer a booster dose of the relevant vaccine if antibodies are below correlate of protection).

Haematopoietic stem cell transplantation

Conditioning therapy before transplantation removes the humoral immune memory from previous infections and immunizations, and makes these children severely immunocompromised.

- Inactivated routine vaccines:
  - Prior to HSCT, vaccination, as per local schedule, should be completed *if* not immunosuppressed and >4 weeks prior to HSCT.
- Live vaccines:
  - MMR and varicella vaccination in children >12 months of age who are not immunosuppressed and >4 weeks prior to HSCT
  - Avoid BCG, unless absolutely necessary; seek expert advice.
- Additional vaccines:
  - Annual inactivated influenza vaccine from first autumn after commencement of re-immunization.
- Passive immunization:
  - Passive immunization for contact with chickenpox/shingles or measles is required until 12 months after HLA-identical sibling donor allogeneic HSCT, syngeneic HSCT, or autologous HSCT, and 18 months after all other allogeneic HSCT. This is required, regardless of pre-chemotherapy antibody status.

Re-immunization

- Re-immunization (i.e. repeating all immunizations received during 1° vaccination course) should begin 12 months after HLA-identical allogeneic HSCT, syngeneic HSCT, or autologous HSCT, and 18 months after all other allogeneic HSCT.
- This should be delayed if
  - Immunosuppressive drugs used within 6 months (12 months for live vaccines)
  - IVIG has been used within 3 months
  - Evidence of chronic GVHD.

Solid organ transplant

- Inactivated routine vaccines:
  - Childhood/adolescent immunizations (including HPV) should be given, whenever possible, *prior to* solid organ transplantation.
- Live vaccines:
  - MMR and varicella vaccine should be given at least 4 weeks prior to transplant (if not immunosuppressed)
  - *Avoid* live vaccines after solid organ transplantation.
- Additional vaccines:
  - Pneumococcal and influenza immunizations
  - Hepatitis B vaccine to be given prior to transplantation.

Hyposplenia/asplenia/functional asplenia

Specific increased risk of pneumococcal disease, with case reports of overwhelming meningococcal infection.

- Live and inactivated routine vaccinations:
  - Administer, as per local routine schedule.
- Additional vaccines:
  - Give pneumococcal and influenza vaccines
  - Meningococcal vaccines.

If undergoing splenectomy, give all vaccines 2 weeks before surgery, if possible.

Nephrotic syndrome

- Inactivated routine vaccines:
  - Administer, as per local routine schedule.
- Live vaccines:
  - Give MMR and varicella vaccines during remission when off steroids for 3 months or off other immunosuppressants for 6 months.
- Additional vaccines:
  - Pneumococcal/influenza immunization.

If on rituximab, immunize.

Renal failure/chronic renal disease/dialysis

- Live and inactivated routine vaccinations:
  - Administer, as per local routine schedule.
- Additional vaccines:
  - Pneumococcal/influenza immunization
  - Hepatitis B vaccine (increased risk due to dialysis).

Chronic liver disease

- Live and inactivated routine vaccinations:
  - Administer, as per local routine schedule.
- Additional vaccines:
  - Pneumococcal/influenza immunization
  - Combined hepatitis A and hepatitis B vaccination to avoid further liver insult.

Cyanotic heart disease/heart failure

- Live and inactivated routine vaccinations:
  - Administer, as per local routine schedule.
- Additional vaccines:
  - Influenza and pneumococcal immunization
  - If on aspirin, consider varicella vaccination from 12 months of age to decrease the risk of Reye's syndrome
  - RSV prophylaxis.

Cystic fibrosis/bronchiectatic conditions/home ventilation

- Live and inactivated routine vaccinations:
  - Administer, as per local routine schedule.
- Additional vaccines:
  - Influenza and pneumococcal immunization
  - RSV prophylaxis.

Premature infants

- Inactivated routine vaccinations:
  - Administer, as per local routine schedule, at the normal chronological age (even if on steroid therapy for chronic lung disease)
  - Particular attention to timely routine booster doses.
- Live vaccines:
  - Administer, as per local routine schedule, at the normal chronological age
  - Rotavirus vaccination should be given, even if the patient still in the NICU.
- Additional vaccines:
  - Consider influenza immunization from 6 months of age where additional risk factors exist, e.g. chronic lung disease
  - For influenza, in preterm infants <6 months, a cocooning strategy of immunizing family members may be considered
  - RSV prophylaxis, as appropriate, for first RSV season.

Monitoring post-immunization

- Infants born ≤28 weeks' gestation in hospital at the time of first immunization should be monitored for 48–72 hours after their first vaccine. If apnoea/bradycardia/desaturation occurs, then the child should be admitted and monitored for their second immunization.
- No requirement for monitoring if the baby was discharged from the neonatal unit by 60 days of age.

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Chapter 19

Infection control in the community

See also Chapter 17.

Introduction

There are numerous settings where the prevention and control of infection in children and babies are important, and these include:

- The home
- Preschool (crèche, nurseries, and childminders)
- Schools and after-school clubs
- Residential care (children's homes, hospices)
- Community health-care settings such as general practices and dentists
- Children's play areas.

Principles of infection control

Applying the principles of infection control in all childcare settings should make a major contribution to preventing infection. By removing or controlling any one of three main links in the chain of infection, the spread may be interrupted:

- Link one—sources of infectious agents
- Link two—susceptible hosts
- Link three—pathways or vehicles of transmission.

Link one—sources of infectious agents

These include:

- Animate sources (humans, animals, and insects)—in blood, faeces, urine, vomit, pus, respiratory droplets, sputum, skin rashes, and food and fluids contaminated by these body fluids
- Inanimate sources (soil, water, food).

It is possible to remove or control certain sources of infection in community childcare settings, e.g.:

- Preventing children with known infection or with symptoms of a possible infection, such as diarrhoea, from attending during the infectious period. This is known as 'exclusion'
- Prohibiting the introduction of potentially contaminated food and fluids into the setting, e.g.:
  - Avoiding high-risk foods, such as soft cheeses, pâtés, eggs, and raw meat

  - Purchasing only pasteurized milk and fruit juices
  - Removing soil from fresh vegetables and washing them prior to consumption.
- Guidance on the exclusion of children with infections from childcare settings is available on the PHE website (<https://www.gov.uk/government/publications/infection-control-in-schools-poster>)
- Outbreaks are defined as two or more people with the same infection or symptoms linked in terms of time, place, or common exposure, or as a greater-than-expected rate of infection, compared with that usually expected. Outbreaks should be reported to local health authorities.

Link two—susceptible hosts

There are many factors that increase an individual's risk of infection, and children may have all or any of these, which include:

- Extremes of age
- Underlying health conditions, such as diabetes mellitus, cancer, and immunocompromised conditions, such as leukaemia, and HIV and AIDS
- Medications such as steroids, cytotoxics, antibiotics
- Pregnancy
- Invasive medical devices such as indwelling urinary catheters, feeding tubes.

Many of these risk factors are intrinsic or unavoidable, though there are measures that can be taken to protect the vulnerable.

The key intervention is immunization against infectious diseases, and the childhood immunization schedule in England is described in *Immunisation against infectious diseases* (also known as the *Green Book*), which is available on the PHE website (<https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book>). Vulnerable children may require additional vaccinations.

In general, vulnerable children and adults in the risk groups described do not need to be excluded from community childcare settings, unless unwell themselves or seriously immunocompromised. Targeting the other links in the chain will minimize infection risks.

Pregnant women and vulnerable children should seek medical advice if they are in close contact with an infectious disease such as chickenpox, rubella, measles, or parvovirus.

Link three—pathways or vehicles of transmission

It is not always possible, practical, or imperative to remove sources of infection from childcare settings. For example, children with minor health problems, such as colds, head lice, or hand, foot, and mouth infection, would not usually be excluded. Some infections are most infectious before symptoms have appeared.

For this reason, targeting vehicles of transmission or protecting susceptible hosts are important interventions.

Infection may be transmitted by the following means:

- Direct contact with an infectious individual or with other sources of infection
- Indirect contact with contaminated articles or environment
- Contact with airborne infectious respiratory secretions or aerosolized body fluids such as vomit.

The risk of transmission may be reduced by avoiding or controlling exposure to infectious agents by practising standard infection control precautions. These include:

- Hand hygiene
- Personal protective equipment (PPE)
- Environmental and equipment hygiene
- Food hygiene
- Safe disposal of waste.

Hand hygiene

- Contaminated hands are a common vehicle of transmission via direct and indirect contact.
- Simple handwashing to remove pathogens or reduce them to a safe level is usually adequate in childcare settings.
- Alcohol hand gels can be effective when used on socially clean hands and are convenient in situations where soap and water are not readily available.
- Whichever method of hand hygiene is employed, a good technique is essential.
- Facilities should be available for hand hygiene in toilets, kitchens, baby changing rooms, and clinical rooms.
- In children's toilets, handwash basins, towel dispensers, and soap should be at an appropriate height.
- Young children should be encouraged to wash their hands, with supervision.

Handwashing technique

1. Remove hand jewellery and wristwatches, and roll up sleeves.
2. Wet hands under warm running water.
3. Apply liquid soap.
4. Rub this into all parts of the hands vigorously, without applying more water, for at least 10–15 seconds.
5. Rinse hands under running water.
6. Dry thoroughly, ideally using paper towels or a clean cotton towel.

Using alcohol hand gels

1. Apply 5mL of alcohol hand gel to visibly clean hands.
2. Rub gel into all parts of the hands until the alcohol has evaporated—especially between the fingers, palms, and the back of the hand and wrists.

Personal protective equipment

Commonly used types of PPE include:

- Gloves
- Aprons/coveralls
- Face protection (masks and eye protection).

Gloves

- Disposable gloves are recommended for use whenever contamination with blood and body fluids is anticipated.
- If gloves are not available, good hand hygiene should be used to remove pathogens from the hands.

Aprons

- Plastic aprons are often used in health care and are worn when undertaking procedures where contamination of clothing/uniform is anticipated.

Face protection

- Face masks and eye protection are used to prevent contact with, and inhalation of, airborne or aerosolized microorganisms.
- Controllable exposure by this pathway is unlikely in community childcare settings; therefore, face protection should not be necessary other than in health care.

Environmental and equipment hygiene

Contaminated equipment, utensils, furniture, toys, and the general environment can act as vehicles of spread. Accumulations of dust, dirt, and liquid residues in the environment will increase infection risks and can be reduced by regular cleaning and drying, and ensuring fittings and fixtures are kept in good repair.

Management of the spillage of blood

- Any spillages of blood must be dealt with quickly and effectively, ideally using a spill-kit for the purpose. Wear disposable gloves and a disposable apron, if available.
- In community childcare settings, the waste should be contained in a plastic bag that is securely tied and discarded in the household waste. In clinical settings, contaminated materials and debris are treated as clinical waste.
- Surface disinfection is usually recommended, using a chlorine-releasing agent such as bleach or sodium dichloroisocyanurate (NaDCC). Specific precautions should be taken to avoid exposure to these agents. If not available, detergent and water can be used.

Food hygiene

Food may pose a risk of infection if not handled correctly, and food-borne outbreaks may occur. Food poisoning can cause serious, even life-threatening, illness in young children and infants. Managers and staff must be aware of food hygiene legislation and good practice. The local environmental health department can advise on this.

Safe disposal of waste

- Local policies should be in place, and staff trained in the correct procedures.

Management of sharps and inoculation injuries and bites

- Every organization should have an inoculation injury policy in place.
- Sharps include: needles, scalpel blades, stitch cutters, and cannulae used in clinical care, and sharp objects, such as broken glass, that are contaminated with blood.

Risk of transmission

- Risks of blood-borne viral infections are associated with inoculation of an infectious dose of infected body fluid into a susceptible recipient.
- A simple injury, which does not break the skin or does not involve the inoculation of body fluid, is unlikely to lead to the transmission of infection.
- Procedures for managing an inoculation injury include:
  - Encourage bleeding (but do not suck or rub the wound)
  - Rinse wounds and contaminated mucous membranes with water or emergency eye wash solution
  - Cover wound with a waterproof dressing
  - Seek advice from the local emergency department, occupational health, or GP as soon as possible.

Preventing zoonotic infections

Zoonotic infections can be acquired by contact with animals, their excreta, and environment, such as contact with pets or animals, e.g. during visits to farms, petting zoos, and other animal centres.

These infections include: *E. coli* O157, *Campylobacter*, and *Salmonella*, cryptosporidiosis, psittacosis, toxoplasmosis, and toxocariasis.

Children <5 years and pregnant women are particularly at risk of complications of infection.

Reducing infection risks during visits to farms and zoos

- Check that the farm/centre is well managed and the grounds and public areas are clean.
- Check that there are good handwashing facilities accessible for children.
- Ensure hands are washed thoroughly with soap and water after contact with animals and their environment, before eating or drinking, and before departure. Young children should be supervised when handwashing.
- Children should not eat, drink, or put anything in their mouths when touring animal settings.
- Clean any faecal matter and soil from footwear and pushchair wheels, and wash hands afterwards.
- Pregnant women should avoid contact with sheep and lambs.

Further information is available on the PHE website (<https://www.gov.uk/government/publications/farm-visits-avoiding-infection>).

Further reading

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Chapter 20

Infection control in the hospital

Introduction

Health care-associated infections (HAIs) are infections that are acquired as a result of health-care interventions. Infections presenting >48 hours after admission to hospital are generally considered to be hospital-acquired.

HAIs are important for many reasons:

- They are costly
- They cause excess morbidity and mortality to patients
- They can be disruptive to running the hospital
- They can result in adverse publicity and/or legal action.

With consistent application of good infection control measures, a large proportion of HAIs are preventable. Growing recognition of this in recent years has led to many initiatives to control and prevent HAIs, including the promotion of hand hygiene, environmental cleanliness, and use of care bundles.

Across Europe, much of the focus on specific HAIs has been on *C. difficile* and BSIs with MRSA, conditions that are less common in paediatrics. However, this does not mean that HAIs are less of a problem in paediatrics.

Epidemiology

Reasons why patients in hospital are at risk of health care-associated infections

- Close proximity to other patients colonized or infected with important microorganisms—this risk can be compounded by movement of patients, within and between hospitals, overcrowding, and reduced staffing.
- Underlying illnesses or chronic medical problems, increasing susceptibility to infection.
- Surgery introduces risk of many types of infection.
- Other manipulations involving breach of normal host defences also increase the risk of infection, e.g. intravascular devices, mechanical ventilation, urinary catheterization, etc.
- Antibiotics used to prevent or treat infections themselves carry a risk of causing superinfections with resistant microorganisms.

Specific points about health care-associated infections in children

- Infection is a commoner reason for children being admitted to hospital: community-associated childhood infections, such as rotavirus, norovirus, and respiratory virus infections, may therefore spread in hospitals.
- Children are less likely to be immune to viral infections such as chickenpox.
- Children are generally less susceptible to some common health care-associated pathogens, e.g. *C. difficile*, MRSA.
- However, they are more susceptible to some other bacterial infections (e.g. invasive infections with *S. aureus*, pertussis).
- Children may be more likely to be colonized with antibiotic-resistant Gram-negative bacteria.
- Modes of treatment of children and adults differ. For example, urinary catheters are used much less frequently in children.
- Children are less able to cooperate with their care (try asking a 5-year-old not to touch their line!).

Incidence

Point prevalence studies are a cost-effective way of estimating the burden of HAIs in hospitals; however, until recently, there have been few good paediatric data. The incidence and prevalence of HAIs depend on the types of patients treated. A recent English study found the HAI prevalence in general paediatric wards was 3%, compared with around 10% in paediatric surgery wards and 14% on NICUs and paediatric intensive care units (PICUs).

Point prevalence studies underestimate the risk of acquiring an infection in hospital, because they do not take account of the length of stay or of infections that do not present until after discharge; up to 20% of patients discharged from hospital may later develop an HAI. Thus, the incidence of HAIs is considerably higher than the prevalence measured in point prevalence studies.

Sources of infection

HAIs may be:

- Endogenous: infections caused by opportunist pathogens that the patient is already colonized with
- Exogenous: infections caused by microorganisms that are acquired in hospital.

Types of health care-associated infections

HAIs can occur at any site of the body. Many are associated with indwelling invasive devices. Rates of infection are best expressed as a proportion of how many days the device has been sited (see Chapter 9).

There are important differences between the causes of HAIs in children and adults (Table 20.1). In particular, BSIs account for a much greater proportion of paediatric HAIs, but health care-associated UTIs are rarely seen in children.

For all rates of nosocomial infection, it is important to have clear denominator data that are comprehensive, easily collectable, and reproducible.

Table 20.1 shows the distribution of various types of HAIs.

Table 20.1 Commonest sites of HAIs in children and adults

Infection type	% of HAIs in:	
	Adults	Children
Lower respiratory tract	34.2	36.9
Urinary tract	25.9	1.9
Surgical site	15.7	18.4
GI tract	13.2	10.7
Bloodstream	10.9	32.0

Infections that may be transmitted between patients and between patients and health-care workers

- Diarrhoea.
- *S. aureus* infections (including MRSA).
- GAS infections.
- TB.
- Varicella-zoster.
- Measles, mumps, rubella.
- Influenza.
- Respiratory virus infections, e.g. RSV.

Infections mainly transmitted between patients and health-care workers

- Blood-borne viral infections.
- HSV infections.
- CMV infections.
- Meningococcal disease.

Infections mainly transmitted between patients

- Infections caused by antibiotic-resistant bacteria.
- *C. difficile* infection.

Infections that may be acquired from the hospital environment

- Legionnaires' disease.
- Aspergillosis.
- Infections caused by Gram-negative bacteria, e.g. *Pseudomonas, Acinetobacter*.
- *C. difficile* infections.
- Glycopeptide-resistant enterococcal infections.

Causative microorganisms

See Tables 20.2, 20.3, 20.4, 20.5, and 20.6, .

Table 20.2 Gram-positive bacteria causing HAIs

Species	High-risk patient groups	Types of HAI
S. aureus	Surgical	Surgical site infections
	Neutropenia	BSI
	Ventilated patients	Pneumonia
	Patients with indwelling medical devices	CVC-related infections; shunt-associated meningitis; dialysis catheter-related peritonitis
	Cardiac surgery	Endocarditis; mediastinitis
	Neonatal intensive care	Pneumonia; BSI
CoNS	Ventilated neonates	Pneumonia
	Patients with indwelling medical devices	CVC-related infections; shunt-associated meningitis; dialysis catheter-related peritonitis
	Cardiac surgery	Endocarditis
	Neonatal intensive care	Pneumonia; BSI
S. pyogenes	Burns	Skin and soft tissue infections
	Surgical	Surgical site infections
Enterococcus spp.	Patients with multiple antibiotic exposure	BSI
	Hepatology; gastroenterology	Intra-abdominal infections
	Patients with indwelling medical devices	CVC-related infections; catheter-associated UTIs

Table 20.3 Gram-negative bacteria causing HAIs

Species	High-risk patient groups	Types of HAI
Enterobacteriaceae (*E. coli*, *Klebsiella*, *Enterobacter*, etc.)	Neutropenia	BSI
	Ventilated patients	Pneumonia
	Liver unit; gastroenterology; surgical	Intra-abdominal infections
	Renal	UTI
	Neonatal intensive care	Pneumonia; BSI
P. aeruginosa	Neutropenia	BSI
	Ventilated patients	Pneumonia
	Burns	Skin and soft tissue infections
Acinetobacter spp.	Patients with multiple antibiotic exposures	BSI
	Burns	Skin and soft tissue infections
	Patients with indwelling medical devices	CVC-related infections; shunt-associated meningitis
Legionella	Immunocompromised	Pneumonia

Table 20.4 Anaerobic bacteria causing HAIs

Species	High-risk patient groups	Types of HAI
C. difficile	Recent/current antibiotic exposure; immunocompromised	Diarrhoea

Table 20.5 Fungi causing HAIs

Species	High-risk patient groups	Types of HAI
Candida spp.	Patients with multiple antibiotic exposures	BSI; oesophagitis
	Patients with indwelling medical devices	CVC-related infections; catheter-associated UTI
	Neutropenia	BSI
	Intensive care	Pneumonia; BSI
	HIV infection	Mucosal candidiasis
Aspergillus spp.	Bone marrow transplantation	Pneumonia
	Some 1° immunodeficiencies (e.g. CGD)	

Table 20.6 Viruses causing HAIs

Virus	High-risk patient groups	Types of HAI
Rotavirus	Infants	Diarrhoea
Norovirus	All	Diarrhoea and vomiting
RSV	Infants	Bronchiolitis
	Immunocompromised children (all ages)	Respiratory infections
Influenza	Neurological, hepatic, renal, pulmonary, and cardiac disease; diabetes mellitus; immunocompromised children	
Varicella-zoster	All non-immune patients	Chickenpox (risk of severe disseminated disease in neonates and immunocompromised)
CMV	Immunocompromised children (especially post-bone marrow or solid organ transplant)	Severe disseminated infection
EBV	Immunocompromised children (especially post-bone marrow or solid organ transplant)	Disseminated disease; post-transplant lymphoproliferative disorder (PTLD)
Herpes simplex	Immunocompromised patients (especially post-bone marrow or solid organ transplant); neonates	Severe disseminated infection
Adenoviruses	Immunocompromised patients (especially post-bone marrow or solid organ transplant)	Severe disseminated infection
Hepatitis B, hepatitis C, HIV	All	Blood-borne virus infections

Prevention

Many elements contribute to the prevention of HAIs, including:

- An effective infection prevention and control service
- Hospital design
- Environmental cleanliness
- Effective decontamination of reusable medical devices
- Infection control policies and protocols
- Isolation of patients
- Hand hygiene
- Care of indwelling medical devices
- Screening and surveillance
- Prevention and management of inoculation injuries
- Appropriate antimicrobial prescribing
- Immunization.

Effective infection prevention and control service

Infection control must be embedded into clinical practice and applied consistently by everyone. This depends on good management and organization, underpinned by good education, training, information, and communication, and an assurance framework.

Key elements

- Commitment to preventing and controlling HAIs from hospital management.
- An infection prevention and control team consisting of an adequate and appropriate mix of nursing and medical staff, with administrative and analytical support.
- An antimicrobial management team, typically consisting of microbiologists, clinicians, and an antibiotic pharmacist.

Hospital design

Hospitals should be designed and maintained to minimize opportunities for the transmission of infection. This includes provision of:

- Adequate isolation facilities
- Adequate space between beds or cots
- Appropriate air quality and ventilation in specialist areas
- Clinical areas that are uncluttered and easy to clean
- Proper separation of clean and dirty medical equipment
- A programme of ongoing maintenance.

Environmental cleanliness

- Poor environmental cleanliness is linked to the risk of HAIs
- Cleaning schedules should be clear and well publicized, and supported by a monitoring programme.

Effective decontamination of reusable medical devices

Reusable devices must be decontaminated in accordance with manufacturers' instructions. Decontamination must be tracked throughout, together

with systems, to identify patients on whom devices have been used. Devices that are designated for single use or single patient use must not be used outside those restrictions.

Infection control policies and procedures

All hospitals should have, and adhere to, evidence-based infection control policies and procedures to ensure that clinical practice is safe for both patients and staff. Many of the other elements of good infection prevention and control described in this section will be covered by these policies.

Isolation of patients

There are two main types of isolation:

- *Source isolation* is used to prevent transmission of pathogenic microorganisms from infected patients to other patients or staff
- *Protective isolation* is used to protect susceptible individuals from potential pathogens carried by their attendants or present in the environment.

Key elements of isolation

- Patient nursed in a single room. Where the number of infected persons exceeds the availability of single rooms, cohort isolation of patients with the same infection may be employed.
- Hand hygiene on entering and leaving the room.
- Wearing of appropriate PPE by all persons entering the room.
- Numbers of people entering the room minimized.

Hand hygiene

Hand hygiene is the single most important measure in preventing HAIs. WHO has developed the 'five moments' strategy toward hand hygiene that identifies the moments when hand hygiene is required to effectively interrupt microbial transmission during the patient care sequence (Fig. 20.1):

1. Before patient contact: to protect the patient from harmful microorganisms carried on the hands of health-care workers.
2. Before an aseptic task: to protect the patient from harmful bacteria, including the patient's own microorganisms.
3. After body fluid exposure risk: to protect the health-care worker and the health-care environment from harmful microorganisms.
4. After patient contact: to protect the health-care worker and the health-care environment from harmful microorganisms.
5. After contact with patient surroundings, including any object or furniture in the patient's immediate environment, even if there has been no direct contact with the patient: to protect the health-care worker and the health-care environment from harmful microorganisms.

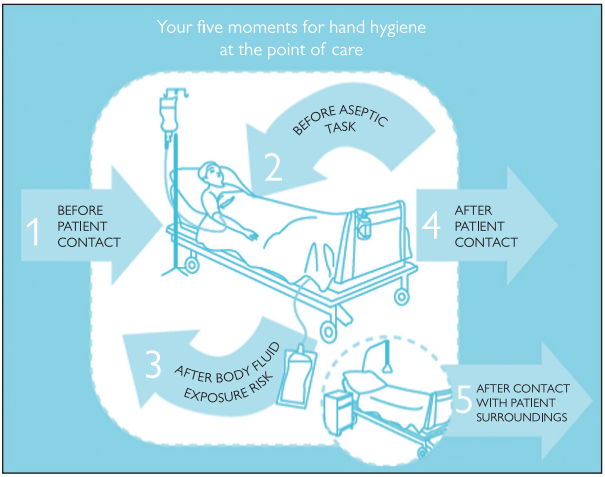

Fig. 20.1 The WHO 'five moments' strategy.

(Reproduced from H. Sax, B. Allegranzi, I. Uçkay, E. Larson, J. Boyce, D. Pittet (2007) 'My five moments for hand hygiene': a user-centred design approach to understand, train, monitor and report hand hygiene. *Journal of Hospital Infection* 2007;**67**:9–21, with permission from Elsevier.)

Care of indwelling medical devices

Indwelling devices, such as urinary catheters, intravascular catheters, and endotracheal tubes, are a frequent source of invasive infections. Adherence to good practice during the insertion and care of these devices can significantly reduce the risk of infection. Evidence-based care bundles are a structured way of improving the processes of care and outcomes of patients with these devices. A care bundle is a small, straightforward set of evidence-based practices (typically 3–5) that, when performed collectively and reliably, have been proven to improve patient outcomes.

Key elements of management of indwelling medical devices

- Indwelling devices only used where there is no suitable alternative.
- Where used, kept in place for as short a time as possible.
- Insertion always undertaken, or supervised, by trained and competent staff.
- Manipulation after insertion always undertaken, or supervised, by trained and competent staff.
- Removal always undertaken, or supervised, by trained and competent staff.

Screening and surveillance

Screening is used to detect people who are asymptomatic carriers of a microorganism that might later cause infection in that individual and/or be transmitted to other individuals. Persons who are screen-positive can be offered appropriate management to reduce their risk.

MRSA screening: many countries now advocate the screening of patients admitted to hospital. Coupled with decolonization treatment for those found to be positive, this approach can reduce the risk of infection for the individual patient and help prevent the transmission of MRSA to others. The place for universal screening of hospitalized children is unclear, because rates of colonization and infection in children are lower than in adults. However, screening of patient groups at higher risk of invasive infection with MRSA (such as neonates, PICU admissions, patients with indwelling medical devices) may be justified. Different hospitals have different risk-based screening strategies for children.

Multiply, extensively, and pandrug-resistant Gram-negative bacteria are a growing threat across Europe. Infants in NICUs are particularly at risk, and a growing number of NICUs now screen babies for these bacteria. In countries with high prevalence of these bacteria, local policies may suggest screening of other high-risk patient groups (e.g. PICUs; children transferred from other hospitals).

Surveillance is the process of monitoring the rates of microorganisms or infections that may give rise to hospital outbreaks. Monitoring infection rates is increasingly regarded as an important contributor to safe and high-quality health care. Surveillance can:

- Allow comparison of infection rates with other hospitals
- Inform planning and allow monitoring of benefits and of infection control initiatives
- Allow early detection of increases in rates of infection, so that remedial control measures can be implemented.

Large multicentre, national, or even international infection surveillance schemes for HAIs are particularly used in neonatology.

Appropriate antimicrobial prescribing

A standardized international terminology has been proposed to describe acquired antibiotic resistance profiles in bacteria that are often responsible for HAIs and are prone to MDR.

MDR is defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories.

Extensively drug-resistant (XDR) is defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories.

Pandrug-resistant (PDR) is defined as non-susceptibility to all agents in all antimicrobial categories.

Selection and maintenance of these antibiotic resistances in hospitals are directly linked to antibiotic use; antibiotic exposure can also increase transmissibility and pathogenicity of multiresistant bacteria, thus contributing directly to increasing the number of HAIs.

Increasingly, point prevalence surveys (PPS) are performed to determine the rates, type, and indications for antibiotic use in hospitals. All hospitals, including children's hospitals, should be performing regular PPS. In children, this is more complicated, as no single methodology has been validated.

Optimization of antimicrobial therapy for hospitalized patients ensures cost-effective therapy, improved patient outcomes, and reduced risks of antibiotic resistance and HAIs.

Components of antibiotic control in hospitals

- Antibiotics prescribed only where clinical evidence of bacterial infection.
- Antibiotic formulary and prescribing guidelines that restrict use of broad-spectrum agents.
- Recommendations on duration of therapy for specific infections. For most patients:
  - IV therapy can be limited to 48 hours, and total treatment to 5–7 days
  - Surgical prophylaxis can be limited to single dose in most cases.
- Control measures, including prescriber education, regular review of drug charts, audit, and restricted availability of certain antibiotics.

Immunization

Both active and passive immunization is used to control HAIs, e.g.:

- Active immunization of non-immune staff, e.g. against hepatitis B, measles, chickenpox, influenza
- Hepatitis B immunization of high-risk patient groups
- Active and/or passive immunization against hepatitis B after inoculation injuries
- Passive immunization with VZIG for non-immune high-risk contacts of persons with chickenpox
- Passive immunization with human normal immunoglobulin for non-immune high-risk contacts of measles.

Future research

Much of the research on hospital infection control has focused on adults, rather than children. There are many opportunities to investigate the prevalence, epidemiology, and prevention of HAIs in children.

What's new?

- Governments continue to set new targets around the prevention of HAIs.
- Children with multiple co-morbidities are being exposed to ever more complex medical procedures that are increasing their susceptibility to HAIs.
- The threat from antibiotic-resistant bacteria continues to grow, as witnessed by the extraordinarily rapid global spread of carbapenemase-producing Gram-negative bacteria.

What's next?

- It is likely that new laboratory technologies will become widely used to speed up the detection of patients who are colonized or of infection with bacteria that are readily transmitted to other patients in hospitals.
- There will be a growing focus in the use of screening to detect patients colonized with MDR bacteria.

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Chapter 21

Laboratory diagnosis of infection

Introduction

The purpose of making a laboratory diagnosis is to assist the clinician in determining whether or not a patient has a significant clinical infection and guide treatment. Even when all stages of laboratory testing are conducted optimally, few, if any, tests are 100% accurate. Test accuracy depends partly on the inherent properties of the test itself, but it is also influenced by variables such as sample volume and quality. This is often a problem in paediatrics. It is important that the requester understands the limitations of the tests that he or she orders, so that only appropriate tests are requested, good-quality samples reach the laboratory, and the results are interpreted appropriately.

Test accuracy (Fig. 21.1) is ascertained by a comparison of measurements obtained with that test with those obtained by a reference standard. A reference (or 'gold') standard is a measure that confirms or refutes the presence or absence of the condition being tested for beyond reasonable doubt.

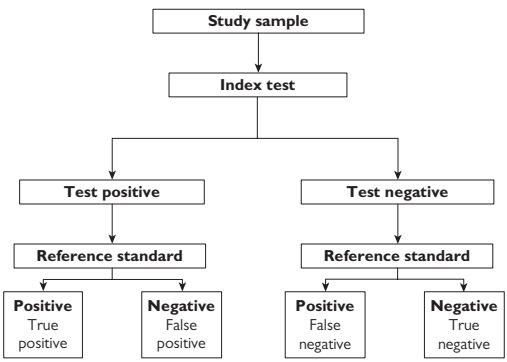

Fig. 21.1 Test accuracy.

Test accuracy can be expressed as sensitivity, specificity, and positive predictive value (PPV) and negative predictive value (NPV).

- Sensitivity is a measure of the ability of a test to identify as positive those individuals who have the condition being tested for.
- Specificity is a measure of the ability of the test to correctly identify those patients who do not have the condition.
- PPV is the probability that an individual with a positive test result has the condition.
- NPV is the probability that an individual with a negative result does not have the condition.

Calculation of test accuracy

See Table 21.1 for equations for measures of test accuracy.

- Sensitivity and specificity are constant measures of a test's performance (or characteristics).
- PPV and NPV are influenced by the prevalence of the condition in the population being tested. This is important, because, when testing a population with a low disease prevalence, even a test with high specificity may only have a low PPV.

Table 21.1 Equations for measures of test accuracy

	Condition present	Condition not present
Positive test	True positive (a)	False positive (b)
Negative test	False negative (c)	True negative (d)

Sensitivity = a/(a + c)

Specificity = d/(b + d)

Positive predictive value = a/(a + b)

Negative predictive value = d/(c + d)

Where a test that is 100% sensitive and 99% specific is used on a population with a condition prevalence of only 1%, half of all positive results will be false positives, giving a PPV of only 50%. For example, a positive rapid screen for respiratory virus infection in the summer (when prevalence is low) would be more likely to be a false positive, whereas a positive rapid screen during the winter is almost certainly a true positive. This is the pre-test probability of the disease.

Stages in laboratory testing

Laboratory functions are grouped into three phases:

- *Pre-analytical* describes events from the time the test is ordered to the time the sample arrives in the laboratory
- *Analytical* describes the handling and analysis of the sample in the laboratory
- *Post-analytical* describes what happens after a result is obtained, including reporting to the requester.

Pre-analytical phase

- Collect appropriate samples as soon as possible. Delays in sample collection mean:
  - It takes longer to get a result, so that patients may receive inappropriate or unnecessary antimicrobial therapy for longer
  - Decreased chance of diagnosing infection once antimicrobial therapy has been commenced.
- Only request tests (Box 21.1) where there is a reasonable likelihood of the patient having the disease or where it is important to exclude a disease:
  - Over-investigating wastes time and resources, as well as being unpleasant for the child
  - Indiscriminate use of tests for rare infections may lead to over-diagnosis and the wrong treatment, because the PPV of the test in such a population may be low (see Calculation of test accuracy, p. 200). Some children with a condition causing a current marked inflammatory activation (e.g. an autoimmune condition) may have a false positive anamnestic 2° immunological response, leading to false acute positive serology to actual past infections.

Box 21.1 Examples of tests that are not usually necessary

- Urine culture in children aged ≥3 years with uncomplicated UTI (empirical treatment is appropriate in most such circumstances)
- Urine culture in children aged ≥3 years who have leucocyte esterase and are nitrite-negative on dipstick testing (they are unlikely to have a UTI)
- Skin swabs from children with uncomplicated impetigo
- Nasopharyngeal swabs for bacterial culture (usually detects only commensal flora)
- Blood cultures from well children with low-grade fever

- Make sure that the laboratory has all the necessary information to allow it to process samples correctly, e.g. travel history, immunocompromise, risk factors for antibiotic resistance, etc. All tests should be requested with legible information on a request form. If you want to discuss the child, ring the lab!
- *Collect samples carefully for the best results.*

Samples for culture

- Take care to ensure the best possible chance of detecting pathogenic microorganisms, and without contaminating the sample with non-pathogenic microorganisms.
- Samples should be timed optimally:
  - Ideally, collect samples for bacterial culture before commencing antibiotics. The exception is in septic patients where antibiotics need to be administered as soon as possible. Here, take a blood culture before giving antibiotics, but do not delay giving antibiotics until any other samples are collected (e.g. CSF, urine)

- Where a patient is already receiving antibiotics, take samples immediately before a dose of antibiotic is due (when the concentration of the antibiotic in blood will be lowest).

- Use the correct sampling technique:
  - When sampling dry sites, moisten the swab first with sterile water or saline
  - Collect samples from sites where the infection is likely to be present (e.g. a deep wound swab is better than a superficial wound swab)
  - Take care to minimize contact with adjacent anatomical areas during swabbing
  - Careful collection of samples, such as blood cultures and urines, to avoid contamination—use closed sample collection techniques, e.g. not dripping blood from a needle!
  - An adequate quantity of material for complete examination must be obtained. Small sample volumes may compromise sensitivity; it may be preferable to collect a second sample, rather than undertake multiple investigations on a single sample.

Samples for analyses for parasites

- Should be undertaken at the time of day when the parasite load is likely to be highest.

Samples for serological assays

- Time must be given for the patient to mount an immune response; sampling too early may give false negative results.

Samples for molecular biological investigations

- Use the correct sampling devices and containers; some materials are inhibitory to nucleic acid amplification techniques (NAATs).
- Ensure appropriate storage and delivery of samples to the laboratory:
  - Samples must be delivered to the laboratory promptly to avoid deterioration. This is especially important for tests that depend on the presence of viable microorganisms to avoid:
    - —Loss of viability of the microorganisms of interest
    - —Overgrowth of non-pathogenic microorganisms in the sample.
  - If you cannot get your sample straight to the laboratory, make sure that it is stored appropriately (e.g. most samples should be refrigerated to prevent sample deterioration and microbial overgrowth; blood cultures should ideally be incubated immediately, and certainly should never be refrigerated)
  - Safety is imperative:
    - —Samples should be contained within leak-proof containers and then sealed in a specimen transport envelope
    - —Samples being transported outside the hospital require additional packaging
    - —High-risk samples must be clearly identified as biohazard.

Analytical phase

Test methods must be reliable and accurate, and give results in a clinically useful time frame. Testing must be undertaken in an appropriately accredited laboratory that participates in internal and external quality assurance.

Although most microbiology testing is undertaken in the laboratory, there are some tests that can be undertaken at the point of care. Such testing must be overseen by the laboratory to provide assurance of quality and safety. There are three broad categories of laboratory tests used to assist in the diagnosis of infection:

- Tests that involve direct detection of pathogenic microorganisms or their components in clinical samples, e.g. microscopy, culture, antigen detection, and molecular biology
- Tests that demonstrate a specific immune response to a specific pathogen, usually antibody detection
- Tests that provide non-specific evidence of an infective (or inflammatory) process.

Post-analytical phase

Accurate and timely reporting, with appropriate interpretation of the results. Laboratories should communicate urgent or important results verbally.

Laboratory diagnostic techniques

Microscopy

Microscopy may be used to give a rapid preliminary or definitive assessment of the cause of infection. It is most useful for examination of specimens that are normally sterile (where the presence of any microorganisms is abnormal), where pathogenic microorganisms have a distinctive morphology, or where a stain that is specific to the target microorganisms is used. There are various different microscopic techniques, including:

- Light microscopy of unstained or stained preparations
- Fluorescence microscopy
- Electron microscopy (EM).

Light microscopy

Examination of unstained preparations (wet mounts) can detect specific types of microorganism, especially parasites, as well as different types of cells that may be important in evaluating infection, e.g. white and red blood cells, bacteria, squamous epithelial cells.

Many stains can be used to detect microorganisms in clinical material. The most important is the Gram stain. By observing the morphological appearance and Gram-staining reaction of bacteria (Table 21.2), their likely identity can be narrowed down to help provisionally identify the cause of infection and select appropriate antibiotic therapy. The Gram stain is quick and easy to perform:

1. Crystal violet, followed by iodine (which acts as a mordant), is applied to the heat-fixed slide and binds to the bacterial cell wall
2. Acetone is then added as a decolorizer, followed by safranin as a counterstain. Gram-positive bacteria, which have a much thicker cell wall, retain the crystal violet stain and appear violet
3. Gram-negative bacteria are decolorized by acetone and take up safranin to appear pink.

Table 21.2 Morphological and Gram stain reactions of medically important bacteria

	Gram-positive	Gram-negative
Cocci	*Streptococcus*	*Neisseria*
	Staphylococcus	
	Enterococcus	
Bacilli	*Listeria*	*E. coli*
	Corynebacterium	*Klebsiella*
	Bacillus	*Enterobacter*
	Clostridium	*Salmonella*
		Pseudomonas
		Haemophilus

The Ziehl–Neelsen (ZN) stain is another important stain in medical microbiology. Heat is used to drive stain (fuchsin) into the waxy cell wall of mycobacteria, which then resists decolorization with acid and alcohol (hence mycobacteria are described as alcohol and acid-fast bacteria). However, both the staining technique itself and the examination of stained preparations are relatively labour-intensive, and the ZN stain has been largely superseded as a screening test by the auramine stain (see ➔ Fluorescence microscopy, p. 204).

Fluorescence microscopy

Here, a fluorescent dye or fluorescence-labelled antibody targeting specific microorganisms is applied to a smear of the sample on a slide. The fluorescent reagent binds to the corresponding microorganisms in the clinical material and can be detected by fluorescence microscopy. Common examples of fluorescence tests are:

- Auramine stain for mycobacteria using a fluorescent dye with an affinity for the waxy cell wall
- Fluorescence-labelled anti-respiratory virus antibodies used to examine NPAs.

Electron microscopy

Viruses are too small to be visible using light microscopy. EM was commonly used to examine for viruses, especially in faeces. However, it has been largely superseded by molecular diagnostic techniques.

Table 21.3 summarizes the value of microscopy in the investigation of infections.

Culture

Culture is the mainstay of laboratory diagnosis of bacterial and fungal infections. Culture readily detects a wide range of different pathogens and provides important additional phenotypic information, including a full range of

Table 21.3 Advantages and disadvantages of microscopy for the diagnosis of infectious diseases

Advantages	Disadvantages
Rapid	Poor sensitivity: microorganisms have to be present in large numbers to be detectable
Additional information, e.g. pus cells, may be obtainable	Gives limited information on the identity of the organisms seen
Inexpensive	May not be able to distinguish between pathogenic and non-pathogenic microorganisms

antimicrobial susceptibilities, that is not readily obtainable with any other diagnostic technique.

Samples are inoculated onto culture media and then incubated (Fig. 21.2). Solid culture media are most widely used; conventional bacteria will grow within 1–2 days. Addition of an initial enrichment culture in the broth can enhance the detection rate of microorganisms present in small numbers. Mycobacteria are much slower-growing than conventional bacteria and may take several weeks to grow.

Once a microorganism has grown, further tests (usually requiring further incubation) are required to determine its identity and antimicrobial susceptibilities. Although most laboratories still rely on traditional culture-based

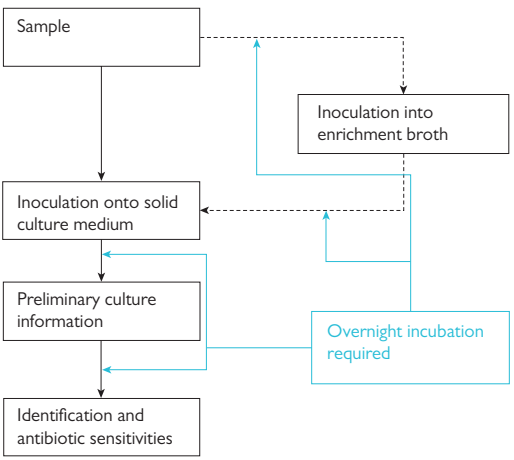

Fig. 21.2 Outline of bacterial and fungal culture.

methods to do this, a range of newer methods that can give faster and/or more accurate results are becoming increasingly used to investigate 1° cultures, e.g.:

- Automated rapid microbial identification and antibiotic susceptibility testing systems (e.g. Vitek2®)
- Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (Maldi-TOF®)
- Real-time PCR, both to identify the causative microorganism and to detect key antibiotic-resistant genes.

Table 21.4 summarizes the value of culture in the investigation of infections.

Table 21.4 Advantages and disadvantages of culture for the diagnosis of infectious diseases

Advantages	Disadvantages
Versatile—a large number of microorganisms can be readily detected, and a wide range of additional phenotypic information is readily available	Variable sensitivity
Excellent specificity (usually regarded as the gold standard test)	Dependent on the target microorganisms remaining viable
Relatively inexpensive	May be difficult to distinguish between pathogenic and non-pathogenic microorganisms
	Takes at least 1 day (and usually longer) to obtain a definitive result

Nucleic acid amplification techniques

These are techniques, such as the PCR, which use primers to anneal to target-specific sequences of the microbial genome, followed by enzymatic amplification of the target sequence and detection of the amplification product. The range of pathogens detectable using these techniques is growing (Table 21.5), but, other than for a few pathogens, they have still to establish themselves as diagnostic techniques.

Table 21.5 Paediatric pathogens for which NAATs tests are widely available

Bacteria and fungi	Viruses
B. pertussis	Influenza viruses
N. meningitidis	Respiratory viruses (including RSV)
S. pneumoniae	Enteroviruses and parechoviruses
GBS	CMV
C. trachomatis	EBV
N. gonorrhoeae	Noroviruses
Aspergillus spp.	Adenoviruses
	HIV 1 and 2
	Hepatitis B, C, and E

Table 21.6 summarizes the value of NAATs in the investigation of infections.

Table 21.6 Advantages and disadvantages of NAATs for the diagnosis of infectious diseases

Advantages	Disadvantages
Potentially rapid results turnaround time (especially with modern real-time assays)	Very expensive
Potentially highly sensitive and specific	Requires expensive hardware
Not dependent on viable organisms	Limited number of organisms can be detected
	Usually provides limited or no additional information about the microorganisms tested

Immunological techniques

Most of these techniques detect either microbial antigens in clinical material or, more commonly, antibodies produced in response to infection. There are many different techniques, and the commonest is enzyme immunoassay (EIA) (Fig. 21.3). Antibody assays can detect total antibody or specific immunoglobulin classes, usually IgG (a marker of infection at some time) and IgM (produced in response to acute infection).

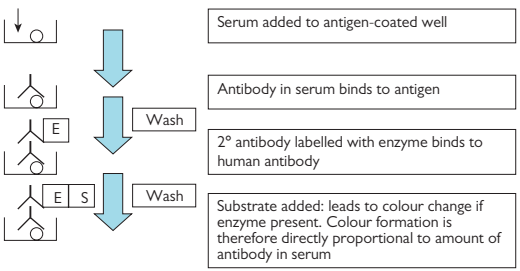

Fig. 21.3 Basic steps in enzyme immunoassay for the detection of antimicrobial antibodies in serum.

Another approach to immunological testing is the use of IGRAs (e.g. QuantiFERON test; T-Spot test) for detecting *M. tuberculosis* infection. These tests detect sensitization to *M. tuberculosis* by measuring IFN-γ release by peripheral blood mononuclear cells in response to antigens representing *M. tuberculosis*.

Table 21.7 summarizes the value of immunological techniques in the investigation of infections.

Table 21.7 Advantages and disadvantages of immunological techniques for the diagnosis of infectious diseases

Advantages	Disadvantages
Inexpensive	Variable accuracy
Technically straightforward	Antibody may not be present (e.g. too early in infection; if patient immunocompromised or had large proportion of blood volume replaced)
Rapid results turnaround time	Limited number of infections can be diagnosed
Not dependent on viable organisms	Provides limited or no additional information about the microorganisms tested

Tests that provide non-specific evidence of infection

Various biochemical tests may be helpful in the initial evaluation and monitoring of the patient with suspected infection.

- CRP is the most widely used acute phase reactant. However, concentrations change relatively slowly and are age-dependent.
- PCT may be a better marker of sepsis. Concentrations change faster that CRP, but the sensitivity and specificity are still relatively low for the prediction of infection.

Interpretation of results

Any laboratory test result must be interpreted in the context of the patient's clinical condition and the accuracy of the test. Additional interpretation is required of microbiological culture results. Relatively few microorganisms are unequivocal pathogens, and the likely significance of positive cultures must be interpreted in the light of the clinical picture. Factors to consider are:

- Whether the microorganism is isolated in abundance
- Whether it is isolated in pure culture
- Whether it is isolated from deep tissues or sites that are normally sterile
- Whether it is isolated on more than one occasion
- Whether it is a microorganism that is a normal commensal
- Whether there is clinical or laboratory evidence of local inflammation
- Whether the presence of the microorganism fits with the clinical picture.

Future research

- More studies are needed to investigate the clinical and cost-effectiveness of newer diagnostic techniques, such as NAATs, to establish how these methods should be used in routine clinical practice.

- Increasingly, multiplex PCR techniques are being used on clinical specimens, with the potential of detecting up to 20 different pathogens, but whether this is helpful clinically is less clear. The importance of dual or triple infections, and the differentiation between colonization and invasive disease, requires considerable further study.
- Development and evaluation of rapid diagnostic tests (RDTs) for infectious diseases.
- The potential role of rapid diagnostics in assisting antibiotic stewardship and optimizing therapy as rapidly as possible to improve outcomes.

What's new?

Increasing automation in laboratories is allowing more rapid and more accurate identification and antimicrobial susceptibility testing of bacteria. This is timely and an important development that can assist in the fight against antimicrobial resistance.

New technologies, especially NAATs, have become widely available in formats that allow 'on-demand' testing. This means that batching of samples and/or sending them to reference laboratories for testing is no longer required; thus, the rapid results turnaround times that these test offer can be fully exploited. Also, a broader range of pathogens (including the ones of paediatric relevance such as RSV and *B. pertussis*) can now be detected using commercially available systems. As a result, NAATs have moved from the domain of specialist reference laboratories to become an important part of the repertoire of most diagnostic microbiology laboratories.

Greater miniaturization and automation of NAATs are making their use as point-of-care tests feasible.

What's next?

Next-generation whole-genome sequencing (WGS) is becoming faster, more available, and more affordable, offering an exciting future for diagnostic and public health microbiology. Initially, it is likely that these techniques will be used mainly for epidemiological purposes (surveillance and outbreak investigation). However, in time, it is possible that WGS will become used as a routine diagnostic tool. Potential benefits include the possibility of predicting the biological impact of an infection in a patient by correlation with the presence of specific microbial virulence genes and the rapid detection of antibiotic resistance genes.

Further reading

Baron EJ, Miller JM, Weinstein MP, *et al*. A guide to utilization of the microbiology laboratory for diagnosis of infectious diseases: 2013 recommendations by the Infectious Diseases Society of America (IDSA) and the American Society for Microbiology (ASM)(a). *Clin Infect Dis* 2013;**57**:e22–121.

Engelkirk PG, Duben Engel-Kirk JL. *Laboratory diagnosis of infectious diseases: essentials of diagnostic microbiology*. Baltimore: Wolters Kluwer Health, 2008.

Köser CU, Ellington MJ, Cartwright EJP, *et al*. Routine use of microbial whole genome sequencing in diagnostic and public health microbiology. *PLoS Pathog* 2012;**8**:e1002824.

Chapter 22

Lower respiratory tract infection

See also Chapters 46, 58, 69, 70, 79, 80, 85, 89, 93, 94, 95, 98, 104, 105, 112.

Epidemiology

- The respiratory tract is the commonest site of childhood infections, and acute respiratory infections make up 50% of all illnesses in children aged <5 years.
- Most involve only the upper respiratory tract, but about 5% will involve the larynx and lower respiratory tract.
- LRTI is commonest in the first year of life.
- During the first decade, LRTIs occur more commonly in boys.
- Hospitalization rates vary considerably, but it is estimated that one in 20 will be hospitalized due to respiratory infection in the first 4 years of life.
- LRTIs show marked and unexplained seasonal variation, being commonest in the coldest months. This is particularly striking for the annual winter–spring epidemics of bronchiolitis and pneumonia due to RSV in infants.

Pathogenesis

- LRTIs develop by two routes: direct respiratory droplet transmission or indirect spread from the bloodstream.
- Most organisms (respiratory viruses, *M. pneumoniae, B. pertussis*, and *C. trachomatis*) produce infection by initial involvement of the airway epithelium, with progression into the parenchyma. The infection typically starts in the upper respiratory tract and then spreads to the lower.
- Bacteria and certain viruses—EBV, CMV, and VZV—spread from the bloodstream into the parenchyma and airways.
- The development and localization of disease in the lower respiratory tract depends on a complex interaction between the organism, the host, and environmental factors (Table 22.1).
- While respiratory viral infections can involve >1 part of the respiratory tract, inflammation usually predominates at a single site.
- Certain organisms have affinities for particular parts of the respiratory tract, e.g. RSV for peripheral airways, for reasons that are not well understood.

Table 22.1 Risk factors for lower respiratory tract infections in children

Host factors	Environmental factors
Age	Passive and active smoking
Sex	Exposure to infection via: • Siblings • Domestic overcrowding • Day care
Low birthweight	
Neonatal lung injury	
Congenital malformation	
Bottle-feeding	Low socio-economic status
Obesity	Air pollution

Organisms

- The spectrum of organisms that cause LRTIs is wide (Table 22.2) and varies with age.
- In the newborn, pneumonia is usually due to organisms acquired from the mother's genital tract before or during delivery, e.g. GBS, Gram-negative bacteria, *L. monocytogenes, C. trachomatis, Mycoplasma hominis*, and *Ureaplasma urealyticum*, CMV, and HSV.
- After the first month of life, the vast majority of respiratory infections are due to viruses (RSV, parainfluenza, influenza, human metapneumovirus, coronavirus, bocavirus, adenovirus, rhinovirus), *Chlamydophila pneumoniae, M. pneumoniae*, and *S. pneumoniae*. *Mycoplasma* infection rarely occurs <3 months of age and is most frequent in schoolchildren.
- *S. pneumoniae* is the commonest bacterial cause of childhood pneumonia. Other causes of bacterial pneumonia, e.g. *S. aureus*, are uncommon in normal children.
- Bacterial superinfection during respiratory viral or mycoplasmal infections can occur also in normal children. There are some well-recognized associations between viruses and 2° bacterial infection (e.g. influenza and staphylococcal pneumonia) which, if they occur, are often serious, e.g. with measles and adenovirus.
- Usually the specific aetiology of an LRTI cannot be clinically determined. Developments in medical microbial diagnostic technology, such as nucleic acid technology and PCR, are increasing the proportion of respiratory infections that can be identified definitively. It may be difficult to tell if an organism detected from an upper respiratory tract specimen is being carried or is the cause of the LRTI. PCR is now detecting dual or triple infections, increasing the complexity of the diagnosis.

Table 22.2 Relative frequency of organisms causing community-acquired pneumonia in otherwise healthy children

Most frequent	Occasional	Rare
Neonates (<1 month)		
GBS	*H. influenzae*	*Mycobacterium* spp.
E. coli	*S. pneumoniae*	*Chlamydia* spp.
Respiratory viruses	GAS	*L. monocytogenes*
Enteroviruses	*S. aureus*	VZV
		CMV
		HSV
Young infants (1–3 months)		
Febrile		
Respiratory viruses	GBS	VZV
Enteroviruses	GAS	CMV
S. pneumoniae	*H. influenzae*	Mycobacteria
	B. pertussis	Gram-negative enteric
	CMV	bacilli
	U. urealyticum	
Afebrile		
Chlamydia	CMV	
Mycobacteria	*U. urealyticum*	
Infants and young children (3 months–5 years)		
S. pneumoniae	*B. pertussis*	*Moraxella catarrhalis*
Respiratory viruses	*S. aureus*	
	GAS	
	H. influenzae	
	Mycoplasma spp.	
	Mycobacteria	
Older children (>5 years) and adolescents		
M. pneumoniae	*C. pneumoniae*	*S. aureus*
S. pneumoniae	Mycobacteria	
Respiratory viruses		

Clinical presentation

- The clinical features of LRTIs can include cough with tachypnoea, chest indrawing, wheeze, and stridor. There are well-defined clinical syndromes (Table 22.3), and these clinical patterns are helpful in narrowing the range of likely infectious agents.
- In infants, clinical features of pneumonia are often non-specific and include fever (>38.5°C), refusal to feed, and vomiting.
- The absence of tachypnoea makes pneumonia very unlikely.
- The respiratory rate is best measured by observing the chest wall over 1min.
- Cut-offs for diagnosing tachypnoea are: >60/min in infants <2 months; >50/min for 2–12 months old; and >40/min for >12 months.

Bronchial breathing and reduced breath sounds are specific, but insensitive, indicators of pneumonia, particularly in infants where auscultation is relatively unreliable.

Table 22.3 LRTI syndromes (infection at or below the larynx) and their clinical features

Syndrome	Presenting symptoms and signs
Croup	Hoarseness, cough, inspiratory stridor with laryngeal obstruction
Tracheobronchitis	Cough and ronchi; no laryngeal obstruction or wheezing
Bronchiolitis	Expiratory wheezing with or without tachypnoea, air trapping and indrawing, end-expiratory crepitations
Pneumonia	Crackles or evidence of pulmonary consolidation on physical examination or CXR. Bronchial breathing

Severity assessment

- For children with pneumonia, the severity can range from mild to life-threatening (Table 22.4).

Indications for admission to hospital

- Hypoxaemia is the key indication for hospital admission.

Indicators for admission to hospital in infants

- Oxygen saturation (SaO_2) <92%, cyanosis.
- Respiratory rate >70 breaths/min.
- Difficulty in breathing.
- Intermittent apnoea, grunting.
- Not feeding (taking less than two-thirds of normal feeds).
- Family not able to provide appropriate observation or supervision.

Table 22.4 Severity assessment

Syndrome	Mild	Severe
Infants	Temperature <38.5°C	Temperature >38.5°C
	RR <60 breaths/min	RR >60 breaths/min
	Mild recession	Moderate to severe recession
	Taking full feeds	Nasal flaring
		Cyanosis
		Intermittent apnoea
		Grunting respiration
		Not feeding
Older children	Temperature <38.5°C	Temperature >38.5°C
	RR <50 breaths/min	RR >50 breaths/min
	Mild breathlessness	Severe difficulty in breathing
	No vomiting	Nasal flaring
		Cyanosis
		Grunting respiration
		Signs of dehydration

RR, respiratory rate.

Indicators for admission to hospital in older children

- SaO_2 <92%, cyanosis.
- Respiratory rate >50 breaths/min.
- Difficulty in breathing.
- Grunting.
- Signs of dehydration.
- Family not able to provide appropriate observation or supervision.

Indications for transfer to intensive care unit

Transfer to intensive care should be considered if the following features are present:

- The patient is failing to maintain an SaO_2 of >92% in fraction of inspired oxygen (FiO_2) of >60%
- The patient is shocked
- There is a rising respiratory rate and rising pulse rate with clinical evidence of severe respiratory distress and exhaustion, with or without a raised arterial carbon dioxide tension ($PaCO_2$)
- There is recurrent apnoea or slow irregular breathing.

Diagnosis

- The gold standard for the microbial diagnosis of pneumonia is a needle aspiration obtained from the lower respiratory tract or bronchoalveolar lavage (BAL). These are very rarely performed for obvious reasons.
- In clinical practice, chest radiographs provide a pragmatic alternative. They are indicated in children with fever and clinical signs of respiratory distress.
- In children with immunodeficiency or cardiorespiratory disease, the signs of an LRTI may be less obvious, and a high index of suspicion is required.
- CXR changes in pneumonia do not distinguish between bacterial and non-bacterial causes.
- CXR findings may also be absent in early bacterial pneumonia. Lobar or segmental consolidation is characteristic of bacterial pneumonia, but bronchopneumonia and interstitial infiltrates can occur in bacterial pneumonia, as can alveolar infiltrates in viral pneumonia. An exception is a large pleural effusion where a bacterial origin is most likely. TB should be considered if hilar lymphadenopathy and pleural effusions are seen, especially in older children.
- NPAs provide excellent material for microbial diagnosis for organisms entering via the respiratory tracts, particularly viruses.
- Rapid, sensitive, and specific immunofluorescence tests are available for many respiratory viruses, most notably RSV, parainfluenza, and influenza virus.
- Newer molecular testing using PCR offers greater sensitivity and is increasingly replacing immunofluorescence and serology.
- There may be polymorphonuclear leucocytosis. CRP is often raised in bacterial infections.
- Cold agglutinins frequently occur in *M. pneumoniae* infections, especially with more severe pulmonary involvement.
- Culture of nasopharyngeal swabs is an unreliable alternative, because colonization with *S. pneumoniae* and *H. influenzae* occurs, particularly in preschool children.
- PCR assays on blood and respiratory secretions are increasingly used in clinical practice.
- In the severely ill or immunocompromised child, more invasive procedures, such as bronchoscopy with BAL or lung biopsy, may be essential to guide therapy.

Special problems

Immunocompromised children

- The lung is the common site of serious infection in immunocompromised children.
- They are prone to infection, particularly when the absolute neutrophil count (ANC) falls to $<500/mm^3$.

- The risk increases with both the severity and duration of neutropenia. Neutropenia for longer than 2 weeks is associated with a high incidence of nosocomial bacterial and/or fungal infections.
- Prompt, accurate diagnosis of an LRTI is crucial, but often difficult in ill, immunocompromised children because of lack of specificity of the clinical signs and the wide range of organisms encountered.
- BAL provides a safe and accurate method of diagnosis and may provide a specific diagnosis in 50–70% of cases.

Treatment

- Respiratory viruses, *M. pneumoniae*, and *C. pneumoniae* cause most of the cases of LRTIs.
- Treatment of RSV infection is mainly supportive.
- Antibiotics should be prescribed in pneumonia because of the difficulty of differentiating bacterial from viral infections, particularly in very young or very sick children. The child's age and likely pathogen can help to determine the initial choice of antibiotic. Antibiotics are not required in infants with classic RSV bronchiolitis.
- Because of the emergence of resistant strains, such as penicillin-resistant pneumococci, it is important that this choice is informed by knowledge of local microbial sensitivities.
- Less severe cases of pneumonia can be managed at home.
- Antibiotics administered orally are safe and effective for children presenting with pneumonia.
- For children <5 years of age, oral amoxicillin is the first choice antibiotic, because it is effective against the majority of causative bacterial organisms. A standard course of 5 days is likely to be adequate in most cases.
- There is limited evidence for the use of macrolide antibiotics for those >5 years of age when *M. pneumoniae* is more prevalent. Macrolides should be used if either *Mycoplasma* or *C. pneumoniae* is suspected.
- In severe cases requiring hospitalization, IV antibiotics should be used if the child is unable to absorb/tolerate oral antibiotics or has severe respiratory distress and clinical findings. Oral treatment should be considered as soon as there is clear clinical improvement.
- IV antibiotics used in Europe for severe pneumonia include penicillin/amoxicillin, co-amoxiclav, cefuroxime, and cefotaxime/ceftriaxone. Consider staphylococcal pneumonia in an ill child with lung abscesses and/or an empyema. Lung abscesses can also be caused acutely by Gram-negative bacteria (*Pseudomonas* and *Klebsiella*), or anaerobes if following an aspiration.
- Pleural (parapneumonic) effusions can be caused by a transudate (pleural:serum protein ratio <0.5) due to non-infectious causes (heart failure/cirrhosis/hypoproteinaemia, etc.) or an exudate (pleural:serum protein ratio >0.5) due to infective or other causes (malignancy/chylothorax/surgical/autoimmune disease/intra-abdominal pathology). The commonest acute infectious causes of a pleural effusion are *Pneumococcus, S. aureus*, Hib, and GAS infection. Always consider TB, especially in a non-toxic older child.

Supportive care and hospitalization

- Most children with LRTIs are managed in the community. Supportive care and antibiotics, where indicated, will be all that is required.
- About 10% will be admitted to hospital. In young children especially, this is usually needed because of respiratory distress, severe systemic features, or difficulty feeding. In these more serious cases, a number of specific points should be considered as follows.

Maintain an adequate airway and ensure oxygenation

- Hypoxaemia is common. Excessive handling aggravates this and should be avoided.
- The development of non-invasive monitoring has allowed SaO_2 to be monitored routinely. Low-flow oxygen, administered via nasal cannulae or a head box, will often be sufficient to maintain the SaO_2 in the normal range (above 92%).
- About 1–2% of infants with severe bronchiolitis will develop respiratory failure and need mechanical ventilation.

Maintain hydration and nutrition

- Children with severe LRTIs often have difficulty with feeding. Nasogastric feeding or IV fluids may be necessary to maintain nutrition and avoid dehydration.
- Children with pneumonia and bronchiolitis can develop excessive ADH secretion, so mild fluid restriction is usually advisable.

Clear nasal secretions, and encourage sputum clearance

- Gentle clearance of nasal secretions may increase comfort and aid feeding in infants.
- There is no evidence that chest physiotherapy is helpful in children with bronchiolitis or pneumonia, but it may have an important role in children with impaired sputum clearance.

Treat/drain pleural effusion

- Pleural effusion with pneumonia is most commonly caused by pneumococcal disease. In a toxic, ill child, consider staphylococcal pneumonia, and add an anti-staphylococcal agent, e.g. flucloxacillin.
- Three stages of empyema have been defined.
  - Stage 1: 'exudative'—fluid within the pleural space, but no loculations present
  - Stage 2: 'fibropurulent'—the fluid becomes loculated due to the presence of fibrin
  - Stage 3: 'organizational'—there are multiple loculations and a thickened pleural layer
  - Empyema has not been clearly defined but denotes a complex parapneumonic effusion. Always think: *could this be TB?*
- When present, it may be useful to aspirate fluid for diagnostic purposes. Therapeutic aspiration may only be necessary if breathing is compromised or if the clinical response to antibiotics is poor.
- Pre-drainage localization of the fluid and selection of the optimal drainage spot using ultrasound scan is useful. Adequate sedation and analgesia are necessary for safe and painless drainage, especially in infants and young children.

- The optimal management remains controversial, with both aggressive and conservative approaches being taken across Europe. Options include conservative management with IV antibiotics only, insertion of a percutaneous chest drain (with or without a fibrinolytic), and video-assisted thoracoscopy (VATS) or decortication in very severe disease. There have been no good large RCTs comparing the length of stay, cost benefit, and long-term outcomes. Empyema rates are falling in Europe, following the introduction of the conjugate pneumococcal vaccine.
- Instillation of urokinase has been shown to reduce the length of hospital stay and is used sometimes for complicated parapneumonic effusions and empyema.
- Surgery should be considered in the presence of persisting clinical and radiological signs and symptoms. The type of surgery depends, in part, on the expertise available locally and the severity and stage of the empyema.
- Outcome of effusions is usually very good in children, irrespective of the treatment modality, as long as a good course of appropriate antibiotics is given.

Follow-up

- For children with pneumonia, careful clinical follow-up to check that the child is better and that signs have resolved is all that is necessary in uncomplicated cases.
- Further CXRs do not appear necessary if clinical resolution is occurring.
- In any child with an unusual, persistent, or recurrent pneumonia, an underlying disorder, such as immune deficiency, cystic fibrosis, or a congenital lung disorder should be excluded.

Outcome

- In developed countries, most LRTIs will resolve satisfactorily with appropriate treatment. However, LRTIs remain an important cause of childhood death.
- Pneumonia kills more children worldwide than any other childhood illness.
- A few LRTIs, particularly with specific serotypes of adenovirus (e.g. 7), can cause lasting damage to the lung—bronchiolitis obliterans.
- A year after recovery from pneumonia, it has been found that children still have residual lung scan defects.
- Children with past respiratory illnesses show evidence of airways obstruction and lung function deficit in later childhood, and young adults with a history of LRTI in the first 2 years of life have an increased incidence of chronic cough.
- It is not yet clear whether low lung function predisposes to, or is a consequence of, LRTIs.

Prevention

- The prevention and improved therapy of LRTIs in early infancy may be vital for later pulmonary health.
- Social and environmental determinants of LRTIs, especially parental smoking, should be avoided. Breastfeeding and the high uptake of childhood immunizations should be encouraged.
- Measles, pertussis, pneumococcal, and influenza vaccinations reduce the impact of paediatric LRTIs.
- Hospital admissions due to pneumonia have fallen significantly in the UK since the introduction of the conjugate pneumococcal vaccines PCV7 and PCV13.
- Immunoprophylaxis, such as with high-titre RSV immunoglobulin or monoclonal antibodies, may have a role in preventing LRTIs in high-risk infants and children, in the absence of an appropriate vaccine.
- One simple measure that would have a substantial impact would be a reduction in parental smoking. Parents of children admitted with an LRTI should be advised to stop smoking.

Future research

- More research is required in the aetiology of LRTI and the reasons for its complications, the better definition of first- and second-line antibiotic therapies (including the doses and duration of parenteral and oral antibiotic treatment), the role of antiviral treatment, and how to follow up patients with LRTIs.
- Further efforts are needed to increase vaccination coverage with the already available vaccines against respiratory pathogens and to conduct prospective studies of their impact, including an evaluation of their cost-effectiveness.
- High-priority vaccines for pneumonia prevention (i.e. protein-based pneumococcal vaccine and *S. aureus* vaccine) represent a priority.

Further reading

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Chapter 23

Neonatal infections

See also Chapters 10, 64, 68, 69, 75, 76, 82, 98, 100, 104, 105, 106, 107.

Introduction

- Infections are a frequent and important cause of morbidity and mortality in the neonatal period.
- One to 2% of fetuses are infected *in utero*.
- The incidence of neonatal infections varies significantly; in the UK, the incidence of culture-proven BSIs is around 8/1000 live births and 70/1000 neonatal admissions. Yet, up to 40% of babies <1000g will have one or more infections during their stay in hospital.
- The timing of exposure, inoculum size, immune status, and virulence of the infectious agent influence the manifestations of disease in a fetus or newborn infant.
- A wide variety of pathogens can affect the newborn, including bacteria, viruses, fungi, and protozoa.
- With advances in neonatal intensive care, increasingly immature, very-low-birthweight (VLBW) newborns are surviving, remaining in hospital for long periods of time where they are at risk for hospital-acquired infections.

Causative organisms

- Infections acquired *in utero* can be viruses (rubella virus, CMV, parvovirus B19, HBV, HCV, HIV, VZV), bacteria (*L. monocytogenes, T. pallidum, M. tuberculosis*), or protozoa (*T. gondii*, malaria).
- Intrapartum infections are often due to bacteria: GBS, Gram-negative bacilli (*E. coli, Serratia* spp., *Enterobacter* spp., *Citrobacter* spp., *Pseudomonas* spp., *Salmonella* spp.), gonococci, *C. trachomatis*, and viruses (HIV, HSV, HBV, HCV).
- Post-partum infections are mainly due to CoNS, *S. aureus, S. pneumoniae*, and Gram-negative bacilli (*E. coli, K. pneumoniae, Salmonella, Enterobacter, Citrobacter, P. aeruginosa, Serratia*), enterococci, and GBS. Viruses play a minor role, even though CMV, RSV, influenza virus, parainfluenza virus, adenovirus, and rotavirus can cause outbreaks of nosocomial infections. Fungi (mainly *Candida*) are responsible for a significant number of systemic infections in children admitted to NICUs.

Epidemiology

- Neonatal infections can be divided by age of onset of symptoms (early-onset if in the first 48–72 hours of life, late-onset if after 48–72 hours of life). Late-onset infection may be community- or hospital-acquired.
- Neonates may be infected at different times via three different routes: *in utero* (transplacental), intrapartum (ascending), and post-partum (nosocomial or community).
- Transplacental infections are the result of a clinical or subclinical maternal infection.
- Intrapartum infections cause mainly early-onset infections.
- Perinatal infections are acquired just before or during delivery, with vertical transmission from mother to neonate.
- Post-natal infections are transmitted by direct contact from various human sources, such as the mother, family contacts, and hospital personnel, breast milk (HIV, CMV), or inanimate sources such as contaminated equipment.
- Several factors influence the incidence of neonatal infections, such as sexual practices, the mode of delivery, gestational age, birthweight, maternal age, maternal immunization status, and the presence of maternal infections such as chorioamnionitis. Moreover, environmental factors can influence the incidence of infection, e.g. the prevalence of organisms in the community, the place of birth and neonatal stay (home or hospital), socio-economic status, and ethnicity. Finally, invasive procedures, the presence of indwelling vascular catheters, ventricular shunts, and endotracheal tubes, and alterations in the skin and mucous membrane barriers may favour infections.
- Previous use of antibiotics increases the likelihood of infections caused by more resistant bacteria and fungi.
- Congenital infections: in industrialized countries, CMV is the most frequent congenital infection, with an incidence of about 0.5/1000 live births. *Toxoplasmosis* seroprevalence varies among European countries, from about 10–15% in the UK to 30–50% in Southern Europe, but it is decreasing over time. Vertical transmission is preventable with good food hygiene, exclusion of raw meat from the diet during pregnancy, and avoiding the handling of cat litter. Vaccine-preventable diseases, such as congenital rubella and hepatitis B, are now rare in most of Europe, as are perinatal HIV and syphilis infections, due to effective prevention programmes. In developing countries, the epidemiology of congenital infections is different and depends on vaccination coverage and uptake of prevention of mother-to-child transmission programmes for diseases such as HIV and syphilis.
- In industrialized countries, the incidence of neonatal bacterial sepsis is between 1 and 4/1000 live births, and that of meningitis between 0.2 and 0.4/1000 live births. In premature infants, especially if admitted to the NICU, these values can be 10-fold higher. These incidences are significantly increased in resource-poor countries.

Clinical presentation and differential diagnosis

Congenital infections

- Infections acquired *in utero* may result in spontaneous abortion, stillbirth, congenital malformations, IUGR, premature birth, acute disease in the neonatal period, or asymptomatic infection with or without neurological sequelae later in life.
- First-trimester infections may alter embryogenesis, with resulting congenital malformations.
- Late-gestational infections may lead to a delay in clinical manifestations until some time after birth (e.g. syphilis).

Neonatal infections

- The initial signs of sepsis are often non-specific. It is very important to re-evaluate infants over time to determine whether the symptoms have progressed. The commonest are:
  - General—temperature instability, hypothermia
  - GI—abdominal distension, vomiting, diarrhoea, hepatomegaly, feeding intolerance, or poor feeding
  - Respiratory—apnoea, dyspnoea, tachypnoea, retraction, flaring, grunting, or cyanosis
  - Renal—oliguria
  - Cardiovascular—tachycardia, hypotension, bradycardia, pallor, mottling, cold peripheries, prolonged capillary refilling time
  - CNS—irritability, lethargy, tremors, seizures, hyporeflexia, hypotonia, irregular respirations, full fontanelle, or high-pitched cry
  - Haematological—jaundice, splenomegaly, petechiae, purpura, or bleeding.
- Specific clinical findings and presentations:
  - *Temperature instability*: only 50% of infected neonates have a fever (axillary temperature >37.8°C), and the presence of fever is not always due to infection (e.g. it may be due to dehydration, overheating). A single temperature elevation is infrequently associated with infection; fever sustained over 1 hour is more likely to be due to infection. Hypothermia or temperature instability can occur, rather than fever, particularly in the preterm infant
  - *Rash*: cutaneous manifestations of infection include impetigo, cellulitis, mastitis, omphalitis, and subcutaneous abscesses. Ecthyma gangrenosum is highly suggestive of *Pseudomonas* infection. A vesicular rash is characteristic of HSV infection. Dermal erythropoiesis (purple papulonodular lesions referred to as 'blueberry muffin'; see Chapter 11, p. 106–7) can be associated with CMV, rubella, or parvovirus infection, as well as congenital neoplastic disease and Rh haemolytic disease
  - *Omphalitis*: infection of the umbilical cord is usually caused by bacteria from the maternal genital tract or the environment. Early manifestations include erythema or serous or purulent discharge; cellulitis can be progressive; complications include necrotizing fasciitis

and spread of infection via the umbilical or portal vessels to cause bacteraemia and sepsis
- *Pneumonia*: early signs and symptoms are frequently non-specific (such as poor feeding, irritability, lethargy, cyanosis, temperature instability, increased oxygen requirement). Tachypnoea, retractions, and nasal flaring may be observed. As the degree of respiratory compromise increases, progressive respiratory failure may develop. GBS, a common bacterial cause of pneumonia, can lead to fulminant infection, whereas atypical bacteria, in particular *Chlamydia*, are associated with an indolent course
- *Sepsis*: despite its multisystem involvement, sepsis can initially manifest with signs affecting only one organ system (e.g. tachypnoea with recession). Late manifestations include signs of respiratory failure as a result of acute respiratory distress syndrome (ARDS), pulmonary hypertension, cardiac failure, shock, renal failure, hepatocellular disease with hyperbilirubinaemia and elevated enzymes, cerebral oedema or thrombosis, adrenal haemorrhage and/or insufficiency, bone marrow dysfunction (neutropenia, thrombocytopenia, anaemia), and DIC
- *Meningitis*: signs of meningitis in babies, especially the premature, may be very difficult to detect. Characteristic features found in older infants may not occur, and non-specific signs of illness are common (see earlier); therefore, neonates with signs suggestive of infection should have an LP to establish whether meningitis is present as soon as possible.

Investigations

Evaluation of a neonate with a suspected infection or sepsis should include the following:
- Detailed pregnancy and delivery history to identify specific risk factors:
  - Maternal infections during pregnancy or at delivery (type and duration of antimicrobial therapy, UTI, chorioamnionitis, STIs)
  - History of GBS infection in current pregnancy or in previous babies
  - Maternal colonization with GBS (screening may be universal or for selected high-risk groups, depending on national policy)
  - History of previous sexually transmitted infections (gonorrhoea, syphilis, *Chlamydia*, herpes, HIV)
  - Multiple birth
  - Duration of membrane rupture
  - Fever during labour
  - Fetal tachycardia
  - Complicated delivery and medical interventions (Caesarean section, ventouse delivery, scalp electrodes)
  - Gestational age/birthweight
  - Age at onset of infection (*in utero*, birth—early or late)
- Identification of underlying conditions that can favour sepsis:
  - Congenital malformations (e.g. neural tube malformations)
  - Necrotizing enterocolitis

- Vascular access, endotracheal intubation, parenteral nutrition
- Recent surgery

- Detailed physical examination:
  - Abnormal vital signs (in relation to age)
  - General appearance, neurological status
  - Feeding, stools, urine output
  - All organ systems should be examined, including the skin and skeletal systems; the liver and spleen size should be noted
  - A particular note should be made of movement and deformity of the extremities
- Laboratory studies:
  - Culture from normally sterile sites such as blood, CSF, urine; demonstration of an organism in tissue or fluid; antigen detection in urine and CSF; maternal and/or neonatal serology for syphilis, toxoplasmosis, CMV, rubella, HIV, HBV, HCV
  - Inflammation (leucocytosis, leucopenia, increased immature/total neutrophil count ratio, neutropenia, acute phase reactants such as CRP and PCT, pleocytosis in CSF or synovial or pleural fluid, fibrin split products for DIC; histological, e.g. placenta)
  - Multi-organ system involvement (pH and pCO_2 for metabolic acidosis; PO_2 and PCO_2 for pulmonary function; blood urea nitrogen and creatinine for renal function; bilirubin, alanine aminotransferase (ALT), AST, ammonia, prothrombin time (PT), partial thromboplastin time (PTT) for hepatic function; neutropenia, anaemia, thrombocytopenia for bone marrow function)
  - In neonates, particularly the preterm, inflammatory markers, such as CRP, might be normal or only moderately elevated.

Treatment

- Treatment is determined by the pattern of disease and the organisms that are common for the age of the infant and the local flora of the nursery.
- Once bacterial infection is suspected and appropriate cultures have been obtained, IV antibiotic therapy must be instituted immediately.
- Narrow-spectrum antibiotics should be used, wherever possible, to reduce the pressure on antimicrobial resistance. Broad-spectrum cephalosporins should be avoided, if possible, on neonatal units. Empiric use of cephalosporins also does not cover infections due to *Listeria*.
- Initial empiric treatment of early-onset bacterial infections is based on penicillin or ampicillin and an aminoglycoside (often gentamicin).
- Initial empiric treatment of late-onset bacterial infections is based on ampicillin or flucloxacillin and an aminoglycoside, usually gentamicin, but the combination chosen should be based on knowledge of local antibiotic resistance patterns.
- Flucloxacillin may be substituted with vancomycin if meticillin (INN)-resistant staphylococci are known to be endemic. Otherwise, in order to avoid the emergence of vancomycin resistance, vancomycin should be limited to ill neonates with an indwelling intravascular catheter, and therapy should be discontinued as soon as possible in the case of negative blood cultures.

- Piperacillin, ticarcillin, carbenicillin, or ceftazidime and an aminoglycoside should be administered when necrotic skin lesions suggest the presence of *P. aeruginosa*.
- Empiric antifungal therapy should be considered in VLBW infants who have had previous antibiotic therapy, have mucosal colonization with *Candida albicans*, and who are at high risk for invasive fungal disease (especially those with GI disease, e.g. necrotizing enterocolitis).
- A third-generation cephalosporin, together with ampicillin or penicillin and an aminoglycoside, should be initiated for presumed bacterial meningitis; alternatives include meropenem where local resistance patterns dictate this.
- Once the pathogen has been identified and the antibiotic sensitivities determined, the most appropriate narrow-spectrum drug(s) should be selected.
- The rational use of antibiotics in neonates involves using narrow-spectrum drugs, whenever possible, treating infection, and not colonization, and limiting the duration of therapy. Antibiotic stewardship programmes should be encouraged and may help in achieving optimal antimicrobial use in neonatal units.
- Therapy for most BSIs should be administered for around 7 days or for 5 days after the clinical response. In the case of meningitis, 14–21 days of therapy after negative cultures is recommended (depending on pathogen).
- Cultures taken 24–48 hours after initiation of therapy should yield negative results. If the culture results remain positive, a change in antibiotics (dose or type), further investigations (e.g. seeking a collection), and/or removal of an existing catheter may be indicated.
- HSV encephalitis requires specific antiviral treatment with high-dose aciclovir for at least 21 days, followed by oral prophylaxis for 6 months. Congenital CMV and toxoplasmosis require specific treatment (see respective chapters).
- Supportive therapy includes correction of hypovolaemia, hyponatraemia, hypocalcaemia, and hypoglycaemia.
- Fluids should be limited if inappropriate secretion of ADH is diagnosed.
- Inotropic agents, fluid resuscitation, and mechanical ventilation can be useful to manage shock, hypoxia, and metabolic acidosis.
- Adequate oxygenation of tissue should be maintained, potentially requiring mechanical support.
- Refractory hypoxia may require ECMO.
- Hyperbilirubinaemia should be monitored and treated aggressively with phototherapy and/or exchange transfusion (the risk of kernicterus increases in sepsis or meningitis).
- DIC is usually treated by management of the 1° infection. However, if bleeding occurs, fresh frozen plasma, platelet transfusion, or whole blood should be considered.
- The effect of G-CSF or granulocyte macrophage colony-stimulating factor (GM-CSF) on sepsis-related mortality is unclear, but the PROGRAMS trial showed no benefits of prophylaxis with GM-CSF in very preterm, growth-retarded babies.
- The INIS trial showed no impact of the use of IVIG on mortality due to neonatal sepsis.

Follow-up and outcome

- Congenital infections: infections acquired *in utero* may cause late sequelae, even if the infant is asymptomatic at birth. These adverse outcomes include SNHL, visual disturbances (including blindness), seizures, and neurodevelopmental abnormalities.
- Some of these infections need specific treatment and close follow-up (see Chapter 61 and Chapter 120).
- Complications of bacteraemic infections include endocarditis, septic emboli, abscess formation, septic joints with residual disability, OM, and bone destruction. Candidaemia may lead to vasculitis, endocarditis, endophthalmitis, and abscesses in the kidneys, liver, lungs, and brain. Sequelae of sepsis may result from septic shock, DIC, or organ failure.
- Reported mortality rates in neonatal sepsis vary from 2% to 35% and depend on the definition of sepsis as well as the proportion of VLBW babies in the study population. The sepsis case fatality rate is highest for Gram-negative and fungal infections.
- The case fatality rate for neonatal bacterial meningitis is between 10% and 35%. Many of these cases have associated sepsis. Risk factors for death or disability include the duration of seizures for >72 hours, coma, inotropic support, and leucopenia. Immediate complications of meningitis include ventriculitis, cerebritis, and brain abscess. Late complications of meningitis occur in 40–50% of survivors and include hearing loss, abnormal behaviour, developmental delay, cerebral palsy, focal motor disability, seizure disorders, and hydrocephalus. A number of these sequelae may also be encountered in infants with sepsis, but without meningitis, as a result of cerebritis or septic shock.

Prevention

- Several intrauterine infections are preventable by immunization (including hepatitis B, polio, rubella, tetanus, varicella).
- Early-onset GBS infections can be prevented by the administration of antibiotics during labour. Either a risk-based or universal screening strategy may be used to identify mothers at highest risk.
- Toxoplasmosis is preventable with appropriate diet and avoidance of exposure to cat faeces.
- Congenital syphilis is preventable by timely diagnosis and appropriate early treatment of infected pregnant women.
- Neonatal infection with *C. trachomatis* can be prevented by identification and treatment of infected pregnant women.
- Mother-to-child transmission of HIV is significantly reduced by maternal ART during pregnancy, labour, and delivery, and PEP of the infant after birth.
- Attention to hygiene in the nursery and in the NICU (including handwashing, avoidance of overcrowding, special isolation precautions, meticulous neonatal skin care, decreasing the number of venepunctures and heelsticks, minimizing the risk of catheter contamination, reducing the duration of catheter and mechanical ventilation days, promoting

oral feeding, reducing the duration of parenteral nutrition, and providing education and feedback to nursery personnel) is the basis for a reduction of nosocomial infection.
- The implementation of routine BSI surveillance, combined with enhanced education and infection control procedures, such as the 'Matching Michigan' scheme, have proven successful in reducing line infections.
- Active monitoring of the pathogens causing infections in the nursery and NICU (surveillance), with timely change of antibiotic guidelines, if required, is essential.
- Use of narrow-spectrum antibiotic for the shortest necessary period is essential.
- The importance of routine screening for colonization of babies with multiresistant organisms in order to reduce outbreaks is uncertain and requires active study.
- Prophylactic use of antifungals in VLBW infants reduces the risk of systemic fungal infections and is advocated in countries or units with a high prevalence of IFIs.
- Oral bovine lactoferrin supplementation is promising in reducing neonatal hospital-acquired infections, but results from further studies are awaited.

Future research

- More studies are required to define key interventions for reducing the incidence and improving the outcome of neonatal sepsis and meningitis.
- Further research on off-label anti-infective drugs for neonates is urgently warranted for the treatment of complicated neonatal infections.
- Development of European surveillance of neonatal infections and harmonized guidelines for the rational use of antibiotics are required for optimizing treatment, while minimizing overuse of broad-spectrum agents.

What's new?

Increasing recognition of the role and importance of antimicrobial stewardship in preventing infections and minimizing antimicrobial resistance.

What's next?

Implementation of a group B streptococcal conjugate vaccine in pregnancy.

Further reading

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Chapter 24

Hereditary autoinflammatory diseases

See also Chapter 33.

Definition

- Also known as periodic fever syndromes where systemic inflammation occurs in the absence of autoantibodies.
- Their pathogenesis is thought to arise from abnormalities of the innate immune system.
- Characterized by episodes of systemic and/or organ-specific inflammation, resulting in a combination of fever, rash, arthritis, and abdominal pain.

Individual autoinflammatory diseases

- Familial Mediterranean fever (FMF).
- TNF receptor-associated periodic fever syndrome (TRAPS).
- Mevalonate kinase deficiency (MKD).
- Cryopyrin-associated periodic fever syndromes (CAPS).
- Periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome (PFAPA).
- Deficiency of interleukin (IL)-1 receptor antagonist (DIRA).

Familial Mediterranean fever

Epidemiology

- FMF is the commonest periodic fever syndrome.
- Autosomal recessive inheritance is the usual pattern, but autosomal dominant inheritance also occurs.
- It is commoner in people of Mediterranean ancestry (Turks, Armenians, Arabs, and Sephardi Jews) but can occur in any ethnic group.
- The first attack of FMF usually occurs in childhood or adolescence.

Clinical features

- High fever may occur alone but most commonly is associated with abdominal pain, which may lead to a misdiagnosis of appendicitis.
- Joint pain and swelling most often occur in one large joint, commonly in the lower limbs.
- Pain may also occur in the chest due to pleuritic, or rarely pericarditis.
- Rash (usually round the ankles).

- Evidence of systemic inflammation with raised CRP, WCC, and ESR.
- Ongoing inflammation with raised amyloid can cause long-term complications if FMF is left untreated.

Diagnosis

- Clinical diagnosis is often delayed due to the lack of awareness of the condition.
- DNA analysis to detect mutations in the *MEFV* gene, which codes for pyrin, can provide a definitive diagnosis in the majority of cases.

Treatment

- Colchicine is very effective in preventing attacks and reducing their severity, with monitoring of serum amyloid to ensure adequate suppression of inflammation to prevent the development of amyloidosis.
- Non-steroidal anti-inflammatories are used for symptoms during attacks.
- In those that appear to be resistant to (or unable to tolerate) colchicine, IL-1 blockade appears to be effective.

Tumour necrosis factor receptor-associated periodic fever syndrome

TRAPS (previously 'familial Hibernian fever') is caused by mutations in a receptor for TNF. These mutations induce a chronic inflammatory process, which may result in amyloidosis if left untreated.

Epidemiology

- The inheritance is autosomal dominant with incomplete penetrance.
- It has now been described in most ethnic groups, though first reports were from Irish–Scottish cases.

Clinical features

- Attacks predominantly start in childhood, usually before the age of 4.
- Symptoms are variable, the presentation overlapping with FMF and MKD.
- Fever typically lasts between 1 and 4 weeks, with variable recurrence.
- Myalgia is more significant than in FMF which may be migratory; arthralgia, and abdominal or chest pain may also occur.
- Conjunctivitis with or without periorbital oedema.
- The typical rash begins over a painful muscle and migrates distally with an annular and/or gyrate pattern.
- Blood tests show raised inflammatory markers (CRP, ESR, WCC).

Diagnosis

- Detection of a mutation in the gene for TNF receptor superfamily 1A (*TNFRSF1A*).

Treatment

- Attacks respond to steroids at the start of an episode.
- Colchicine is not effective, which helps distinguish TRAPS from FMF.
- TNF-α blockade (either etanercept or infliximab) is effective in some patients.
- IL-1 inhibitors (anakinra, canakinumab) appear to be effective, even in those who do not respond to TNF-α blockade.

Mevalonate kinase deficiency

- MKD, also known as hyperimmunoglobulinaemia D with periodic fever syndrome (HIDS), is caused by mutations in the *MVK* gene coding for the enzyme mevalonate kinase.
- This results in reduced enzyme activity to 5–10% of normal.
- Mevalonic aciduria is the more severe/fatal form, in which the enzyme activity is virtually undetectable.

Epidemiology

- Autosomal recessive disease.
- Most commonly described in the Netherlands and north European populations; however, it is reported in all ethnic groups.
- Attacks of fever begin early in childhood, usually in first year of life.

Clinical features

- Episodes of fever occur every 4–6 weeks and last for 3–7 days.
- Fever may be associated with headaches, lymphadenopathy, diarrhoea and vomiting, arthritis, and non-migratory rash.
- Attacks may be precipitated by immunizations, minor infections, trauma, or stress.
- Disease may attenuate or resolve in adult life and does not usually cause amyloidosis.
- In mevalonic aciduria, febrile episodes occur, but with profound developmental delay, retinal dystrophy, cataracts, and myopathy.

Diagnosis

- Immunoglobulin D (IgD) is usually raised, but not in all patients, especially in children under 3 years.
- Eighty per cent of cases will have a high IgA.
- Raised inflammatory markers are seen during attacks.
- Urine organic acids during attack show raised mevalonic acid.
- Identification of the commonest mutations in both *MVK* genes.
- Reduced mevalonate kinase activity can be demonstrated from WBCs in fibroblast culture.

Treatment

- Although immunizations may precipitate fever attacks, the risks of remaining unimmunized may well outweigh the benefit of avoiding a potential trigger.

- Simvastatin reduces the production of mevalonic acid, with possible clinical benefit, although the numbers of cases reported are small.
- Steroids at the onset of an attack may reduce the severity and duration.
- Anti-TNF drugs (e.g. etanercept) and IL-1 inhibitors (e.g. anakinra) have been used with good effect.

Cryopyrin-associated periodic fever syndromes

- These cryopyrinopathies result in three recognized distinct clinical syndromes, which may have some overlap.
- Familial cold autoinflammatory syndrome (FCAS) is the mildest, and Muckle Wells syndrome (MWS) and CINCA/NOMID syndrome (chronic infantile neurological, cutaneous, and articular syndrome/neonatal-onset multisystem inflammatory disorder) which may be fatal.

Epidemiology

- Autosomal dominantly inherited conditions, with varying severity.
- Most reported patients of European ancestry, but seen in all ethnic groups.

Clinical features

- All three conditions comprise intermittent episodes of fever, arthralgia, urticarial rash, and conjunctivitis.
- In addition, each syndrome has distinct clinical features.

Familial cold autoinflammatory syndrome

- Attacks are associated with exposure to cold.
- Other symptoms include headache, nausea, drowsiness, sweating, and extreme thirst.

Muckle Wells syndrome

- Fever persists longer than FCAS, and without exposure to cold.
- MWS is characteristically associated with the development of sensorineural hearing loss in early childhood.
- Severe fatigue, headaches, and various inflammatory conditions of the eyes.

CINCA/NOMID syndrome

- Presents in the neonatal period.
- Characterized by urticarial rash, with typical facies (frontal bossing, saddle nose, and mid-face hypoplasia) and bony overgrowth of the patella.
- Chronic polyarthropathy, usually bilateral.
- Aseptic meningitis, severe uveitis, chronic papilloedema.
- SNHL may also occur.

Diagnosis

- Raised inflammatory markers (CRP, ESR, serum amyloid) between episodes.
- Skin biopsy of the rash shows a perivascular neutrophilic infiltrate without mast cells or vasculitis.
- Sequencing the *NLRP3* gene will detect most mutations.

Treatment

- All three syndromes of CAPS respond dramatically to IL-1 antagonist therapy such as anakinra, canakinumab, and rilonacept.
- Improvement occurs within days of starting treatment, and complete resolution of signs and symptoms can occur.

Periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome

- PFAPA is also known as Marshall's syndrome.

Clinical features

- Typical onset at around 2 years of age.
- Episodes occur regularly (every 2–6 weeks) with abrupt onset of high fever lasting for 2–6 days.
- Fever is usually associated with mouth ulcers, pharyngitis, and cervical lymphadenopathy.
- Headache, abdominal pain, and arthralgia may also be present.

Diagnosis

- Raised inflammatory markers during febrile episodes.
- Clinical diagnosis is from the typical history and an absence of upper respiratory infections.

Treatment

- Attacks may respond to a 1- to 3-day course of steroids.
- For frequent episodes, tonsillectomy may result in complete resolution.
- By the second decade of life, most will have resolved spontaneously.

Deficiency of the interleukin-1 receptor antagonist

Clinical features

- DIRA is a very rare genetic autoinflammatory syndrome that presents in the first days of life with severe skin and bone inflammation.
- The inflammatory reaction resembles an acute infection or OM, with raised inflammatory markers.

Diagnosis

- Mutations in both *IL1RN* genes confirm clinical suspicion.

Treatment

- The IL-1 receptor antagonist anakinra has resulted in good results in the small number of patients treated so far.

Other autoinflammatory diseases

- Paediatric granulomatous arthritis (Blau syndrome): autosomal dominant, mutation in the *NOD2* gene, with rash and granulomas in the skin, joint, and eyes.
- Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome (PAPA): autosomal dominant, mutation in the *PSTPIP1* gene, sterile neutrophilic arthritis, ulceration, pyoderma gangrenosum, or severe cystic acne.
- Chronic non-bacterial osteitis (CNO), also called chronic recurrent multifocal osteomyelitis (CRMO): bony pain, swelling, and tenderness, with mildly raised inflammatory markers.
- Majeed's syndrome: mutations in the *LPIN2* gene, CNO plus dyserythropoietic anaemia, neutrophilic infiltration of the skin.

Future research

While the development of biological agents has transformed the outlook for many of these diseases, the evidence is largely anecdotal. RCTs will be necessary to discover the optimal management but are extremely difficult due to the rarity of these conditions.

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Chapter 25

Pyrexia of unknown origin

See also Chapters 32, 34.

Introduction

Pyrexia of unknown origin (PUO) remains a clinical challenge due to its wide differential diagnosis. PUO is not a common paediatric problem. Children with persistent fever may have a serious underlying disease. Early diagnosis of these conditions is important. The main conditions which present as PUO are *infections, non-infectious inflammatory conditions*, and *malignancies*. Paediatricians need to rely on *detailed history, repeated clinical examination*, and *pattern recognition* in managing these patients. Since there are over a hundred causes of PUO, investigations need to be directed according to the history and clinical examination. Despite recent advances, there are a significant proportion of cases where no diagnosis is made.

Definition

- In 1961, Petersdorf and Beeson defined PUO as fever higher than 38.3°C (101°F) on several occasions, persisting without a diagnosis for at least 3 weeks, with at least 1 week of investigations in hospital
- With the development of newer diagnostic tests and increasing cost of hospitalization, the management of PUO has changed
- Newer definition of PUO: fever on three outpatient visits or 3 days in the hospital without elucidation of a cause or fever where no cause is found after 1 week of 'intelligent and invasive' ambulatory investigations[1–4]
- In addition, there are three other categories added to this new definition: nosocomial PUO, neutropenic PUO, and HIV-associated PUO.

Table 25.1 outlines the different definitions of PUO with possible causes.

Table 25.1 Definitions of PUO with possible causes

	Definition	Causes
Classic PUO Revised PUO	Temperature >38.3°C Duration >3 weeks 1 week of inpatient evaluation Evaluation of at least 3 days in hospital/three outpatient visits/ 1 week of logical and intensive testing	Infection, rheumatologic conditions, malignancy, others
Nosocomial PUO	Temperature >38.3°C Patient hospitalized >48 hours, negative blood cultures, no fever incubating on admission	HAI, including *C. difficile*, drug-induced, catheter-related, pulmonary embolism
Neutropenic PUO	Temperature >38.3°C, negative blood cultures, neutrophil count $<1 \times 10^9$, evaluation of at least 3 days	Febrile neutropenia, other opportunistic bacterial infection, CVC infection, fungal or viral infection
HIV-associated PUO	In known HIV patients: Temperature >38.3°C, negative blood cultures, duration >4 weeks in outpatient OR >3 days as inpatient	CMV, mycobacterial (atypical and typical), PCP, malignancies, depends on CD4 count

Differential diagnosis

- There is a wide differential diagnosis for cases presenting with PUO.
- In both developed and developing countries, the broad categories include infections, non-infectious inflammatory (autoimmune/ rheumatologic) conditions, malignancy, and a miscellaneous group
- The disorders listed in Table 25.2 are those which may be encountered in Europe and North America
- Organisms causing infection vary between developed and developing countries (Box 25.1)
- Certain diagnosis and evaluation tests have changed over time. The incidence of conditions like rheumatic fever and vaccine-preventable diseases has declined in many countries. On the other hand, there are additions of conditions like HIV infection, Kawasaki disease, and drug fever
- With the availability of newer diagnostic tests, autoimmune conditions and malignancies are diagnosed earlier
- On a ward round—'If you do not know what this can be, think of TB, SLE, and malignancy'.

Table 25.2 Conditions causing PUO in Europe and North America

Bacterial	TB, brucellosis, cat scratch disease, *Salmonella typhi* infection, *Campylobacter* infection, *Spirochete* infection, rheumatic fever
	Localized or occult bacterial infection, abscess, sinusitis, osteomyelitis, pyelonephritis, arthritis, endocarditis, meningitis, UTI
Viral	EBV, CMV, HIV infection, hepatitis, enterovirus
Atypical	*Mycoplasma*, *Chlamydia*, *Rickettsia*
Parasitic	Malaria, toxoplasmosis, giardiasis, toxocariasis, trypanosomiasis
Fungal	*Histoplasma*
Autoimmune diseases	SLE, polyarteritis nodosa, systemic-onset JIA, vasculitis, sarcoidosis, post-infectious inflammatory syndromes
Neoplastic	Leukaemia, lymphoma, solid tumours (Wilm's tumour, neuroblastoma), histiocytosis
Miscellaneous	Endocrine diseases (thyroiditis); Kawasaki disease; Kikuchi–Fujimoto syndrome; drug fever; inflammatory bowel disease; head injury; periodic fever, factitious fever

Box 25.1 Infection presenting as PUO in developing countries

- BACTERIAL: brucellosis, TB, typhoid fever, abscess, septicaemia, *Rickettsia*, OM, endocarditis, UTI, *Mycoplasma*
- PARASITES: *Leishmania*, malaria, *Toxoplasma*, infected hydatid cyst
- VIRAL: EBV, CMV, HIV, hepatitis, dengue
- FUNGAL: *Candida*, histoplasmosis, rarer deep fungal infection

History and clinical examination

- A good clinical history and a thorough clinical examination, repeated every day, remain the mainstay in the diagnosis of PUO.
- Frequently, new signs arise that were not present on admission, including the evanescent rash of JIA, which only comes in the evening, or the slowly enlarging lymph nodes in lymphoma.
- In history-taking, the following points may help in the diagnosis:
  - Type, pattern for fever
  - History of associated symptoms, e.g. weight loss, night sweats, rash
  - History of contact with infectious illness
  - Travel history is important to exclude specific infections (typhoid, amoebiasis, malaria)
  - History of common and unusual pets—snakes, parrots, pigeons (psittacosis)

- History of parent's occupation and family hobbies—a water sport raises the possibility of leptospirosis and forest walking of Lyme disease
- A family history of autoimmune disease, immunodeficiency, or recurrent/unusual infections should be taken
- A detailed drug history, as drug allergy may present with a fever and no rash.

Table 25.3 summarizes some of the common presenting symptoms and likely diagnoses.

Table 25.3 Common presenting symptoms and likely diagnoses

History	Likely diagnosis	Investigations
Fever—type, duration, pattern	Quotidian fever—systemic-onset JIA Tertian/quartan (rare)—malaria Recurrent fever—periodic fever, brucellosis Nocturnal fever—TB, lymphoma	Raised inflammatory markers Malarial film Genetic studies, IgD Mantoux test, QuantiFERON®, tissue biopsy, bone marrow
Travel abroad	Asia, sub-Saharan Africa—malaria, typhoid North America—Rocky mountain fever, Lyme disease East Asia—filariasis, dengue	See Chapter 27
Exposure to wild/domestic animals	Toxoplasmosis, leptospirosis Lyme disease	Specific serology test
Rash	JIA	
Lymphadenopathy	Infections, autoimmune diseases, malignancies	Serology, autoimmune test, biopsy, bone marrow
Abdominal pain, GI symptoms	Inflammatory bowel disease, intra-abdominal collection, GI infection	Faecal calprotectin, endoscopy and biopsy, ultrasound, MRI, barium studies
Uveitis	Sarcoidosis, JIA, SLE, Kawasaki disease	ACE level, inflammatory markers, autoimmune screen
Chorioretinitis	CMV, toxoplasmosis, syphilis	Virus isolation, PCRs, specific serology
Weight loss	TB, malignancies, inflammatory bowel disease	Tests for TB, bone marrow, endoscopy

Investigations

- There is an art to the investigation of PUO (obtaining the correct diagnosis as quickly as possible and ordering appropriate investigations). The child, the family, and often the doctor find the uncertainty difficult to deal with
- Investigations should be directed by clues from the history and examination
- A stepwise approach to investigations should be taken, and a period of inpatient observation is very useful, as some conditions evolve over time
- Blind imaging studies, such as bone scans and whole-body MRI, or bone marrow aspiration are rarely helpful.

Table 25.4 gives guidance regarding initial investigations that may be considered. Further investigations should be directed, depending on the clinical picture and organ involvement, if any (Table 25.5).

Table 25.4 Investigations for evaluating children presenting with PUO

Baseline investigations should include	
Haematology	FBC, blood film, ESR, malaria films (if travelled)
Chemistry	CRP, LFT, U&Es, bone profile, LDH
Microbiology	Blood cultures × 3, urine, stool culture, CSF, throat swab
Serology	Anti-streptolysin O titre, *Mycoplasma*, EBV, Lyme serology
Viral isolation	PCR—EBV, CMV, adenovirus
Radiology	Chest radiograph, ultrasound of abdomen

Table 25.5 Targeted/specific investigations in fever of unknown origin

A. Infections	
Mantoux test QuantiFERON® γ	Exposure to active case of TB, weight loss, night sweats, cough, immigration, travel, etc.
Bartonella serology (cat scratch disease)	Pets at home or exposure to cats
Brucella serology	Consumption of unpasteurized milk
Toxoplasma serology	Consumption of poorly cooked meat, exposure to cats
Anti-streptolysin O, anti-DNAse antibody—for streptococcal infection	History of sore throat, migratory polyarthritis, erythema marginatum
B. Malignancy	
Bone marrow, flow cytometry, LDH LN/liver/kidney/skin biopsy	Lump, swellings, fatigue, weight loss, night sweats, unexplained bruising, pain

(*Continued*)

Table 25.5 (*Contd.*)

Ferritin, triglycerides, genetic studies—haemophagocytic lymphohistiocytosis	Sepsis-like
CT, MRI, bone scan, white cell scan, PET scan	Localizing site and involvement
C. Autoimmune	
Autoantibodies, ANA, double-stranded DNA, immunoglobulin, complements, lymphocyte subsets	History of rash, joint swellings, multisystem involvement
D. Miscellaneous	
Endoscopy, video capsule endoscopy, barium studies, MRI of abdomen, faecal calprotectin	Bloody diarrhoea, weight loss, abdominal pain, extra-intestinal manifestations
Thyroid function tests	Tremors, sweating, weight loss, family history of thyroid problems
Echocardiography—endocarditis, Kawasaki, autoimmune conditions	History of cardiac conditions, clinical criteria for Kawasaki

Outcome

- In various studies between 5% and 35% of cases, there was no cause found for PUO.
- Infection, malignancy, and autoimmune conditions are the main causes of PUO. Except for differences in the organisms causing infections, there is not a major difference between various aetiologies in developed and developing countries.
- Factitious illness and periodic fever syndromes are rare causes of PUO and should be considered.

Table 25.6 shows the final diagnosis of PUO in different paediatric studies conducted in the past 20 years.

Table 25.6 Summary of final diagnoses of PUO

First author, country (year)	No. of patients	Infection (commonest causes) (%)	Malignancy (%)	Auto immune (%)	No cause found (%)
Joshi *et al.*[5] India (2008)	49	69	12	2	12
Iwanczak *et al.*[6] Poland (2007)	10	10	0	0	0
Chemli[7] Tunisia (2006)	110	58	3	7	24
Pasic[8] Serbia (2006)	185	37.8	6	12.9	29.1
Bakashvili,[9] Georgia (2006)	52	61	4	3.8	13.4
Chouchane,[10] Tunisia (2004)	67	56.7	3	20.9	19.4
Ciftçi[11] Turkey (2003)	102	44	12	7	12
Cogulu,[12] Turkey (2003)	80	58.7	3	13.2	19.4
Gratz[13] Germany (1998)	30	50	17	17	17
Jacobs[14] USA (1998)	146	44	3	0	42
Rico Mari[15] Spain (1994)	32	72	3	22	3
Chantada,[16] Argentina (1994)	113	36.2	14	13.2	19.4

Future research

A key area of research is the development of the most cost-effective and time-efficient algorithms in the management of PUO.

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Chapter 26

Rash

Introduction

- Skin rashes or exanthems are among the commonest clinical presentations in childhood. They are associated with diseases ranging from benign self-limiting illnesses caused by viruses to severe life-threatening bacterial infections.
- Enanthems are eruptions on the mucous membranes of the oral cavity.

Causative organisms

Rashes in childhood are most commonly caused by viruses but may also be bacterial or non-infectious in origin (Table 26.1).

UK- and European-focused prevalence and epidemiology

- In recent studies, with modern molecular diagnostic techniques, the proportion of rashes which have a cause determined approaches 50%.
- In the UK, the most commonly identified causes of a maculopapular rash are:[1]
  - Parvovirus B19 (17%)
  - GAS (15%)
  - HHV-6 (6%)
  - Enterovirus (5%)
  - Adenovirus (4%).
- The proportions are similar in studies in Spain, the Netherlands, and Finland.
- The incidence of varicella is around 25/10 000 in the UK and Europe.
- Although measles and rubella account for <1% of cases in these highly immunized populations, the numbers of cases were increasing in the UK until 2012. The widespread media reporting of now discredited studies has led to decreased uptake of the MMR vaccine and subsequent outbreaks.
- According to PHE, the number of laboratory-confirmed cases of measles in the UK in 2013 was 1843, which compares to 58 in 1998, although a slight decrease from 2030 in 2012[2] (Fig. 26.1).
- MMR uptake is increasing once again, and, although currently only 89% of children in the UK have had two doses by their fifth birthday, this reflects a steady increase from 75% in 2008.

Table 26.1 Aetiology of different types of rash in children

Type of rash	Viral	Bacterial	Other infectious	Other
Maculopapular	Measles Rubella EBV Erythema infectiosum (parvovirus B19) Roseola infantum (HHV-6, HHV-7) Enterovirus Adenovirus Gianotti–Crosti syndrome Unilateral laterothoracic exanthem Dengue fever HIV (acute) West Nile virus	Staphylococcal and streptococcal toxic shock Scarlet fever Syphilis Leptospirosis *Borrelia* Typhoid Brucellosis *Arcanobacterium haemolyticum*	Toxoplasmosis *Rickettsia* Ehrlichiosis *Mycoplasma* Psittacosis	Kawasaki disease Pityriasis rosea Juvenile chronic arthritis Drug reaction (including drug reaction, eosinophilia, and systemic symptoms (DRESS) syndrome Eczema SLE Dermatitis
Petechial/ purpuric	Enterovirus EBV Papular purpuric gloves and socks syndrome VHFs Congenital CMV/rubella	Meningococcus Pneumococcus Leptospirosis Bacterial endocarditis	*Rickettsia* Malaria Leishmaniasis	Henoch–Schönlein purpura HUS Idiopathic thrombocyto-penic purpura Leukaemia Neuroblastoma
Vesicular/ bullous	Varicella Herpes simplex Smallpox Enterovirus, esp. Coxsackie	Staphylococcal scalded skin Staphylococcal and streptococcal impetigo	*Mycoplasma*	Stevens–Johnson syndrome
Scaly			Fungal, e.g. tinea	Eczema Psoriasis Pityriasis rosea

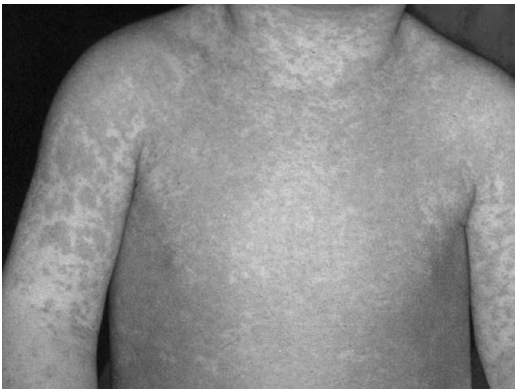


Fig. 26.1 Morbilliform maculopapular erythematous rash in measles. Please see colour plate section.

- Studies undertaken outside Europe feature dengue fever, measles, and rubella as common causes of rash, and these should therefore be considered when a child presenting with a rash has recently travelled abroad or been in contact with recent travellers, particularly if not immunized.

Clinical presentation and differential diagnosis

- Most of the organisms associated with rashes discussed in this chapter are detailed in other specific chapters, so the emphasis here is the clinical distinction between different causes of rash.
- Diagnosis is particularly important in:
  - Severe infection
  - The immunocompromised host
  - When there is contact with a pregnant woman.
- The causes of rash in childhood are frequently difficult to differentiate from each other. However, the incidence of many infections peaks in specific age groups, and the aetiology can be narrowed down by careful history and examination.

History

- Prodromal symptoms:
  - Most infectious rashes in childhood are associated with systemic symptoms, such as fever, and these symptoms may precede the onset of rash (Table 26.2)

- The differential diagnosis of prodromal symptoms, such as fever, conjunctivitis, and lymphadenopathy, includes Kawasaki disease and adenoviral infection, both of which also manifest with a rash.

Table 26.2 Prodromal symptoms associated with common exanthems

Infection	Duration	Symptoms
Measles	3–4 days	Fever, coryza, conjunctivitis, cough
Rubella	1–5 days	Fever, lymphadenopathy, conjunctivitis (less in children)
Varicella	1–2 days	Fever, cough, coryza, sore throat (less in children)
Erythema infectiosum	2–3 days	Mild fever, malaise (less in children)
Roseola infantum	3 days	High fever which defervesces when rash appears
Scarlet fever	1–2 days	Fever, sore throat, headache, abdominal pain

- Evolution of the rash:
  - Some rashes appear as generalized rashes over the entire body at onset, while others change in nature or distribution
  - The rash of chickenpox starts as macules and papules and then develops into vesicles that eventually crust over. Lesions at different stages exist at the same time (Fig. 26.2)
  - The rash of rubella starts with a facial rash that spreads to the remainder of the body
  - The rash of erythema infectiosum starts as an erythematous rash on the cheeks that may also progress to include a lacy rash of the trunk and limbs
  - The rash of roseola infantum starts on the neck and trunk and then spreads to the face and limbs
  - The rash of Rocky Mountain spotted fever starts on the hands and feet and spreads up the limbs to the trunk
  - The rash of Lyme disease classically begins with a circular red lesion, expanding outward from the site of the tick bite, which develops into a bullseye lesion (erythema chronicum migrans). After several days, macular lesions may develop at other sites on the body, distant from the original bite
  - Several rashes desquamate with time, including scarlet fever, Kawasaki disease, syphilis, and various toxin-mediated infections (Fig. 26.3).
- Associated symptoms:
  - Respiratory symptoms may be associated with roseola infantum and more severely with pneumonitis in measles, chickenpox, and psittacosis
  - GI symptoms may be a feature of measles, roseola infantum, toxic shock syndrome (TSS), typhoid, leptospirosis

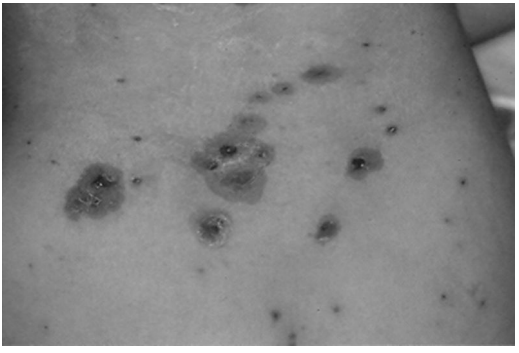
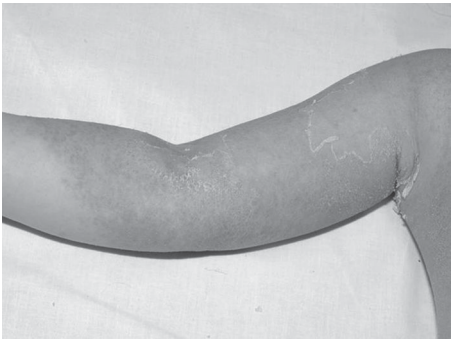


Fig. 26.2 Lesions at various stages, including bullae in haemorrhagic chickenpox. Please see colour plate section.

(A)



(B)

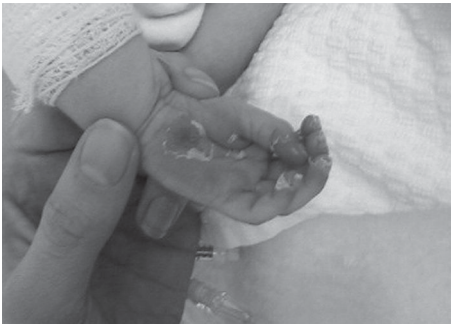


Fig. 26.3 Desquamation in (A) scarlet fever and (B) syphilis. Please see colour plate section.

  - Hepatitis may occur in roseola infantum, Gianotti–Crosti syndrome, leptospirosis
  - There may be coexisting meningitis in meningococcal sepsis, enteroviral infection, and leptospirosis, or rarely an encephalitic picture with measles, rubella, chickenpox, erythema infectiosum, and roseola infantum
  - Joint symptoms may be associated with rubella, erythema infectiosum, psittacosis, and brucellosis, and at a late stage in Lyme disease.
- Exposure to infections:
  - Contact with other people with similar symptoms is important, as some diseases are highly infectious, e.g. chickenpox and erythema infectiosum
  - Exposure to insects that might transmit infections is relevant, e.g. in Lyme disease (deer ticks) and dengue fever (mosquitoes)
  - Contact with animals that might transmit infections is relevant, e.g. in leptospirosis (rats), toxoplasmosis (puppies and kittens), and psittacosis (birds)
  - Ingestion of potentially infected foods is relevant, e.g. in toxoplasmosis (soft cheeses and pâté) and brucellosis (unpasteurized milk).
- Foreign travel:
  - With increasing worldwide travel, imported infections are an important cause of rashes
  - Typhoid fever is a common infection in febrile children who have returned from travelling, which may present with rose spots on the abdomen in older children
  - Dengue fever is the most commonly identified cause of maculopapular rash in endemic areas. In certain circumstances, it can also present with a haemorrhagic rash
  - Malaria is a common infection and a rare cause of purpuric rash
  - VHFs, e.g. Ebola, are rare
  - Countries other than tropical countries are also the source of infections, e.g. Rocky Mountain spotted fever and West Nile virus in the US and leishmaniasis in southern Europe.
- Time of year:
  - Many infections are seasonal, so awareness of prevailing microorganisms is important
  - Enterovirus infections (echovirus, Coxsackie virus, and enterovirus) occur predominantly in the summer months
  - Erythema infectiosum tends to occur in late winter and early spring
  - Tropical infections also have seasons of increased incidence, e.g. dengue fever and malaria.
- Immunization history.
- Drug history:
  - The administration of amoxicillin during EBV infection has traditionally been considered to cause a widespread rash, although the strength of this association has recently been questioned (Fig. 26.4)

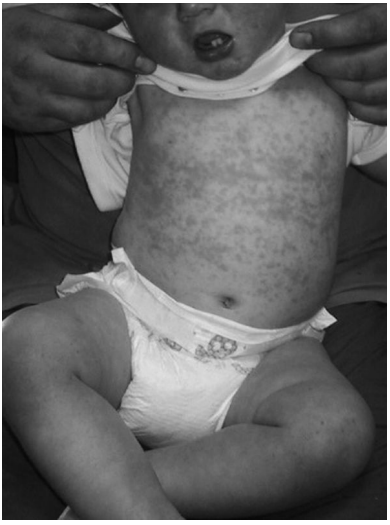


Fig. 26.4 Rash in EBV infection after amoxicillin administration. Please see colour plate section.

- Drugs may cause rash, even without a concomitant infection, and may be due to an allergy or a side effect. Drugs with rash as a well-recognized side effect include anti-epileptics, antibiotics, and antimalarials
- Sun exposure may exacerbate rashes caused by drugs
- Drugs may cause different types of rash, e.g. maculopapular, urticarial, erythema multiforme (Fig. 26.5), and severely Stevens–Johnson syndrome.

Examination

- Nature of the rash:
  - The key to diagnosis is the nature of the rash—maculopapular, petechial/purpuric, vesicular/bullous, or scaly (Table 26.1)
  - Some organisms cause several different types of rash, e.g. enteroviruses which can cause maculopapular, petechial, and vesicular rashes
  - In chickenpox, different stages of the rash can occur at the same time—maculopapular, vesicular, and crusted. Historically, this differentiated it from smallpox where all the vesicles had similar morphology
  - Some rashes have classical morphology, e.g. the rash of TSS which is described as looking like sunburn, the bullseye lesions in Lyme disease, the sandpaper rash of scarlet fever, and the salmon pink macules in juvenile chronic arthritis (Fig. 26.6). However, a lack of classical features does not necessarily preclude the diagnosis.

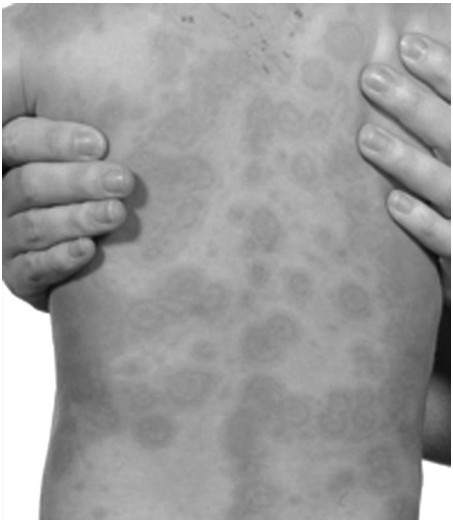


Fig. 26.5 Erythema multiforme. Please see colour plate section.

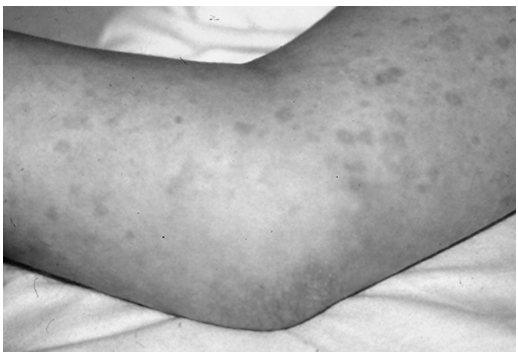


Fig. 26.6 Macular rash in juvenile chronic arthritis. Please see colour plate section.

- Rash distribution:
  - The distribution of the rash also differentiates between pathogens. It may change with time, so the history of its evolution and re-examination are important
  - The main classifications regarding distribution are local versus generalized (Table 26.3), and centripetal versus centrifugal.

Table 26.3 Distribution of childhood rashes

Localized rashes Infection	Rash site	Generalized rashes Infection
Erythema infectiosum	Cheeks	Measles
Hand, foot, and mouth disease	Hands, feet, perioral, buccal cavity	Enterovirus infection other than hand, foot, and mouth
Shingles	One or two dermatomes	Rubella
Herpes simplex	Mouth, genitals, fingers	Roseola infantum
Gianotti–Crosti syndrome	Face, buttocks	Chickenpox
Unilateral laterothoracic exanthem	Axilla, flank	Adenovirus
Papular purpuric gloves and socks syndrome	Hands, feet	EBV (especially with amoxicillin)
Lyme disease	Site of tick bite	Acute HIV
Typhoid fever	Abdomen	Scarlet fever
Psittacosis	Face	Meningococcal septicaemia
Early Rocky Mountain spotted fever	Palms, soles	Toxic shock syndrome
Bacterial endocarditis	Ends of fingers and toes	Leptospirosis
Pityriasis rosea	Trunk, often a single lesion	Kawasaki disease
Fungal infections	Scalp or skin, but often a single or few lesions	Juvenile chronic arthritis
SLE	Face	Leukaemia
Henoch–Schönlein purpura	Legs and buttocks	Drug reaction

  - Centripetal rashes predominate or start on the extremities and include hand, foot, and mouth disease (HFMD), syphilis, Rocky Mountain spotted fever, dengue fever, and historically smallpox, which was one of the ways to differentiate it from chickenpox
  - Centrifugal rashes predominate or start on the trunk and include measles, rubella, chickenpox, and scarlet fever.

- Oral enanthems:
  - Several skin rashes have associated oral lesions (enanthems) that can easily be missed if the buccal cavity is not specifically examined (Table 26.4, Fig. 26.7).

Table 26.4 Oral enanthems associated with common exanthems

Infection	Symptoms
Measles	Koplik spots—white spots on the buccal mucosa
Rubella	Forscheimer's spots—red papules on the hard palate
Varicella	Vesicles which may ulcerate
Erythema infectiosum	Red macules on palate and buccal mucosa, erythematous tongue
Roseola infantum	Nagayama spots—erythematous papules on the soft palate
Scarlet fever	Red exudative tonsils, strawberry tongue, palatal petechiae
EBV	Red enlarged tonsils, palatal petechiae
Hand, foot, and mouth	Erythematous lesions on hard palate that become vesicular

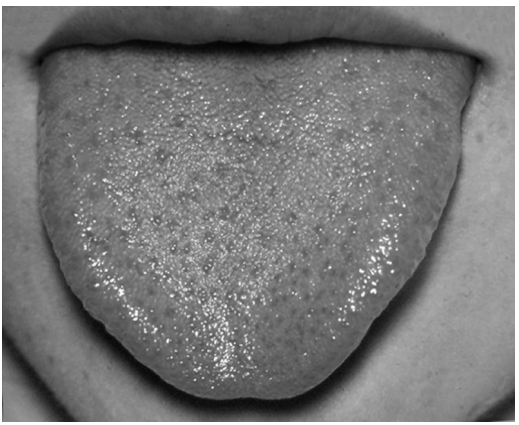


Fig. 26.7 Strawberry tongue in scarlet fever. Please see colour plate section.

- Other clinical findings:
  - Conjunctivitis may occur in measles, rubella, adenovirus infection, scarlet fever, and Kawasaki disease
  - Mucosal changes may a feature of scarlet fever, Kawasaki disease, TSS, and drug reactions, including Stevens–Johnson syndrome
  - Lymphadenopathy may occur in rubella, EBV, scarlet fever, and Kawasaki disease
  - Hepatomegaly and/or splenomegaly may be found in EBV infection, rubella, acute HIV infection, leukaemia, juvenile chronic arthritis
  - Genital lesions may be found in herpes simplex infection, Kawasaki disease, and Stevens–Johnson syndrome.

Immunocompromised individuals

Rashes associated with benign self-limiting illnesses in immunocompetent children may have a much more severe course in the immunocompromised host. See specific chapters for more details, but examples include:

- Measles
- Varicella
- Erythema infectiosum
- Roseola infantum.

Pregnant women

Several infections with rashes have severe consequences for the fetus if they occur in a non-immune pregnant woman, and may also present with a rash in the neonatal period. See specific chapters for more details, but examples include:

- Rubella
- Toxoplasmosis
- CMV
- Syphilis
- Herpes simplex
- Varicella
- Erythema infectiosum.

Specific rashes not covered elsewhere

Gianotti–Crosti syndrome (papular acrodermatitis of childhood)

- The commonest cause is EBV, and other infectious agents implicated include hepatitis B, enteroviruses, respiratory viruses, parvovirus B19, and CMV.
- There are a few reports of Gianott–Crosti syndrome following immunizations.
- It is generally a self-limiting condition, usually lasting 10–14 days and predominantly affecting preschool children. It is rarely seen in adults, and then exclusively in women.
- The exanthem is an erythematous papular or vesicular rash, affecting the extensor surface of the extremities, face, and buttocks which may be pruritic. The rash is often asymmetrical, and lesions may coalesce to form plaques.
- It is associated with fever and/or lymphadenopathy in about one-third of individuals.

- Occasionally, acute hepatitis develops, particularly when the causative organism is hepatitis B, EBV, or CMV, and very rarely this may become chronic.
- Treatment is symptomatic.

Unilateral laterothoracic exanthem (asymmetric periflexural exanthem of childhood)

- No single causative organism has been identified, although parvovirus B19 and EBV have been associated.
- It usually occurs in winter and early spring.
- It is commonest in children aged 1–5 years, and rare in adults.
- There is usually a prodrome of low-grade fever and mild respiratory and GI symptoms.
- The rash begins unilaterally on the trunk, most frequently in the axilla, and may be accompanied by an enlarged axillary lymph node. It is a morbilliform or eczematous rash that may spread bilaterally but retains a unilateral predominance. It is self-limiting and usually resolves in about 4 weeks without complication.

Papular purpuric gloves and socks syndrome

- This exanthem is most commonly caused by parvovirus B19. HHV-6, HHV-7, CMV, and measles virus have also been implicated in the aetiology.
- Erythema, oedema, and pruritus of the hands and feet in a glove and sock distribution are associated with mild fever. The erythema progresses to petechiae and purpura on the palms and soles, which may be painful.
- Treatment is symptomatic with antihistamines, and the rash usually resolves in 1–2 weeks without sequelae.

Pityriasis rosea

- This is an exanthem of unknown origin, although a viral cause is suggested by seasonal and geographic clustering.
- It predominantly affects older children and young adults.
- A sore throat may precede the exanthem, and constitutional symptoms, such as headache and low-grade fever, may accompany the rash.
- The rash is characterized by pink or red scaly oval lesions, often heralded by a single lesion before others develop, predominantly on the trunk. It may be pruritic, and treatment with antihistamines provides symptomatic relief.
- The rash usually resolves within several weeks without treatment. Ultraviolet (UV) light has been used anecdotally to shorten the course in pityriasis, but comparative studies in a few patients have not shown good evidence for its use.

Rickettsial rashes

- Classical rickettsial infection is Rocky Mountain spotted fever, caused by the bacteria *R. rickettsii*.
- The infection is transmitted by ixodid ticks, which can be associated with both deer and domestic dogs. It occurs across most of eastern and central US, as far as the Rocky Mountains, as well as Canada, and Central and South America.
- Rocky Mountain spotted fever has a prodromal phase of fever, headache, myalgia, and nausea, lasting several days.

- The rash frequently starts as a maculopapular rash on the palms and soles that spreads up the limbs to the trunk and progresses to a petechial rash.
- Treatment is with doxycycline for up to 10 days.
- Without antibiotic treatment, mortality is up to 30%.
- Other tick-borne diseases associated with rash that are not caused by rickettsia are Lyme disease (*B. burgdorferi*) and ehrlichiosis (*Ehrlichia* spp.).

Investigations

Investigation of rash in childhood should initially be tailored toward likely causes and may include the following:

- Culture—of blood, respiratory specimens, CSF, and stool for bacteria and viruses
- Serology—IgM, paired IgG
- PCR:
  - Most viral exanthems can be diagnosed by PCR of blood or CSF, including the herpesviruses, measles, rubella, parvovirus B19, adenovirus, enterovirus
  - Specific bacterial PCR, e.g. meningococcal or pneumococcal, or 16S PCR may be used.
- Antigen tests—poor sensitivity, so less frequently used, although urine pneumococcal antigen test may be useful in over 5 year olds.
- Specific tests:
  - Salivary IgA or IgM for measles
  - Immunofluorescence of vesicle fluid for varicella or herpes infections (Fig. 26.8)
  - Immunofluorescence of NPAs for adenovirus.

In most studies of childhood rashes, in about half of patients, no cause is identified.

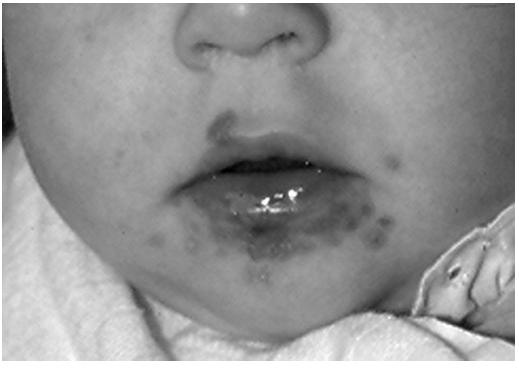


Fig. 26.8 Herpes simplex stomatitis. Please see colour plate section.

Management and treatment

Management of the different causes of rash is dealt with in specific chapters.

- As most causes of rash are benign and self-limiting, treatment is usually supportive:
  - Fluids—particularly in severe illness or where oral lesions prevent drinking
  - Antipyretics—not always necessary, but may provide symptomatic relief
  - Antihistamines—for itchy rashes, e.g. chickenpox.
- Urgent antibiotics, e.g. a third-generation cephalosporin, should always be given in a child with suspected meningococcal septicaemia (Fig. 26.9).

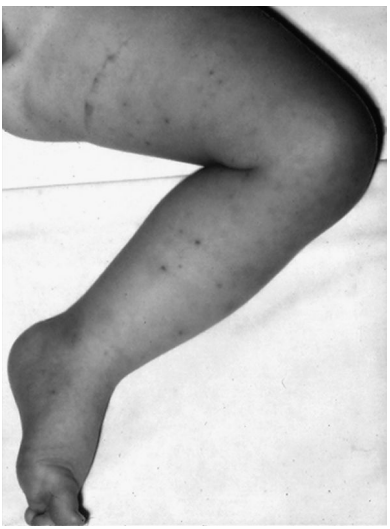


Fig. 26.9 Petechial rash in meningococcal septicaemia. Please see colour plate section.

Follow-up and outcome

The outcome of different causes of rash is dealt with in specific chapters.

- Many of these rashes are highly infectious, and contact tracing may be necessary if there is contact with an immunocompromised child or pregnant woman.
- It is useful to know the incubation and infectivity periods for common childhood rashes (Table 26.5).

Table 26.5 Incubation and infectivity periods for acute viral exanthems

Exanthem	Incubation (days)	Duration of infectivity
Measles	8–12	Two days before prodrome to 5 days after rash appears
Rubella	14–21	Seven days before rash to 5 days after rash appears; in congenital infection, viral shedding can persist for months
Varicella	10–21	Two days before rash to 5 days after rash appears
Erythema infectiosum	4–14	Prior to the onset of the rash
Papular purpuric gloves and socks syndrome	10	During shedding of virus which can persist until after the rash disappears after 7–14 days
Roseola infantum	9	During shedding of virus which can persist
Hand, foot, and mouth	4–7	During shedding of the virus which can persist in the stool for several weeks

Key references

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2 Health Protection Agency (2014). *Confirmed cases of measles, mumps and rubella 1996–2013*. Available at: <http://www.hpa.org.uk>.

Further reading

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Chapter 27

Gram-positive bacteria

Name and nature of the organisms

Clinically important Gram-positive bacteria can be conveniently categorized, based on microscopic appearances, cultural characteristics, and some simple laboratory tests (Fig. 27.1).

Epidemiology

- Gram-positive bacteria, such as *S. aureus, S. pneumoniae*, and β-haemolytic streptococci are among the commonest causes of infections of all degrees of severity in children. Asymptomatic colonization with these bacteria is also common.
- Other serious infections with Gram-positive bacteria, such as listeriosis, diphtheria, and anthrax, are rare in the developed world.
- Gram-positive bacteria also include the predominant commensals of skin and mucosa: CoNS, viridans streptococci, *Corynebacterium* spp. These low-virulence bacteria are important opportunistic pathogens in some settings.
- Some types of Gram-positive bacteria are commoner in hospitalized patients, especially antibiotic-resistant strains, including MRSA, and VRE.

Transmission and incubation period

- Staphylococci and streptococci are transmitted from person to person via direct or indirect contact, or the respiratory route. Many infections are endogenous; these occur where an organism previously carried harmlessly by the individual is able to breach the normal host defences and cause infection.
- Without control measures, some staphylococci and streptococci can readily spread in hospitals, especially MRSA and GAS.
- Listeriosis is usually food-borne.
- Diphtheria is highly infectious, usually via the respiratory route.
- Clostridia are anaerobic, spore-bearing bacteria that are found in the GI tracts of humans and animals and in contaminated soil. Infections may be endogenous or acquired through ingestion or wound contamination with bacterial spores.
- *Bacillus* spp. (e.g. *B. cereus, B. anthracis*) are aerobic, spore-bearing bacteria that are found naturally in the environment. Infections occur through exposure to spores; *B. cereus* food poisoning is caused by ingestion of the toxin produced by bacteria multiplying in food.

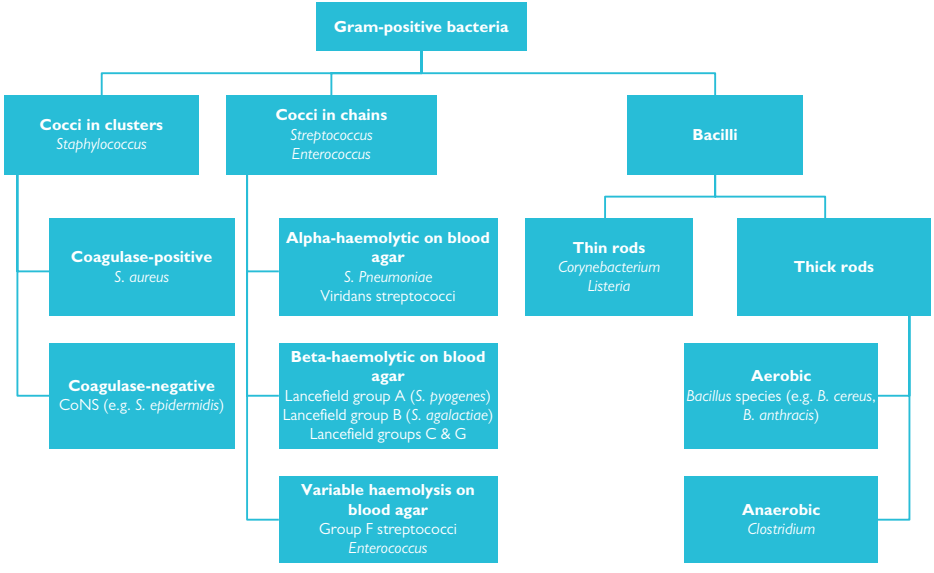

Fig. 27.1 Categorization of Gram-positive infections.

- Incubation periods vary according to the type of infection, size of the inoculum, and route of entry into the body: 1–7 days for most exogenous infections, but can be longer for clostridial diseases (e.g. tetanus). Food poisoning due to preformed bacterial toxins occurs within hours of ingestion.

Clinical features and sequelae

Gram-positive bacteria cause a diverse range of infection.

- *Respiratory tract infections*:
  - *S. pneumoniae* is the commonest cause of bacterial pneumonia. *S. aureus* is a much less common, but potentially serious, cause of pneumonia in certain circumstances (PVL-producing strains; post-influenza)
  - *S. pyogenes* is the commonest cause of bacterial sore throat. Non-suppurative complications include acute rheumatic fever, post-streptococcal glomerulonephritis (PSGN)
  - Diphtheria is a very rare cause of sore throat in western countries but should be borne in mind when assessing travellers returning from countries where it remains prevalent.
- *Skin and soft tissue infections*:
  - Staphylococci and streptococci are by far the commonest causes of these infections. Infections range from mild folliculitis, through conditions such as impetigo, cellulitis, and wound infections, to life-threatening necrotizing fasciitis
  - Clostridial myonecrosis is a highly lethal necrotizing soft tissue infection of skeletal muscle caused by toxin- and gas-producing *Clostridium* spp.
  - Anthrax is rare in developed countries; cutaneous anthrax is the commonest presentation.
- *UTI*:
  - Gram-positive bacteria account for around 10% of all UTIs: mainly staphylococci (*S. aureus* and CoNS) and enterococci. Commoner in children with urinary tract abnormalities or who are catheterized.
- *GI infections*:
  - *Clostridium perfringens* and *B. cereus* can cause toxin-mediated food-borne disease. These spore-bearing bacteria contaminate food and are able to multiply in the food or in the intestine after ingestion, producing toxin
  - Staphylococcal food poisoning is caused by ingestion of preformed toxin in food that has been incorrectly stored, allowing enterotoxigenic *S. aureus* to multiply and produce toxin
  - *C. difficile* infection occurs where the bacteria multiply and produce toxins in the colon.
- *Meningitis*:
  - Streptococci are important cause of meningitis:
    - —*S. pneumoniae* is the second commonest cause of bacterial meningitis after *N. meningitidis*
    - —GBS are the commonest cause of neonatal meningitis

  - Staphylococci are the commonest cause of meningitis post-neurosurgery (especially shunt-associated meningitis)
  - Meningitis occurs in up to half of cases of listeriosis.
- *BSIs*:
  - Staphylococci and streptococci are common causes of paediatric bacteraemia. Bacteraemia is usually secondary to a local focus of infection; 1° bacteraemia may occur in neonates and patients with neutropenia.
- *Intravascular device-related infections*:
  - Staphylococci, especially CoNS, are the commonest causes of intravascular device-related infections.
- *Bone and joint infections*:
  - *S. aureus* is much the commonest cause of both SA and OM.
- *IE*:
  - Viridans streptococci are the commonest causes of native valve endocarditis; staphylococci are the main cause of prosthetic valve endocarditis.
- *Toxin-mediated diseases*:
  - Many Gram-positive bacteria produce exotoxins that are important virulence factors. Some conditions are almost entirely mediated by toxins, e.g. staphylococcal TSS, botulism, tetanus.

Diagnosis

- Culture of samples from the suspected site of infection is the mainstay of diagnosis of these infections.
- Microscopy of some samples (urine, CSF, blood cultures, lower respiratory tract secretions) can give an early indication of Gram-positive infection; but it is not always possible to distinguish between pathogenic and commensal bacteria.
- Serological tests have limited use; anti-streptolysin O titre may help in the retrospective diagnosis of GAS infection; antigen tests for GAS, *Pneumococcus*.
- Diagnosis of toxin-mediated diseases is difficult and requires specialist techniques.

Management and treatment

- Acquired antibiotic resistance is common in staphylococci, streptococci, and enterococci; MRSA, penicillin-resistant pneumococci (PRP), and VRE are of particular concern.
- β-lactam antibiotics are a mainstay of treatment of streptococcal and staphylococcal infections. Macrolides and clindamycin are possible alternatives; however, rising resistance rates to these agents are a concern, directly related to the greater use of clarithromycin and azithromycin for respiratory tract infections:
  - β-haemolytic streptococci are universally sensitive to penicillin
  - Most *S. aureus* have β-lactamase-medicated penicillin resistance but remain susceptible to flucloxacillin, cephalosporins, and carbapenems

  - MRSA and many CoNS are resistant to all β-lactams, except ceftaroline (a novel cephalosporin). Resistance is mediated by the low-affinity penicillin-binding protein (PBP 2a) encoded by the *mecA* gene. This gene is part of a mobile genetic element SCC*mec* that commonly also contains genetic structures encoding resistance to other antibiotic classes
  - Penicillin resistance in *S. pneumoniae* is also PBP-mediated; rates vary widely across Europe. Third-generation cephalosporins (cefotaxime, ceftriaxone) remain active against some of these strains.
- Enterococci are treated with amoxicillin or a glycopeptide; addition of an aminoglycoside gives a synergistic effect in serious infections. Linezolid is the usual treatment for vancomycin-resistant strains.
- *Listeria* spp. are resistant to cephalosporins. Treatment is with high-dose amoxicillin or ampicillin, often combined with an aminoglycoside such as gentamicin.
- Diphtheria is treated with penicillin and erythromycin.
- Clostridial infections are usually treated with penicillin or metronidazole.
- *B. cereus* produces broad-spectrum β-lactamases that hydrolyse penicillins, cephalosporins, and carbapenems; antibiotic choices should be based on sensitivity testing—ciprofloxacin, vancomycin, and linezolid are usually active. Anthrax is treated with ciprofloxacin, sometimes combined with one or two other antibiotics.
- There are few paediatric data on some of the newer anti-Gram-positive antibiotics such as daptomycin, telavancin, ceftaroline.
- Antitoxins are an important part of the treatment of serious toxin-mediated diseases, although antibiotics are usually also given to terminate further toxin production.

Prevention

- Vaccine-preventable Gram-positive diseases include diphtheria, *Pneumococcus*, and tetanus.
- Intrapartum antibiotic prophylaxis to prevent early-onset GBS infection.
- Screening and decolonization for MRSA; sometimes used for MRSA as well (e.g. PVL).
- Follow-up and prophylaxis or treatment of close contacts of serious infections, e.g. invasive GAS infections, diphtheria.
- Prevention of transmission of Gram-positive bacteria in hospitals:
  - General hygiene
  - Care of invasive medical devices, e.g. intravascular devices, endotracheal tubes
  - Antibiotic stewardship
  - Isolation of patients with infections that are serious or antibiotic-resistant, e.g. diphtheria, MRSA.

Future research

Groups A and B β-haemolytic streptococci are still important causes of morbidity and mortality in children. There have been many obstacles to vaccine development, but work continues, the best prospects seeming to be for a vaccine against GBS.

One of the main areas of unnecessary antibiotic use is in the treatment of respiratory tract infections; better rapid tests that could diagnose or exclude streptococcal infections would facilitate less antibiotic prescribing.

MRSA in Europe is changing, with the emergence and spread of new strains of community-associated MRSA. Research into the best ways of identifying, controlling, treating, and monitoring these pathogens is required.

Serious Gram-positive bacterial infections are still associated with high rates of mortality and morbidity; further research into the management of these conditions is required.

What's new?

- Use of care bundles has substantially reduced the incidence of device-related infections, caused predominantly by Gram-positive bacteria.
- At the same time, developments in medical care mean that more children with multiple co-morbidities and increased susceptibility to Gram-positive bacterial infections are surviving.

What's next?

- While the incidence of bacteraemia with many Gram-positive bacteria has decreased, little progress has so far been made in preventing BSIs with MSSA, one of the commonest causes of paediatric bacteraemia.
- New rapid diagnostic techniques for Gram-positive bacteria will become increasingly used to assist with the rational use of antibiotics.

Further reading

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Chapter 28

Gram-negative infections

Name and nature of the organisms

These bacteria fall into two categories:

- *Enterobacteriaceae* (coliforms): bacteria whose natural habitat is the GI tract of humans and other animals.
- Non-(lactose) fermentative bacteria whose natural habitats are principally the environment inside and outside hospital. The most important species are:
  - *Pseudomonas* spp., especially *P. aeruginosa*
  - *Acinetobacter* spp., especially *Acinetobacter baumanii*
  - *Burkholderia cepacia* complex (Bcc)
  - *Stenotrophomonas maltophilia*.

Enterobacteriaceae

These can be considered in three groups:

- Species that are common commensals of the human GI tract and are common opportunistic community- and hospital-acquired pathogens, e.g. *E. coli, P. mirabilis*
- Species that are uncommon GI commensals of healthy individuals and are seen mainly as hospital-acquired pathogens, e.g. *Enterobacter, Klebsiella, Serratia* spp.
- Strains that are unequivocal GI pathogens, e.g. *Salmonella, Shigella, Yersinia* spp.; enteropathogenic strains of *E. coli*.

Epidemiology

- Almost all children are asymptomatic carriers of one or more strains of *E. coli* in the GI tract. *Proteus* is also a common GI commensal.
- For species that are commoner in hospitalized patients, antibiotic exposure, the duration of hospitalization, invasive medical procedures, and serious underlying disease are important risk factors.
- *Salmonella enterica* subspecies *typhi* and *paratyphi* and *Shigella* spp. are human pathogens. Other GI pathogens, including other salmonellae and *E. coli* O157, are also frequently carried by animals.

Transmission and incubation period

- Outside the neonatal period, most *E. coli* infections are endogenous, although person-to-person spread can also occur, especially in hospitals. Early-onset neonatal *E. coli* infections are acquired via mother-to-infant transmission.
- Without control measures, all *Enterobacteriaceae* can readily spread in hospitals by direct or indirect person-to-person transmission; the hands of health-care workers are an especially important route of spread (e.g. *Klebsiella*).

- GI pathogens may be spread directly from person to person or animal to person via the faecal–oral route, or indirectly via contaminated food or water.
- Incubation periods vary according to the type of infection, the size of inoculum, and the route of entry into the body—typically 1–5 days for exogenous infections.

Clinical features and sequelae

Infections in vulnerable patients can occur at almost any anatomical site.

- *UTI*:
  - *E. coli* and *Proteus* are the commonest causes of UTI.
  - Other species also cause UTI, especially in children with recurrent infections, urinary tract abnormalities, or who are catheterized.
- *GI infections*:
  - Strains of *E. coli* that are are enteropathogens include:
    —Enteropathogenic *E. coli*—causes diarrhoea in infants
    —Enteroinvasive *E. coli*—causes dysenteric illness
    —Verotoxin-producing *E. coli*—causes diarrhoea (often bloody). Sequelae include HUS
    —Enterotoxigenic *E. coli*—causes traveller's diarrhoea
  - *Shigella sonnei* accounts for most cases of shigellosis in industrialized countries—usually mild and self-limiting (other *Shigella* spp. cause more serious illness). Complications include convulsions and changes in mental status (usually self-limiting)
  - Non-typhoidal serovars of *S. enterica* are the second commonest cause of bacterial gastroenteritis (after *Campylobacter*); complications include bacteraemia (infants and the immunocompromised are at increased risk); prolonged convalescent excretion of *Salmonella*
  - *S. enterica* subspecies *typhi* and *paratyphi* cause a systemic infection (enteric fever), often with little or no GI upset
  - Any *Enterobacteriaceae* colonizing the GI tract can be opportunistic pathogens in intra-abdominal infections, e.g. appendicitis, intra-abdominal abscesses.
- *Meningitis*:
  - Meningitis caused by *Enterobacteriaceae* has a poor prognosis
  - *E. coli* is second only to GBS as a cause of neonatal meningitis; *Serratia* is an important cause of nosocomial meningitis on NNUs
  - Rare outside infancy, except post-neurosurgery (especially shunt-associated meningitis).
- *Respiratory tract infections*:
  - Most important as a cause of ventilator-associated pneumonia.
- *Intravascular device-related infections*.
- *BSI*.
  - *Enterobacteriaceae* are the commonest causes of Gram-negative septicaemia:
    —May be 2° to a local focus of infection
    —1° septicaemia occurs in patients who are neutropenic; the GI tract is presumably the source of infection.

Diagnosis

- Culture of samples from the suspected site of infection is the mainstay of diagnosis of these infections.
- Microscopy of some samples (urine, CSF, blood cultures) can give an early indication of Gram-negative infection—useful in guiding antibiotic treatment.

Management and treatment

- β-lactam antibiotics are a mainstay of treatment. However β-lactamase production is common; different species produce different types of β-lactamase.
  - *E. coli* and *Klebsiella* typically produce plasmid- or chromosome-encoded β-lactamases that confer resistance to amoxicillin, but co-amoxiclav and cephalosporins remain active.
  - *Enterobacter* and *Serratia* produce chromosomally mediated cephalosporinases (AmpC) that confer resistance to cephalosporins and co-amoxiclav, as well as amoxicillin. Production of these enzymes may be induced by exposure to β-lactams; therefore, isolates that appear sensitive on initial testing may become resistant during treatment.
  - ESBL are seen increasingly often in both community-acquired and hospital-acquired *Enterobacteriaceae*, especially *E. coli* and *Klebsiella*. These plasmid-encoded enzymes confer resistance to penicillins and cephalosporins, and often coincide with resistance to other antibiotic classes, including aminoglycosides and fluoroquinolones.
  - Carbapenems are the β-lactamase class that has the most reliable activity against *Enterobacteriaceae*, but carbapenemase-producing strains are now spreading rapidly; treatment options for these strains are limited to a few toxic antibiotics, e.g. polymyxin.
- Trimethoprim and nitrofurantoin remain useful for UTIs, although *Proteus* spp. are always resistant to nitrofurantoin.
- Fluoroquinolones are used mainly to treat strains that are resistant to commonly used antibiotics. No longer recommended as first-line treatment for infections with *S. enterica* subspecies *Typhi* and *Paratyphi*, because of antibiotic resistance.
- For more serious infections, aminoglycosides may be used, often in combination with a β-lactam antibiotic.
- Fluoroquinolones (e.g. ciprofloxacin) are also useful, especially for treating GI infections and infections with MDR *Enterobacteriaceae*; however, increasing resistance is threatening their usefulness.

Prevention

- Prevention of transmission of *Enterobacteriaceae* in hospitals:
  - General hygiene
  - Care of invasive medical devices, e.g. intravascular devices, endotracheal tubes
  - Antibiotic stewardship
  - Isolation of patients in high-risk situations (e.g. *Serratia* on NNUs, MDR strains, GI pathogens).

- Prevention of GI infections in the community:
  - General hygiene, food hygiene
  - Care during contact with animals, e.g. animal petting farms
  - Exclusion of symptomatic children from school or nursery.

Non-fermentative Gram-negative bacteria

Epidemiology

- Opportunistic human pathogens, especially in hospitalized patients. Important risk factors for infection include:
  - Antibiotic exposure
  - Intensive and high dependency care
  - Cystic fibrosis, neutropenia, burns.
- Hospital outbreaks can occur, especially on NICUs and PICUs.
- Some species, e.g. *P. aeruginosa* and Bcc, are important pathogens in cystic fibrosis outside hospital.

Transmission

- Direct or indirect person-to-person transmission in hospitals.
- Bacteria also found in the hospital environment, especially moist settings (e.g. taps, sinks, ventilator equipment); *Acinetobacter* also found in dust.
- Routes of acquisition of bacteria outside hospital poorly understood.

Clinical features and sequelae

Infections in vulnerable patients can occur at almost any anatomical site.

- *UTI*:
  - Especially in children with recurrent infections, urinary tract abnormalities, or who are catheterized.
- *Respiratory tract infections*:
  - Ventilator-associated pneumonia
  - Lower respiratory tract colonization and infection in cystic fibrosis and bronchiectasis.
- *Skin and soft tissue infections*:
  - Infections with *P. aeruginosa* range from mild folliculitis to serious infections such as cellulitis, malignant otitis externa:
    - —Infections in the presence of neutropenia can be fulminant or intractable
  - Important pathogens in patients with non-surgical wounds, especially burns (especially *P. aeruginosa, Acinetobacter*).
- *Intravascular device-related infections*.
- *Septicaemia*:
  - May be 2° to a local focus of infection (e.g. urinary tract)
  - 1° septicaemia occurs in preterm, patients with neutropenia
  - *P. aeruginosa* is particularly serious, with a high mortality rate.

Diagnosis

- Culture of samples from the suspected site of infection is the mainstay of diagnosis of these infections.

Management and treatment

- All of these bacteria are usually resistant to commonly used antibiotics.
  - *P. aeruginosa* is usually sensitive to:
    - —Some third-generation cephalosporins (e.g. ceftazidime) or anti-pseudomonal penicillins (piperacillin, ticarcillin)
    - —Aminoglycosides: tobramycin more active than gentamicin *in vitro*, and often preferred for cystic fibrosis treatment
    - —Carbapenems (meropenem, imipenem, doripenem, but not ertapenem)
    - —Fluoroquinolones (e.g. ciprofloxacin)
    - —Polymyxins
    - —Resistance to all of these agents may occur—commonest with carbapenems and fluoroquinolones.
  - Antibiotic sensitivities of *Acinetobacter* spp. are unpredictable—pathogenic strains often MDR. Carbapenems are the most reliable antibiotics.
  - *S. maltophilia* is highly antibiotic-resistant. Strains may appear sensitive to anti-pseudomonal antibiotics *in vitro*, but clinical response to these agents usually poor—co-trimoxazole is the most reliable antibiotic.
  - Bcc also MDR—combinations of two or more agents generally used, based on results of sensitivity testing.

Prevention

- General hygiene, care of invasive medical devices, e.g. intravascular devices, endotracheal tubes.
- Antibiotic stewardship.
- Isolation of patients in high-risk situations (e.g. NICUs, PICUs, cystic fibrosis clinics).

Future research

The rapid emergence and spread of MDR Gram-negative bacteria means that the control and treatment of these infections is a major priority.

There is a need to better understand the epidemiology of these bacteria and the relationship between the genotype and clinical phenotype, and a need to establish clinically and cost-effective methods of control.

Increasing antibiotic resistance makes the development of new antibiotics a major priority.

The relationship between colonization and invasive disease needs further study, especially in NICUs. In particular, is it always necessary to use carbapenems as empiric treatment for suspected infections in children colonized with MDR Gram-negative bacteria?

Serious Gram-negative bacterial infections are still associated with high rates of mortality and morbidity; further research into the management of these conditions is required.

What's new?

- MDR Gram-negative bacteria, especially ESBL producers, have become increasingly common as hospital- and community-acquired pathogens across Europe.
- Of particular concern, the past 5 years has seen the global spread of carbapenemase-producing Gram-negative bacteria that are resistant to all, or almost all, commonly used antibiotics.

What's next?

- Increasingly stringent infection control guidance is being produced to try to prevent MDR Gram-negative bacteria from becoming entrenched in European hospitals.
- Studies are underway to establish the optimal duration of antibiotic treatment for serious Gram-negative infections.

Further reading

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Chapter 29

Refugees and internationally adopted children

See also Chapters 19, 42, 75, 76, 106, 112.

Introduction

Child migration is an important international issue. The pattern of migration varies from country to country and year to year, and so appropriate resources will vary. Recently there has been a large upsurge in migrants to Europe from North Africa.

Children may arrive in Europe from abroad for short-term stays on holiday or visiting relatives. These children will not usually come in contact with health services, unless they become acutely unwell. This is covered in other chapters. On the other hand, there are children who come here intending to stay long-term. Some already have European citizenship, and data on how many children this includes are not readily available. There are also those who are seeking asylum or are being adopted ('inter-country adoption'). It is these two groups who are the subjects of this chapter.

Epidemiology

It is difficult to obtain accurate figures for asylum-seeking children. In 2008, 4285 unaccompanied asylum-seeking children (UASC) aged ≤17 years applied for asylum in the UK. This fell to 1168 in 2012, of whom 50% were 16 or 17 years old and <8% were under 14. Over 80% were ♂. In the 28 EU countries, in 2012, the greatest number of UASC were received by Sweden (3580), followed by Germany (2095) and Austria (1375). The country of origin varies from year to year and by destination. In the UK, in 2007:

- Thirty-two per cent (1135) were from Afghanistan, 26% (900) from sub-Saharan Africa (mainly Somalia and Eritrea), 21% (735) from the Middle East and North Africa, 9% (315) from China, 8% (295) from the Indian subcontinent, and 2% (80) from Europe (mainly Eastern Europe)
- A further 3825 children were dependents of asylum seekers. These children tended to be younger (46% <5 years old and only 9% 15–17), and the distribution of countries of origin was different—39% (1500) were from sub-Saharan Africa, 22% (825) from the Indian subcontinent, 15% (570) from the Middle East and North Africa, 6% (240) from Europe, and 3% (125) from China
- In 2012, the number of dependent children was little changed at 4128, of whom 53% were ♂

- Worldwide, the pattern of international adoptions rose to a peak in 2004, since when it has fallen. Per head of population, the UK has one of the lowest rates of inter-country adoption of all industrialized nations, with Scandinavian countries having the highest. In 2008, the Department for Children, Families, and Schools in England received 2232 applications for inter-country adoption: 41% (920) from China, 11% (252) from Russia, 9% (202) from India, 8% (170) from Guatemala, 6% (123) from the US, and 5% (116) from Thailand
- In addition, there are an unknown number of undocumented children.

In 2013, in the US, of 7094 adoptions, 2036 children (29%) were from China, 993 (14%) from Ethiopia, 438 (6%) from Ukraine, 388 (6%) from Haiti, 313(4%) from Democratic Republic of the Congo, and 276 (4%) from Uganda.

All these groups of children are scattered throughout the country, in private homes, foster care, detention centres, etc. In 2009, the House of Commons Home Affairs Committee was told that 'Nearly 1000 children a year are detained in UK Border Authority's immigration detention centres. On average, children spend over a fortnight in detention. Detention for up to 61 days is not uncommon. On 30 June 2009, 10 of the 35 children in detention had been held for between 29 days and 61 days.' In 2012, the total number of children detained was 240.

The majority of these children come from countries where the health-care systems are very different, as is the spectrum of endemic infectious illnesses. Many of the children will not have received the basic preventative health measures in their country of origin and may be harbouring unrecognized infectious diseases.

In terms of health care related to infectious diseases, there are three issues:

- Screening for current infection
- Prevention of future infection
- Protection of carers and household members.

Arrangements should be made for all children to sign on with a GP. Children for adoption should have an inter-country adoption form (ICAF), or something similar, completed. Unfortunately, documentation relating to potential adoptees from abroad may be inaccurate, or even fraudulent. Unless the source is known and can be trusted, it may be best to ignore the information and not let it influence management in relation to infection and immunization.

Screening for current infection

Many of the countries from which the children arrive have a relatively high prevalence of infectious diseases; however, there are few data on infectious diseases in child immigrants in the UK. Most originate from the US, with some also coming from mainland Europe.

In a US study of children adopted from China in the early/mid 1990s:

- Nine of 242 (4%) were positive for hepatitis B surface antigen
- None of those tested were HIV-positive

- Twenty-one of 184 (11%) had parasites in their stools—*Giardia* in 13; *Ascaris* in five; *Dientamoeba* in one; and one child had both *Giardia* and *Ascaris*
- Of stool cultures from 86 children, four were positive for *Salmonella*, two for *Campylobacter*, two for both *Salmonella* and *Campylobacter*, and one for *C. difficile*
- Six of 164 (4%) had a positive Mantoux test, but none had symptoms, and all had normal CXRs.

Although the exact proportions vary, this is a common pattern.

There are some data suggesting that children with latent TB have an increased risk of developing clinical disease on moving to temperate climates. It is therefore important to determine whether the child has latent TB and treat accordingly.

The British Association for Adoption and Fostering (BAAF) has made recommendations in 'Health Screening of Children Adopted from Abroad'.[1] These could equally well be applied to refugees, except that, where refugees are accompanied by parents/relatives, more information may be available, allowing one to reduce the number of investigations. Table 29.1 is based on BAAF recommendations. It only applies to asymptomatic children. The recommendations are very similar to those of American Academy of Pediatrics (AAP), except that AAP recommends screening all adoptees for hepatitis B, hepatitis C, and HIV. As it is often difficult to assess the risk in these circumstances, it is probably better to screen, unless there is good reason not to.

Prevention of future infection

- A full immunization history should be taken, and any records consulted.
- Where immunizations that are part of the local schedule have been omitted, they should be given, in line with the standard protocol.
- When there is doubt as to whether a vaccine has been given, it should be assumed not to have been given, and the schedule completed accordingly. Guidance is available on country-specific sites, e.g. PHE (🔗 <https://www.gov.uk/government/publications/vaccination-of-individuals-with-uncertain-or-incomplete-immunisation-status>).
- If BCG vaccine has not been given, depending on the country of origin of the child, it may need to be given after a Mantoux test has been administered.
- If the child is to travel back to the country of origin, the appropriate immunizations should be given. Other advice, e.g. about antimalarial medication and other precautions, should be given.

Table 29.1 Screening for infection in international adoptees or asylum seekers

Condition	Investigation	When to do	Comments
TB (if >3 months old)	Mantoux test	On arrival—if negative and malnourished, repeat in 6 months	A positive result may be difficult to interpret, if BCG has been given previously
Hepatitis B	Hepatitis B surface antigen	On arrival and routinely after 3 months[a] for all children with an increased risk of horizontal or vertical transmission or from endemic areas	If present, indicates ongoing infection, which may be acute or chronic. If persists for 6 months, is likely to indicate chronic carriage Susceptible household contacts should be immunized[b]
	Hepatitis B core antibody		If present, indicates past or present infection, depending on the presence of hepatitis B surface antigen
	Hepatitis B surface antibody		If present, may be due to past infection or immunization. In the latter case, hepatitis B core antibody is absent
Hepatitis C	Hepatitis C antibody	On arrival and routinely after 3 months[a] for all children with an increased risk of horizontal or vertical transmission or from endemic areas	If present, indicates past or present infection. Further investigation is required
HIV	HIV 1 and 2	On arrival and routinely after 3 months[a] for all children with an increased risk of horizontal or vertical transmission or from endemic areas	If the child is <18 months, a positive antibody test may be due to transmission of maternal antibodies, rather than infection.
Syphilis	VDRL	On arrival	
GI infections and infestations	Stool for ova, parasites, and cysts Stool culture if symptomatic	On arrival	Children may carry parasites without any obvious symptoms and signs. Any parasites found should be appropriately treated

[a] Seroconversion may occur after arrival in the UK, and therefore these tests should be repeated after an interval of 3 months.

[b] Transmission has been recorded within households, even in the absence of obvious risk factors.

Protection of carers and household members

- All routine immunizations, including routine boosters, should be up-to-date. Measles, mumps, and rubella have been transmitted to adopters in the US by children incubating infection on arrival in the country.
- If adopting or caring for a child who is at high risk of hepatitis B, all household contacts should be immunized, unless the child is reliably known not to be hepatitis B surface antigen-positive.

The recommendations relate only to infection. All children moving into a country from abroad need a much broader assessment. This should include a full medical history, including checking which screening tests have been done, and an assessment of their broad physical and emotional well-being.

Future research

There is very little literature on the rates of infections and health outcomes of children migrating to Europe.

Key reference

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Chapter 30

The unwell child returning from abroad

See also Chapters 33, 34, 41, 49, 54, 61, 67, 84, 103, 113, 114, 115, 116.

Introduction

The number of families travelling abroad with their children has increased, exposing them to infections they would not normally encounter at home. The reason why most children travel to the tropics is to visit friends and relatives in their parents' country of origin. Often this means:

- They are less likely to seek pre-travel advice or take preventive measures
- They travel to rural areas for longer periods and have an increased risk of infections such as malaria, traveller's diarrhoea, enteric fever (typhoid or paratyphoid), and hepatitis A
- They may delay seeking medical help when they return to their country of residence because of cultural and language barriers.[1]

Children have a 3-fold increased risk of illness when they travel abroad.[2] Sixty per cent of children have an episode of illness during or after travel to the tropics, despite taking preventive measures:[3]

- Common complaints are diarrhoea, insect bites, and fever
- Many episodes of illness occur during the overseas visit, rather than after return (median onset 7 days from start of the visit). However, children may have returned from abroad within the incubation period of many infections
- Fifty-two per cent of children are given medication because of these episodes, but only 19% seek medical attention
- Although children are infrequent travellers to the tropics, those who do travel have an increased risk of infection, compared with adults, especially for malaria, traveller's diarrhoea, and hepatitis A.

It is essential to take a travel history in all children presenting with fever. In febrile children who have recently travelled to the tropics, common infections (such as infectious mononucleosis or respiratory tract infections) are as common as tropical infections.

Children who present with fever after travel to the tropics need assessment for both common and tropical infections, especially malaria.

Common conditions

The commonest reasons for seeking medical advice in returned travellers are fever, diarrhoea, respiratory tract illness, and skin lesions.

Fever

Causes of fever in children returning from abroad include malaria, and viral and non-specific illnesses. One-third of these children are admitted to hospital.

- The commonest tropical infections in children admitted to hospital with fever after travel to the tropics are malaria, diarrhoea, hepatitis, and typhoid (Table 30.1).
- The usual European infections are as common as tropical infections.
- Antibiotic-resistant bacteria are more frequent in some countries and need to be considered. These include:
  - Community-acquired MRSA in the US
  - Penicillin-resistant Pneumococcus in Spain, Greece, and the US
  - Carbapenem-resistant Enterobacteraciae in India/Pakistan/Asia
  - Quinolone-resistant *Salmonella typhi* in India or Pakistan.

Table 30.1 Causes of fever in 229 children admitted to hospital after returning from the tropics (some children had >1 infection)[4]

Tropical		Universal		Other	
Malaria		Respiratory infection		Acute leukaemia	1
Vivax	30	Lower	27		
Falciparum	9	Upper	12		
Diarrhoea		UTI	7	Systemic lupus	1
Traveller's[a]	21				
Bacterial	22				
Giardiasis	6				
Cryptosporidiosis	3				
Hepatitis	15	Cellulitis/ lymphadenitis	6	Kawasaki disease	1
Typhoid	8	Viral gastroenteritis	4	No diagnosis	69
Dengue	2	Meningococcal disease	2		
Pulmonary TB	2	Measles	1		
Rickettsial infection	1				

[a] Culture-negative diarrhoea, beginning during travel.

Source data from Riordan FA. Fever in the returned paediatric traveller. *Adv Exp Med Biol* 2009;**634**:217–30.

Diarrhoea

- Traveller's diarrhoea is one of the commonest illnesses to affect people who travel to the tropics or subtropics. Young children have the highest risk of traveller's diarrhoea. The clinical course in infants may be severe and protracted, and very rarely some develop a severe enteropathy, needing parenteral nutrition.
- Children admitted to hospital with traveller's diarrhoea are usually older and more likely to have bacterial and protozoal infections than local children admitted with gastroenteritis, who commonly have a viral infection.
- The organisms found in the stools of children with traveller's diarrhoea include *Campylobacter, Shigella, Salmonella* spp., enteropathogenic *E. coli*, and *Cryptosporidium parvum*.
- Children who have been to resource-poor countries may return with intestinal parasites which can cause asymptomatic infections (such as helminths, *Giardia*, or *Entamoeba*).

Respiratory illness

Respiratory tract infections are common in children returning from abroad (Table 30.1), but pulmonary TB always needs to be considered as a cause.

Skin lesions

These can be discrete lesions (e.g. infected insect or animal bites (common), cutaneous larva migrans, and cutaneous leishmaniasis (rare)) or generalized rashes (dengue, measles).

Immigration

Recent immigrants may have special health needs, including children adopted from other countries. Infections to consider include hepatitis B and C, syphilis, HIV infection, TB, and intestinal parasites.

Routine immunizations

Many children born abroad are likely to have received the following vaccines: BCG, diphtheria/polio/tetanus (DPT), oral polio, hepatitis B, and measles in the first year of life. Hib vaccine is now available in an increasing number of resource-poor countries. Overseas children are unlikely to have received MMR, pneumococcal, meningococcal, or HPV vaccines.

Children arriving from areas experiencing long-term conflict may not have been immunized and are thus at risk of vaccine-preventable disease such as measles or diphtheria.

Epidemiology

In recent years, an increase in international migration has resulted in more people living in countries where they were not born, but who may return to their country of origin at intervals.

In the UK, between 2000 and 2010, the number of visits abroad to see friends and relatives increased by 45%, compared to an overall decrease of 0.5%, for all reasons for travel.[5]

Imported infections were responsible for 1.3% of admissions to a paediatric ward.[6] However, deaths from imported infections are rare in children (0.15% for imported malaria).

In travellers returning from abroad, the likely infections vary with the area visited. Malaria is one of the commonest causes of fever among travellers returning from any region worldwide, especially Africa, whereas enteric fever is seen mostly in travellers returning from South Asia (Table 30.2). Children account for 15–20% of imported malaria, and 25–33% of imported enteric fever (typhoid and paratyphoid infection).

Table 30.2 Common causes of febrile illness in travellers returning from developing countries by region visited[6,7]

Region	Illness
Caribbean	Dengue, infectious mononucleosis, enteric fever
Central/South America	Dengue, malaria, infectious mononucleosis
Sub-Saharan Africa	Malaria, rickettsial infection
South Asia	Dengue, enteric fever, malaria
Middle East/North Africa	Diarrhoea

Source data from Hagmann S, Neugebauer R, Schwartz E, Perret C, Castelli F, Barnett ED, Stauffer WM; GeoSentinel Surveillance Network. Illness in children after international travel: analysis from the GeoSentinel Surveillance Network. *Pediatrics*. 2010;**125**:e1072–e1080 and Freedman DO, Weld LH, Kozarsky PE, *et al*., GeoSentinel Surveillance Network. Spectrum of disease and relation to place of exposure among ill returned travelers. *N Engl J Med*. 2006;**354**:119–30.

Clinical presentation and differential diagnosis

The differential diagnosis should take into account a detailed travel history that includes:

- Exact cities, country, and regions visited (including visits to rural areas)
- Common diseases in the region at this time
- Traveller's activities while away
- Vaccines, antimalarials, and other preventive measures taken.

Many common bacterial and viral infections have short incubation periods and will have their onset either abroad or within the first 3 weeks of return.

Diseases with longer incubation periods, such as giardiasis, viral hepatitis, *Plasmodium vivax* malaria, and TB, can present weeks to months later.

Examination

Fever

Children with imported infections often present with non-specific symptoms (fever, lethargy, malaise). The pattern of fever is unreliable for predicting imported malaria in children, as the 'classic' pattern occurs in less than a quarter of cases. Most children have no clinical focus of infection.

Hepatosplenomegaly

- The most helpful clinical findings are hepatomegaly, splenomegaly, and jaundice in children with malaria, hepatitis, and enteric fever.
- Splenomegaly is found in fewer than half of children with imported malaria.
- The combination of jaundice and fever is uncommon in young children with acute viral hepatitis. Children with this combination should be investigated to exclude malaria, enteric fever, infectious mononucleosis, or leptospirosis.

Diarrhoea

Although diarrhoea affects many people who travel to the tropics, other infections, such as malaria, enteric fever, or pneumonia, can also present with fever and diarrhoea, and these should always be considered.

Rash

Skin problems may present as discrete lesions or a generalized rash.

Causes of discrete skin lesions include:

- Infected insect bites (often due to *S. aureus* infection)
- Cutaneous larva migrans
- Cutaneous leishmaniasis

Causes of a generalized rash include:

- Maculopapular rash—measles, dengue
- Non-blanching rash—meningococcal disease or rickettsial infection.

Children with rickettsial infection may have an eschar (black scab) at the site of the infecting tick bite.

Investigations

Almost 50% of febrile children presenting to hospital after returning from the tropics have a treatable condition, and the most important is malaria. Children can die of untreated malaria.

The majority of diagnoses requiring treatment can be made, using simple investigations:

- Stool microscopy and culture
- Blood film for malaria
- CXR
- Blood culture.

Children presenting with fever should be investigated, as described in the NICE guideline *Feverish illness in children: assessment and initial management in children younger than 5 years* (<http://www.nice.org.uk/CG160>).

Febrile children who have travelled abroad in the preceding year should have the following investigations:

- FBC
- Blood film for malarial parasites
- Stool culture
- CXR.

For children who have travelled in the preceding month, a blood culture should also be taken (to look for enteric fever). Other investigations should be done, as clinically indicated (e.g. LFTs).

All children presenting with fever who have travelled to a malarious area in the past 12 months should be investigated for malaria.

- The diagnosis of malaria is made by examination of thick and thin blood films, or now more commonly an antigen test. Thick blood films are more sensitive, whereas thin films help to confirm the malaria species.
- Children with suspected malaria, who have a negative blood film/antigen tests, should have at least two repeat blood films, since the initial blood film may be negative in up to 7% of cases.

Thrombocytopenia is often present in children with malaria. A platelet count above 190×10^9/L had an NPV of 97% for malaria versus all other causes of fever.[8] WCC and CRP are generally unhelpful, although these may be raised in malaria.

A markedly raised eosinophil count may indicate an invasive helminth infection or schistosomiasis. An elevated eosinophil count often may indicate an asymptomatic helminth infection—think worms!

Management and treatment

Management and treatment depend on the differential diagnosis of the cause(s) of fever. If a child remains febrile, but no diagnosis has been made, it may be worth:

- Repeating initial investigations (blood film for malaria, CXR, blood culture, LFTs)
- Checking serology for other infections (hepatitis, dengue, *Rickettsia*, EBV)
- Looking for non-infectious causes of fever (connective tissue disorder, Kawasaki disease, malignancy)
- Discussing the case with a paediatric infection specialist.

The treatment of specific infections is described elsewhere in the manual (e.g. malaria, hepatitis, enteric fever, and TB) (see Chapters 18, 84, 112, and 113).

Traveller's diarrhoea

- Traveller's diarrhoea in children is often different from other forms of gastroenteritis.
- It is more likely to be due to bacterial and protozoal infections than viral infections. Traveller's diarrhoea is usually self-limiting; however, antibiotic treatment (depending on the causative organism) may be needed.

Follow-up and outcome

Follow-up and outcome depend on which infection(s) are the cause(s) of fever. Most children recover well with timely, appropriate treatment.

Children travelling to the tropics often do not take preventive measures. This consultation may be a good opportunity to stress the need for malaria prophylaxis and travel vaccines for future visits. Only 3–15% of children with imported malaria had taken malaria prophylaxis, and few children with imported infections have received pre-travel vaccinations. Of children in the UK with malaria, 26% have previously been diagnosed with malaria, suggesting missed opportunities to educate families on malaria prevention.

Future research

- Studies of methods to improve uptake of malaria prophylaxis and travel vaccines.
- Improved surveillance of travel-associated infections to help identify at-risk groups and assess the effectiveness of public health interventions.

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Chapter 31

Sepsis syndrome

See also Chapters 39, 70, 82, 86, 104, 105.

Introduction

- Infections remain a major cause of childhood mortality and morbidity throughout the world. Although most infections are of viral origin and self-limiting, a minority are bacterial, some of these leading to sepsis syndrome. Adverse outcomes are often mediated via septic shock. Most children who develop septic shock present first with fever, although some, especially in the first weeks of life, may become hypothermic.
- Differentiating between self-limiting illnesses and potentially life-threatening bacterial infections is a diagnostic challenge; rapid evolution of the clinical picture further complicates the problems of assessment and diagnosis, especially in younger children.
- Clinicians perceive a need to improve recognition of the causes of fever in order to offer early treatment to those with evolving sepsis.
- Some children with fever have symptoms and signs suggesting a serious infection, such as the non-blanching rash of meningococcal septicaemia, thus facilitating early treatment. Many children have a fever without an apparent source.

Terminology and definitions

Sepsis in children is defined as *systemic inflammatory response syndrome* (SIRS) in the presence of, or as a result of, a suspected or proven *infection*.

SIRS is defined as the presence of at least two of four criteria, one of which must be abnormal temperature or leucocyte count (Box 31.1 and Table 31.1).

Infection is defined as a suspected or proven infection caused by any pathogen *or* a clinical syndrome associated with a high probability of infection (Box 31.1). Evidence of infection includes positive findings on clinical exam, imaging, or laboratory tests (e.g. WBCs in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or purpuric rash, or purpura fulminans).

Severe sepsis is defined as sepsis plus one of the following: cardiovascular organ dysfunction *or* ARDS, *or* two or more other organ dysfunctions (Box 31.2).

Septic shock is defined as sepsis and cardiovascular organ dysfunction (Box 31.2).

Box 31.1 Definitions of systemic inflammatory response syndrome

SIRS

The presence of at least two of the following four criteria, one of which must be abnormal temperature or leucocyte count:

- Core temperature of >38.5°C or <36°C
- Tachycardia, defined as a mean heart rate >2 standard deviations (SD) above the normal for age in the absence of an external stimulus, chronic drugs, or painful stimuli; or otherwise an unexplained, persistent elevation over a 0.5- to 4-hour time period; or for children <1 year old—bradycardia, defined as a mean heart rate <10th percentile for age in the absence of an external vagal stimulus, β-blocker drugs, or CHD; or otherwise unexplained persistent depression over a 0.5-hour time period
- Mean respiratory rate >2 SD above the normal for age or mechanical ventilation for an acute process not related to an underlying neuromuscular disease or the receipt of general anaesthesia
- Leucocyte count elevated or depressed for age (not 2° to chemotherapy-induced leucopenia) or >10% immature neutrophils.

Brahm Goldstein, Brett Giroir, Adrienne Randolph, *et al*., International paediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in paediatrics, Paediatric Critical Care Medicine, Vol 6, No 1.[1]

Table 31.1 Age-specific vital signs and laboratory variables

Age group	Heart rate (beats/min)		Respiratory rate (breaths/min)	Leucocyte count (× 10^3/mm^3)	Systolic BP (mmHg)
	Tachycardia	Bradycardia			
0 days to 1 wk	>180	<100	>50	>34	<65
1 wk to 1 mo	>180	<100	>40	>19.5 or <5	<75
1 mo to 1 yr	>180	<90	>34	>17.5 or <5	<100
2–5 yr	>140	NA	>22	>15.5 or <6	<94
6–12 yr	>130	NA	>18	>13.5 or <4.5	<105
13 to >18 yr	>110	NA	>14	>11 or <4.5	<117

BP, blood pressure; mo, month; NA, not applicable; wk week; yr, year.

Lower values for heart rate, leucocyte count, and systolic BP are for the 5th, and upper values for heart rate, respiration rate, or leucocyte count for the 95th, percentile.

Brahm Goldstein, Brett Giroir, Adrienne Randolph, *et al*., International paediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in paediatrics, Paediatric Critical Care Medicine, Vol 6, No 1.[1]

Box 31.2 Organ dysfunction criteria

Cardiovascular

Despite the administration of an isotonic IV fluid bolus ≥40mL/kg in 1 hour:

- Decrease in BP (hypotension) <5th centile for age or systolic BP >2 SD below normal for age[a]

OR

- Need for vasoactive drug to maintain BP in normal range (dopamine >5 micrograms/kg/min or dobutamine, adrenaline, or noradrenaline at any dose)

OR

- Two of the following:
  - Unexplained metabolic acidosis: base deficit >5.0mmol/L
  - Increased arterial lactate >2 times the upper limit of normal
  - Oliguria: urine output <0.5mL/kg/hour
  - Prolonged capillary refill >5 seconds
  - Core to peripheral temperature gap >3°C

Respiratory[b]

- PaO_2/FiO_2 <300 in the absence of cyanotic heart disease or pre-existing lung disease

OR

- $PaCO_2$ >65mmHg or >20mmHg over baseline $PaCO_2$

OR

- Proven need[c] or >50% FiO_2 to maintain saturation >92%

OR

- Need for non-elective invasive or non-invasive mechanical ventilation[d]

Neurological

- Glasgow coma score (GCS) <11

OR

- Acute change in mental status with a decrease in GCS score ≥3 points from abnormal baseline

Haematological

- Platelet count $<80 \times 10^9$/L or a decline of 50% in the platelet count from the highest value recorded over the past 3 days (for chronic haematology/oncology patients)

OR

- International normalized ratio (INR) >2

Renal

- Serum creatinine ≥2 times the upper limit of normal for age or 2-fold increase in baseline creatinine

(*Continued*)

Box 31.2 (*Contd.*)

Hepatic

- Total bilirubin ≥40mg/L (not applicable for newborn)

OR

- ALT two times the upper limit of normal for age

[a] See Box 31.1.

[b] ARDS must include a PaO_2/FiO_2 ratio ≤200mmHg, bilateral infiltrates, acute onset, and no evidence of left heart failure. Acute lung injury is defined identically, except the PaO_2/FiO_2 ratio must be ≤300mmHg.

[c] Proven need assumes oxygen requirement was tested by decreasing flow, with subsequent increase in flow, if required.

[d] In post-operative patients, this requirement can be met if the patient has developed an acute inflammatory or infectious process in the lungs which prevents extubation.Brahm Goldstein, Brett Giroir, Adrienne Randolph, *et al*., International paediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in paediatrics, Paediatric Critical Care Medicine, Vol 6, No 1.[1]

Causative organisms

Organisms responsible for sepsis syndrome in infants and children include *N. meningitidis* (commonest), *E. coli*, *Klebsiella* spp., *Salmonella*, Hib, and other Gram–negative bacteria. *S. pneumoniae* and *S. aureus* are the most frequent Gram-positive pathogens. GBS, *E. coli*, and *L. monocytogenes* are the commonest bacterial causes of sepsis syndrome <3 months of age. Occasional cases are caused by viruses.

Immunosuppressed patients may develop septicaemia due to unusual and opportunistic organisms, though Gram-negative bacteria cause most mortality. Surgical patients usually develop sepsis due to enteric organisms.

Epidemiology

Up to 1% of children aged 0–5 years have a serious bacterial illness, such as meningitis, septicaemia, UTI, or pneumonia, each year. The incidence of sepsis in this age group is around 10–20 per 100 000.

The epidemiology of sepsis has been radically altered by immunization programmes. In the UK, immunization against Hib (1992), serogroup C *N. meningitidis* (1999), and *S. pneumoniae* (2006) all resulted in a dramatic drop in incidence of sepsis caused by these organisms. A four-component serogroup B *N. meningitidis* vaccine has recently been licensed for use in the EU.

Pathophysiology of sepsis

- Rapid bacterial multiplication produces bacterial toxins in the bloodstream. Sepsis is the clinical expression of the host's response to the recognition of pathogen-associated molecular patterns (PAMPs),

among which constituents of the cell wall of Gram-negative bacteria (endotoxins) and exotoxins of Gram-positive organisms, by pattern recognition receptors (PRRs) of the innate immune system. PRRs can also recognize endogenous danger signals, termed alarmins or DAMPs (danger-associated molecular patterns), which are released during inflammatory stress (e.g. burns, trauma, and tissue necrosis), leading to SIRS. Infection results in activation of macrophages that produce the lymphokines γ-IFN and GM-CSF, TNF, and ILs, especially IL-1 and IL-6. These substances normally benefit the host by mediating protective inflammatory responses, but, in severe infection, an exaggerated, harmful response occurs, and high levels of TNF and IL-1 lead to serious damage.

- Other inflammatory mediators, such as prostaglandin E2 (PGE2) released by neutrophils, nitric acid released by macrophages, and platelet-activating factor, lead to endothelial cell damage which results in leakage of plasma from the circulation.
- Meanwhile, abnormal activation of clotting can lead to DIC. The convergence of these pathways precipitates multiple organ failure and death.
- Moreover, the host response to sepsis involves a state of immune suppression, the so-called compensatory anti-inflammatory response syndrome (CARS) which is characterized by the induction of several anti-inflammatory mechanisms. This syndrome leads to enhanced susceptibility for 2° infections and late mortality.

Clinical presentation and differential diagnosis

Early diagnosis of sepsis syndrome depends on thorough assessment of the ill child. In the seriously ill, child history and examination proceed simultaneously. Diagnostic clues, such as a spreading non-blanching rash, may be the reason for presentation.

- Immediately life-threatening features, including compromise of airway, breathing, or circulation, and decreased level of consciousness or confusion (often difficult to assess in a young child), should be sought.
- Full clinical assessment includes observations of temperature (ideally peripheral and central), pulse rate, capillary refill, respiration rate and pattern, BP, skin turgor and status of mucous membranes, mental status, conscious level, and urine output. Body weight and height should be measured or estimated. Recent travel abroad should be elicited.
- Early features of sepsis typically include fever and tachycardia. Respiratory rate may be normal or mildly raised, with an irregular breathing pattern. Urine output may be mildly reduced, reflecting mild dehydration. Limb pain and cold hands and feet are early signs of sepsis. Later features may include hypothermia, a marked tachycardia, sustained tachypnoea and respiratory irregularity, depressed conscious level, and a clinically appreciable reduction in the urine output.

- SIRS requires deviation from age-specific vital signs (Table 31.1). Impaired perfusion may be recognized by cold peripheries, poor capillary refill, tachycardia, tachypnoea, and oliguria. A prolonged capillary refill time of 3 seconds or more in a room-warm limb suggests reduced skin perfusion and, in a tachycardic, feverish child, may indicate serious illness, particularly septic shock (see NICE guidance on fever).[2] Hypotension is not essential to the diagnosis of septic shock in children (Box 31.2). BP is often maintained surprisingly well, especially in young children who develop a marked tachycardia and impaired microcirculation in limbs and organs from hypovolaemia before suddenly hypotension appears. Skin core temperature gradient (toe and rectal thermistor probes) of >3°C is a sensitive marker for severe shock, although rectal temperature measurement is not recommended in the NICE guidance. BP should be measured if heart rate or capillary refill time is abnormal in a feverish child.
- Dehydration can be assessed by considering the capillary refill time, skin turgor, respiratory pattern, pulse strength, and temperature of extremities. Measurement of SaO_2 is an essential adjunct to clinical examination. Hypoxaemia or poor cerebral perfusion results in restlessness, irritability, or 'bad behaviour'.
- The source of fever and symptoms and signs associated with specific diseases should be sought. Meningococcal septicaemia presents with fever, malaise, and a non-blanching rash (especially skin lesions >2mm in diameter (purpura) or spreading), or capillary refill time ≥3 seconds. Meningitis should be considered if a child is feverish with decreased level of consciousness, convulsions, and/or a bulging fontanelle.

If a diagnosis is not immediately apparent, look for predictors of serious illness.[2] Predictors of serious illness and septic shock include:

- Infants <3 months with fever ≥38°C
- Infants 3–6 months with fever ≥39°C
- Bile-stained vomiting
- Unrousable
- Respiratory rate ≥60 breaths/min or grunting
- Weak, high-pitched, or continuous cry
- Pale/mottled/blue/ashen skin, especially centrally
- Severely reduced skin turgor
- Moderate/severe chest recession
- Children appearing ill to another health-care professional.

Predictors for intermediate risk of serious illness include:

- Waking only with prolonged stimulation
- Decreased activity
- Poor feeding in infants
- Not responding normally to social cues/no smile
- Dry mucous membranes.

Infants <3 months of age can have a serious bacterial infection without any clinical features. They may benefit from observation for 4–6 hours, and reassessment with investigation results.

Investigations

Children with features of septic shock and a clinically evident underlying cause should have appropriate investigations taken (see Chapters 8, 17, 20, 22, 27, 29, 38, 40, and 43).

If a child has fever without an apparent source, but ≥1 feature predicting serious illness, tests should include:

- FBC
- Blood culture
- CRP
- Urine dipstick, microscopy, and culture.

Investigations may follow clinical assessment, including:

- CXR
- Plasma U&Es
- Blood gas
- Stool culture if diarrhoea is present.

An LP should be considered at all ages but is contraindicated with clinical evidence of septic shock, to avoid deterioration during the procedure.

In sepsis, clinical deterioration progresses and rapidly accelerates. Haemoglobin may fall rapidly. The WCC may show leucocytosis >15 × 10^9/L (or, more seriously, leucopenia <5 × 10^9/L). Blood lactate may be elevated, but blood glucose is often low. Potassium and calcium may be low and need correcting. Clinical and laboratory evidence of DIC, ARDS, acute renal failure, hepatobiliary dysfunction, and CNS dysfunction may presage multi-organ failure.

Management and treatment

Successful management requires rapid response and continuing care following diagnosis. SIRS is initiated by organisms, but sustained by an inflammatory cascade determined by genetic predisposition and inflammatory pathways, often sensitized by recent minor viral infection. Killing organisms with antibiotics takes hours, but the inflammatory cascade may self-perpetuate well beyond that time.

Management of sepsis syndrome requires:

- Urgent antibiotics to cover the likely causative organisms
- Parenteral fluid therapy (resuscitation, continuing replacement, and maintenance); early drainage of purulent foci
- Vasoactive (usually inotropic) support
- Oxygen and paediatric intensive care measures.

Frequent monitoring is required, with reassessment of vital signs, signs of shock, and detection of new problems.

Immediate management

- Management recommendations are supported by consensus guidelines, but sparse evidence. Paediatric life support guidelines should be broadly followed.

- The most experienced clinician available should stay with the child. Call for extra help, including senior nursing staff, and alert the anaesthetic staff that a child with severe sepsis may require ventilatory support.
- Blood cultures should precede, but not delay, antibiotics. Causative organisms can be isolated within 24 hours. PCR can detect bacterial DNA up to 72 hours after killing by antibiotics.
- Parenteral antibiotics should be given at the earliest opportunity (ideally within half an hour after appropriate cultures have been obtained), especially if a child presents with shock, is unrousable, or shows signs of meningococcal disease, or in a child with fever and reduced level of consciousness (meningitis might be responsible). Antibiotics should not be delayed, pending the results of investigations.
- Children with suspected meningococcal disease or community-acquired infection with no chronic underlying disease should be given a third-generation cephalosporin (e.g. ceftriaxone/cefotaxime). Antibiotic regimens may need variation in HAIs and in children with chronic underlying disease, or surgical or immunocompromise, to cover them from Gram-negative sepsis (e.g. piperacillin/tazobactam). Local or tertiary centre protocols may cover certain groups (e.g. oncology patients with febrile neutropenia). In infants <3 months of age, an antibiotic active against *L. monocytogenes* should be given as well (e.g. ampicillin or amoxicillin).
- Children with impaired peripheral perfusion or septic shock should receive 20mL/kg of 0.9% sodium chloride over 10–30 min, repeated if the response is poor, and then receive further boluses as necessary (see also ➔ Fluid and electrolyte balance, p. 288). Albumin 4.5% can be used, instead of 0.9% sodium chloride, for further boluses but must be obtained from the blood transfusion service.
- The child should be nursed in a high dependency care area in the emergency department or paediatric ward (high dependency unit, HDU) where intensive care can commence, if needed. Facilities for intermittent positive pressure ventilation and cardiopulmonary resuscitation should be available. Children with impaired mental state and reduced perfusion may need attention to the airway.
- Children with fever who are shocked, unrousable, or showing signs of meningococcal disease should be urgently reviewed by an experienced paediatrician (i.e. senior middle grade or consultant) to consider discussion with a PICU about management and possible admission.

Fluid and electrolyte balance

- Fluid balance is calculated as: volume restoration, maintenance fluids, and replacement of ongoing losses. IV (intraosseous, if necessary) access for aggressive fluid resuscitation is essential. If large resuscitation volumes are needed, crystalloid at half maintenance should be given. Ongoing fluid losses (e.g. nasogastric aspirates) should be replaced volume/volume with IV 0.9% saline hourly.
- Regular electrolyte and blood glucose measurements should be made. Potassium balance may need attention. If blood glucose is low, 10% glucose (INN) infusion at 0.5mL/kg/hour should be commenced, with higher concentrations if a poor response.

Further management of septic shock

- Preventing septic shock with marked tachycardia from progressing to hypotension and cardiovascular collapse may require saline or colloid administration (initial volumes of 40–60mL/kg) until central venous pressure (CVP) is +12 to +15cmH_2O, which will reduce the core peripheral temperature difference and improve capillary refill.
- Fluid administration should not be slowed or discontinued too early. Children with Gram-negative septic shock may ultimately require several times their own circulating volume (i.e. several times 80mL/kg) of resuscitation fluid to replace capillary leakage.

Cardiovascular support

- With adequate volume replacement (normal CVP and BP), persisting signs of impaired peripheral perfusion (raised pulse rate, prolonged capillary refill time) suggest that myocardial failure due to either endotoxinaemia or peripheral vasoconstriction may be present. Myocardial function can be assessed echocardiographically, measuring the end-diastolic volume.
- Inotrope introduction should follow local tertiary PICU protocols, which differ across the UK and Europe. Dopamine, an inotrope with vasodilator action, is usually first-line supportive treatment when there is impaired perfusion unresponsive to volume replacement. If hypotension persists despite adequate CVP, dopamine can be increased up to a maximum of 20 micrograms/kg/min. In dopamine-refractory shock, adrenaline or noradrenaline may be used, instead of dobutamine. Vasodilators (which include glyceryl trinitrate (INN), glyceryl trinitrate patch, and nitroprusside) reduce the afterload on the heart and improve perfusion, but a role in management of septic shock has not been established in double-blind placebo-controlled trials in children.
- The successful endpoint of resuscitation of septic shock should be the return of normal heart rate, capillary refill (i.e. <2 seconds), pulse rate, warm extremities, urine output >1mL/kg/hour, and normal mental state. CVP should return to +8 to +12cmH_2O. Blood tests should show decreased lactate and an improved base deficit.

Disseminated intravascular coagulation

- Septic shock causes DIC, with deranged clotting studies, thrombocytopenia, and raised fibrin degradation products. A combination of small-vessel thrombosis and DIC is called purpura fulminans and may lead to extensive tissue necrosis or limb ischaemia. Management is supportive during correction of the underlying cause. If clotting studies are severely deranged, fresh frozen plasma or cryoprecipitate should be given. Platelet infusions (which last 6–8 hours) may be required for patients with severe thrombocytopenia and active bleeding (e.g. from puncture sites).
- Low-dose heparin for impending peripheral gangrene and severe coagulation derangement is controversial. Results of trials of specific treatments for DIC in children are awaited.

High dependency unit care

Children have low functional residual capacity. They may require early intubation and ventilation, which reduces the work of breathing and myocardial workload. Children with emergent septic shock should be electively intubated and ventilated, i.e. before deterioration occurs, and emergency intubation is required for airway compromise or abnormalities of the breathing rate or pattern. Early use of intermittent positive pressure ventilation can avert severe deterioration, which occurs during a period of unexpected decompensation, and reduces the risk of pulmonary oedema. Midazolam sedation is often used during ventilation; it is also an anticonvulsant. IV opiate infusions, such as morphine or alfentanil, convey sedative and analgesic effects.

Admission to paediatric intensive care unit

Patients who do not respond to immediate treatment or are very ill at presentation require admission to a PICU. A senior paediatrician should contact a paediatric intensivist for early discussion. The interchange may provide relevant management advice and facilitate early transfer.

Ventilatory support is not a prerequisite for PICU admission requests, though most patients will be ventilated for transfer. Other reasons include the diagnosis, deterioration, degree of shock, treatment given, and respiratory pattern.

Transfer to PICU will be needed when children require >40mL/kg of IV fluids, need ≥1 inotrope, develop a raised respiratory rate or an irregular breathing pattern (indicating emergent pulmonary oedema) and show persisting acidosis, or have a significantly depressed conscious level.

Continued resuscitation and stabilization

Active management must be continued, while awaiting the transfer team. Senior members of medical and nursing staff should remain with the transfer team during optimal stabilization prior to departure from the HDU.

The child should be accompanied by paediatric, anaesthetic, and nursing staff experienced in transfer care of the critically ill paediatric patient. Fluid resuscitation and inotropes should be continued. Final outcome depends on maintenance or improvement of the condition during transfer.

Areas of controversy

Adrenal insufficiency in severe sepsis in children is associated with a poor prognosis. Low-dose corticosteroids to replace potential adrenal insufficiency in septic shock, are controversial. Children who have clear risk factors for adrenal insufficiency (previous steroid therapy, chronic illness, or pituitary or adrenal abnormalities) should receive steroids; otherwise, hydrocortisone therapy should be used in catecholamine resistance, or suspected or proven adrenal insufficiency. When low-dose hydrocortisone is given, continuous infusion is suggested, rather than repetitive bolus injections.

Plasmapheresis, haemofiltration, and blood exchange have been used in PICU to reduce the concentrations of circulating endotoxins and cytokines. There is no double-blind trial evidence of their success.

There is no evidence that modulators of the inflammatory response are efficacious or safe (e.g. monoclonal antibodies against endotoxins and cytokines, nitric oxide synthase inhibitors, and other agents such as antithrombin and activated recombinant protein C). Consensus guidelines advise against their use.

Supportive care

Post-pubertal children with severe sepsis should also receive:

- Prophylaxis against deep vein thrombosis
- H2 blocker prophylaxis against stress ulcers
- Renal replacement therapy, if required, with continuous veno-venous haemofiltration, (may be clinically useful in children with anuria/severe oliguria and fluid overload)
- Correction of hypo- or hyperglycaemia
- Sedation and analgesia, as required
- Blood products and (polyclonal) immunoglobulin preparations, as necessary.

ECMO should be reserved for refractory paediatric septic shock and/or respiratory failure unresponsive to conventional therapies.

Follow-up and outcome

Children with sepsis syndrome should be examined at discharge for possible sequelae and followed up to detect late-onset sequelae. This is especially the case for infants who may not manifest minor neurodevelopmental sequelae or learning difficulties until school years. Children who have had septicaemia or meningitis should have audiological testing.

Children who have been immunized against Hib, *Meningococcus* type C, and *S. pneumoniae* may need immunological investigations if infected with these organisms.

What's new and what's next?

Diagnostic research should be aimed at differentiating emerging sepsis from non-life-threatening infections in childhood populations. Studies are needed to improve the prediction of the early signs of serious bacterial infections, which include:

- Confirm normal ranges for the heart rate and respiratory rate at various body temperatures; PPV of vital signs, non-specific features (such as limb pain, and cold hands and feet), and blood investigations (e.g. PCT and CRP), alone or in combination
- Clinical scoring systems.

Research into the prevention and management of sepsis with anti-infective, anti-inflammatory, or anti-sepsis drugs (often agents antagonistic to endotoxins, the cytokines, or inflammatory mediators) are required. Novel

non-mortality endpoints, such as organ failure-free days or ventilator-free days, have been proposed for paediatric clinical trials, given the relatively low incidence of mortality in paediatric sepsis. Biomarkers, such as PCT, D-dimer, IL-6, and IL-8, may also be used as 1° endpoints. Longer-term outcomes, such as the overall level of functioning at 3- or 6-month follow-up, may also be useful endpoints.

New approaches in sepsis trial design, which take into account patient heterogeneity and the phase of the immunological response, should lead toward the development of new therapeutic strategies in sepsis.

Key references

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Chapter 32

Sexually transmitted infections

See also Chapters 19, 43, 58, 68, 70, 75, 76, 78, 87, 106.

Introduction

- STIs in young people (<25 years) are a public health crisis.
- The use of barriers, such as male condoms, and vaginal and anal dams, reduce the likelihood of transmission but cannot always protect against infections caused by skin-to-skin contact such as warts.
- Multiple sexual partners increase the risks of acquisition.
- Adolescent girls are more susceptible than older women to infection, possibly due to cervical ectopy and a relatively immature immune system.
- Findings of STIs in prepubertal children raise concerns about possible sexual abuse, but some, in young children, may have been acquired from the mother during pregnancy, delivery, or breastfeeding.
- It should be remembered that the wide variety of receptive and insertive sexual activity practised requires investigation of multiple sites.
- When post-pubertal girls attend services for contraception (particularly if condoms have not been used) or are pregnant, it is appropriate to offer testing for sexual infections, in particular *Chlamydia*, and gonorrhoea, depending on the local prevalence. Staff should also be aware of the norms for different ages in terms of sexual awareness and be alert to identifying sexually exploitative relationships.

Causative organisms

Viruses

- HSV types 1 and 2.
- Hepatitis A.
- Hepatitis B.
- Hepatitis C.
- HIV.
- Molluscum contagiosum virus.
- HPV, usually types 6 and 11.

Bacteria

- *C. trachomatis*.
- *C. trachomatis* serovars 1, 2, and 3 causing lymphogranuloma venereum (LGV).
- *N. gonorrhoeae*.

- (Bacterial vaginosis may be associated with the presence of STIs, but there are insufficient data in children to determine the significance of bacterial vaginosis alone in relation to sexual abuse.)
- *T. pallidum* (syphilis).

Protozoa

- *Trichomonas vaginalis*.

Prevalence

- There is often coexistence of more than one STI.
- Teenagers and those in their early 20s have the highest rates of *Chlamydia* and gonorrhoea. The rates of infection vary by gender, sexual orientation, and ethnicity (Table 32.1).
- The English National *Chlamydia* Screening Programme opportunistically tests people aged 15–24 at settings outside genitourinary medicine (GUM) clinics. Previously, it aimed to test as many people as possible but now concentrates on those with high sexual risk-taking to increase the diagnostic rate. The Public Health Outcomes Framework in England (2012) suggests a target of 2400 positive samples per 100 000 residents aged 15–24. A change in reporting data sets between 2011 and 2012 does not allow direct comparisons.
- Increasing numbers of non-GUM settings are commissioned to test and treat young people for the whole range of STIs, e.g. in conjunction with their contraceptive needs.

Table 32.1 Rates of sexually transmitted infections in England, 2013 (rates per 100 000 population)

	♂ (13–14)	♂ (15–19)	♂ (all ages)	♀ (13–14)	♀ (15–19)	♀ (all ages)
C. trachomatis	15.5	947.0	328.6	156.3	2719.2	442.7
N. gonorrhoeae	1.4	91.8	82.2	8.5	149.9	0.2
Warts	1.1	229.1	154.9	12.5	509.5	120.1
HSV	0.5	40.5	46.5	8.2	207.0	73.7
Syphilis (1° and 2°)	0.0	3.7	11.3	0.3	1.9	1.0

Methods of ascertainment have varied, and so trends have not been calculated. Data are for new diagnoses, not individual patients.

Source: Public Health England. Sexually Transmitted Infections Annual Data. 2013. Table 3: Selected STI diagnoses & rates by gender, sexual risk and age group. (℞ <http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/STIs/STIsAnnualDataTables/#5._STI_data_for_the_UK>).

European prevalence

It is more difficult to assess the true prevalence or percentage changes across Europe, as people access STI care in a greater variety of settings. Only some STIs in some countries require mandatory reporting, and so direct comparisons are not possible. In Holland, where there is a national database of STI diagnoses both in general practice and specialist centres, the reported trends in prevalence of the various STIs roughly equate to those seen in UK data. Within Europe, only the UK, France, Germany, and Slovenia have estimates of national population prevalence.

Clinical presentation

Mother-to-child transmission may result in presentation at birth or early childhood. The possible modes of transmission are summarized in Table 32.2.

- Presentation in infants includes no symptoms, conjunctivitis (*Chlamydia* and gonorrhoea), lung infections (*Chlamydia*), encephalitis (HSV), rashes, failure to thrive, laryngeal warts (HPV), and hepatosplenomegaly (HIV).

Table 32.2 Possible modes of transmission to the infant

Infection	Mode of transmission		
	Transplacental	During labour	Via breast milk
HIV	+	+	+
Hepatitis B and C	+	+	
Syphilis	+	+	
HSV, gonorrhoea, *Trichomonas*, warts, and *Chlamydia*		+	

Prepubertal children

- None.
- Discharge.
- Itching.
- Dysuria, frequency, or enuresis.

However, all the above are also very common symptoms in prepubertal girls and are very rarely 2° to an STI.

By definition, sexual intercourse with a person under 13 years old is sexual abuse and may present with symptoms other than those due to infection, e.g. pain with defecation, soiling or withholding, and emotional problems, e.g. school refusal.

A recent whole population study of STIs in children over 12 months and under 13 years old identified 15 cases of *N. gonorrhoeae, T. pallidum, C. trachomatis*, or *T. vaginalis* in the UK and Republic of Ireland over a 25-month period.

This is an overall incidence of 0.075 cases per 105 per year. There were seven cases were of gonorrhoea, six of *Chlamydia*, and one each of syphilis and *Trichomonas*. Fourteen of the 15 were ♀. Ten of the children were aged 1–4 years old, and five were aged 5–12 years. In three cases, sexual abuse was confirmed in court or as a result of a case conference, but it was suspected in seven other cases, and no conclusions were reached in the remainder.

Paediatricians with concerns about possible sexual abuse should take into account whether mother-to-child transmission has been possible. Unfortunately, the evidence base is lacking, and maternal infection does not exclude subsequent acquisition by the child due to abuse. When a child has an STI, sexual intercourse should be the main differential diagnosis.

Sexually active teenagers

- None (*Chlamydia* is asymptomatic in 70% of girls and 50% of boys).
- Vaginal, penile, or anal discharge.
- Vulval itching or discomfort.
- Dysuria.
- Intermenstrual or post-coital bleeding in girls.
- Testicular pain.
- Prostatitis.
- Pelvic pain during intercourse.
- Genital ulcers.
- Genital warty lesions.
- Throat infections where receptive or insertive oral sex has occurred.
- Skin rashes.
- Inguinal lymphadenopathy.
- Tenesmus in LGV.
- Later sequelae such as iritis, arthritis, ectopic pregnancy, infertility, chronic pelvic pain, and cancer of cervix, oropharynx, or rectum.

Differential diagnosis

- Most commonly, vulvitis and vulvovaginitis in prepubertal girls is non-infectious.
- Non-STIs—*Candida*, bacterial vaginosis, GAS disease causing perineal erythema and bleeding in younger children, although scratching as a result of *Trichomonas* may also cause skin changes.
- Physiological vaginal discharge.
- Retained tampon or self-inserted foreign body in younger children. This is rare.
- Skin conditions such as lichen planus, lichen sclerosus, psoriasis, eczema, blistering conditions.
- Urethral prolapse in prepubertal girls.
- Labial adhesions in prepubertal girls.
- Unscheduled, heavy, painful, or prolonged vaginal bleeding related to side effects of hormonal or intrauterine contraception.

Investigations

Knowledge of incubation periods determines the timing of testing. Details of which investigations should be performed will vary, depending on the age of the child, the nature of any sexual contact, and the background prevalence of the various STIs. Samples are taken for clinical management and, where abuse is possible, as supporting evidence. What follows is a broad outline. For detailed guidance, *The Physical Signs of Child Sexual Abuse* (2015) by the Royal College of Paediatrics and Child Health should be consulted.

Baseline samples, taken soon after contact, may need to be repeated at 2 weeks (for *C. trachomatis* and GC) and 3 months (for HIV, hepatitis B, and syphilis) after the last contact.

- Swabs taken from the relevant areas, as dictated by the sexual history:
  - Vulvovaginal area (or the introitus, avoiding the hymen in prepubertal girls which is extremely sensitive and painful when touched) for NAAT for *Chlamydia* and gonorrhoea. Cervical culture, where possible, in post-pubertal girls for antibiotic sensitivity if NAAT swab is positive for gonorrhoea
  - Rectum (NAAT for LGV)
  - Pharynx (NAAT for gonorrhoea and *Chlamydia*)
  - Viral culture for herpes from blister fluid.
- First-pass urines >1.5 hours since last voiding for *Chlamydia* and gonorrhoea in boys (and girls if swabs not possible). Rectal NAAT for LGV.
- Dark ground microscopy of scrapings from the base of (usually painless) ulcers, and serology for syphilis.
- Serology for HIV antibody and p24 antigen, from 6 weeks post-exposure if high-risk, otherwise from 12 weeks.
- Serology for hepatitis B surface antigen.
- Examination under anaesthesia is only rarely required to look for foreign bodies in young children. Most prepubertal children with vulvo/vaginal symptoms, e.g. itch or discharge, are managed conservatively. Only if there is a diffuse or offensive discharge with unusual symptoms, such as pelvic pain and/or concerns about a possible STI or evidence of 'damage' or a disclosure, would more invasive tests be arranged.
- Paediatricians have opportunities to consider early detection of STIs when young women present with urinary symptoms with culture-negative mid-stream urine samples, and when there are concerns about possible pregnancy.

Management and treatment

- Management will depend on the age of the child or young person, and whether a safeguarding children assessment and referral are required.
- Where sexual abuse is considered, specialist examination with samples taken to preserve a forensic chain of evidence will be required.
- For young people who are having sex consensually, knowledge of the legal age of consent in different countries plus assessment of the Gillick competence, using the Fraser rules to consent to treatment, must guide clinicians. The legal age of consent varies across Europe (from 13 to

18 years); in all countries of the UK, it is16, but people of similar ages (except those under the age of 13) can give consent to sexual activity as long as no power imbalance is present.
- Clinicians should be alert to the possibility of coercion possibly involving drugs and/or alcohol, providing sex for money, and trafficking.
- Partner notification is a vital public health intervention to break the chain of infection, and this is most often facilitated by health advisers in genitourinary clinics.
- Treatment must be followed by abstention from all sexual activity until all current partners have completed their own treatment. Unsurprisingly, this is not always followed, so reinfection occurs. Adherence to medication may be a particular concern in young people, and directly observed treatment as a single dose may be best for *Chlamydia*.
- Liver enzyme-inducing antibiotics, such as rifampicin and rifabutin, and some antiretroviral drugs lower the efficacy of oestrogens and progestogens, affecting combined hormonal methods, subdermal implants, and emergency hormonal and progestogen-only oral contraception. The effect of the reduction in contraception continues for 28 days after cessation of the interacting medication. Up-to-date evidence about which drugs cause this effect is available on <http://www.fsrh.org/pages/Clinical_Guidance_4.asp>.
- Consider the need for emergency contraception if there has been recent unprotected vaginal intercourse.
- Post-exposure prophylaxis for sexual exposure to HIV may be advisable in high-risk situations—see the British HIV Association website (<http://www.bhiva.org/PEPSE-guidelines.aspx>).
- Hepatitis B immunoglobulin, followed by an accelerated course of immunization, may also be indicated in acute situations.

Follow-up and outcome

- Health advisers contact patients to ensure compliance with treatment and advice not to restart having sex until completion of treatment for all partners. Re-treatment of all partners may be required, if not compliant.
- Test of cure required, following treatment for gonorrhoea.
- Test of cure for *Chlamydia* is only required if a young person is pregnant or has been treated with less effective medication such as erythromycin.
- Re-testing around 3 months after treatment is recommended. (<http://www.chlamydiascreening.nhs.uk/ps/resources.asp>).
- Review of clinical response to treatment for warts and continuation or change of treatment, if required.

Prevention

- Health promotion to help the young person consider if they feel ready to start or continue having sex and strategies to avoid peer pressure.
- Teach correct use of condoms, and encourage their use with all new partners or where the faithfulness of the current partner is in doubt (safest to always doubt).

- Interventions to reduce other related risk-taking behaviour such as alcohol and recreational drugs.
- In England, the National Chlamydia Screening Programme aims to decrease the incidence in the community by case finding on an annual basis or where there has been a partner change and partner notification. The highest uptake for screening is currently in the white ethnic population, but the highest positivity rate is in the black Caribbean and other black groups. Scotland does not have universal screening but targets areas of greatest prevalence.
- In the UK and many other countries, a vaccine, containing HPV types 6, 11, 16, and 18, is currently offered to 12- to 13-year old girls to prevent most cases of cervical cancer and anogenital warts. A bivalent vaccine, previously used in the UK and currently used in many countries, appears to give some protection against warts, although it only contains two oncogenic serotypes.
- Hepatitis B vaccination should be offered to all young men who have sex with men (MSM), people who themselves share drug-injecting equipment or whose sexual partner does so, and people who sell sex.

Future research

- Cost-effectiveness of adopting HPV vaccination for young men to prevent orogenital warts and cancers and increase protection for women and homosexual men against oncogenic strains.
- Ongoing assessment of the efficacy and cost-effectiveness of the *Chlamydia* screening programme.

Further reading

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Chapter 33

Skin and soft tissue infections

Introduction

The skin consists of the superficial epidermis and the deeper dermis (Fig. 33.1), and forms an important barrier as part of the body's innate resistance to infection. Soft tissues consisting of adipose tissue, fascia, and muscle lie beneath the skin. Infections of the skin and subcutaneous tissues are common in childhood.

Bacterial infections

Impetigo

- Impetigo is an infection of superficial layers of the epidermis. It can be bullous or non-bullous (>70%). Bullae are caused by exfoliative toxins which cleave the dermal–epidermal junction. Impetigo can occur at any age but is more common in early childhood. Like cellulitis, it often develops at a break in the skin. It is highly contagious; young children may auto-innoculate at a variety of sites. Outbreaks are commonplace.

Causative organisms

- *Staphylococcus aureus*—classically with golden crusts
- *Streptococcus pyogenes* (GAS) (less common)
- Mixed *S. aureus* and GAS infection can also occur.

Clinical features

- Superficial ulcer-like lesions, 0.5–6cm in diameter, usually with crusting, typically golden in colour
- Early lesions may be vesicular
- Non-tender
- May be single or multiple lesions
- Bullae are round, fluid-filled blisters that burst easily, leaving a moist ring-like lesion.

Investigations

- Gram stain and culture of exudate, bullae, or bullous fluid.

Treatment

- Mild, localized cases can be treated with topical antibiotics for 5 days, e.g. fusidic acid or mupirocin. There are increasing reports of topical fusidic acid resistance in skin infections
- Multiple lesions or outbreaks should receive oral therapy for 7 days.

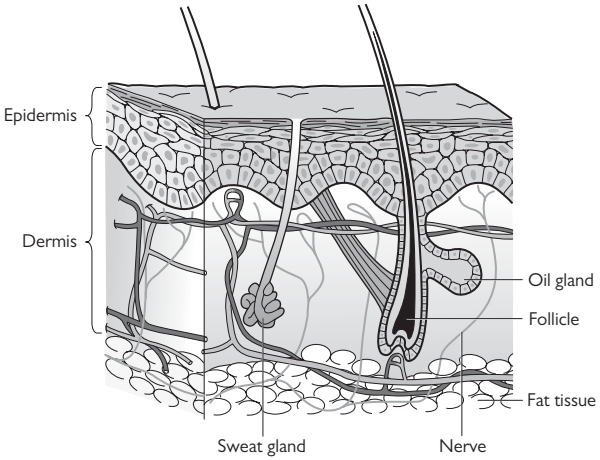

Fig. 33.1 Human skin showing the epidermis, dermis, and subcutaneous tissue.

Cellulitis and erysipelas

Cellulitis and erysipelas describe diffuse, spreading bacterial infections of the dermis and subcutaneous tissues. These terms should not be used to describe skin inflammation above an underlying suppurative process where management depends on incision and drainage of pus and treatment of the 1° infection.

Erysipelas

- Limited to the upper dermis, involves the lymphatics
- A raised red border and sharp demarcation from surrounding normal skin is characteristic.

Cellulitis

- Involves the deeper dermis and subcutaneous fat
- Most commonly on the arms and legs
- Usually, not invariably, beneath broken or damaged skin
- Varies in severity from a localized, self-limiting condition to a more extensive multisystem life-threatening infection, with signs and symptoms of toxicity.

Causative organisms

- *S. aureus* (commonest cause of cellulitis)
- Streptococcal spp. (GAS commonest cause of erysipelas)
- Rarely *H. influenzae* and various other organisms.

Clinical features

- Red (rubor), painful (dolor), warm (calor), and swelling (tumor) of the skin and subcutaneous tissues (the four classic signs of inflammation described by Celsus in the first century AD)
- Low-grade fever
- Systemic features of toxicity if extensive or progressive
- Disproportionate pain associated with livid red/purple discoloration, purpura, or the presence of overlying bullae are suggestive of necrotizing fasciitis
- *H. influenzae* cellulitis may have a characteristic bluish tinge and associated bacteraemia.

Investigations

- None needed in typical cases, but blood culture (<5% yield), skin biopsy, and aspirate culture indicated in severe infection, clinical sepsis, or immunocompromised hosts.

Treatment

- Mild cases treated with oral flucloxacillin for 5 days
- IV flucloxacillin or cefazolin if signs of systemic infection
- Consider MRSA cover, depending on the local prevalence or if poor response to first-line therapy. Oral options for community MRSA include clindamycin or co-trimoxazole.

Omphalitis

Omphalitis is a purulent infection of the umbilical stump ± surrounding tissues, generally occurring in the first 2 weeks of life. It is more common in developing countries, with an estimated incidence of 6 per 100 live births (<0.5 per 100 in developed countries). 1° immune defects, such as leucocyte adhesion defect, can present with non-purulent omphalitis.

Causative organism

- *S. aureus*
- GAS (may cause nursery outbreaks)
- Gram-negative enteric organisms
- Can be polymicrobial.

Clinical features

- Serous or purulent discharge from the umbilicus, with surrounding erythema
- Systemic signs of infection often present
- Can extend to the portal vein and liver or lead to necrotizing fasciitis and abscess formation.

Treatment

- IV broad-spectrum antibiotics.

Staphylococcal scalded skin syndrome

Staphylococcal scalded skin syndrome (SSSS) is a toxin-mediated condition, causing widespread desquamation of the skin. It occurs most frequently in neonates. NICU epidemics are reported. Exfoliative toxin targets desmoglein 1, disrupting keratinocyte connectivity. Mucous membrane involvement is absent, as the toxin has no activity against mucosal desmoglein 3.

SSSS is characterized by widespread large, delicate bullae and sheet-like exfoliation. Despite the dramatic appearance, the skin usually heals quickly and without scarring.

Causative organism

- *S. aureus*.

Clinical features

- Rapid onset of fever, generalized erythroderma, and skin tenderness. The infant may be very irritable
- Early lesions appear bullous. Followed by widespread shedding of the superficial layers of the skin, leaving raw red areas, sometimes with serous discharge
- Positive Nikolsky's sign.

Investigations

- Throat and nasal swab, Gram stain, and culture of any likely source lesion.

Treatment

- IV flucloxacillin or cefazolin
- Consider clindamycin if severe
- Supportive care, including IV fluids, may be necessary, as insensible losses may be similar to an extensive burn.

Necrotizing fasciitis

Necrotizing fasciitis was described by Hippocrates in the 5th century BC. It is an extensive infection of the fascia or muscle compartments that can lead to massive tissue destruction and death. Bacteria infecting fascial layers can spread rapidly and extensively. Urgent surgical inspection and debridement are necessary. Necrotizing fasciitis is comparatively rare in children. TSS can occur concurrently.

Causative organism

- *GAS (commonest cause in children)*
- *S. aureus can be implicated*
- Polymicrobial necrotizing fasciitis caused by aerobic and anaerobic organisms (e.g. *Clostridium, Bacteroides, Enterobacteriaceae*) may be associated with diabetes or post-surgery.

Clinical features

- Disproportionately painful swelling of soft tissue, usually of a limb or the abdomen—pinpoint tenderness
- Livid red/purple skin discoloration is a late sign of necrosis
- Most cases occur without an apparent preceding factor but may follow blunt or trivial trauma
- Antecedent varicella infection can be a precipitating factor.

Investigations

- Blood culture, Gram stain, and culture of operative samples and any superficial lesions
- FBC, CRP, serum lactate, renal, liver, and coagulation profiles
- Diagnostic imaging, ideally MRI, can help delineate the extent of disease but should not delay surgical exploration or debridement.

Treatment

- Urgent surgical debridement, based on clinical signs alone
- Supportive care, often in an ICU as may have multi-organ failure
- Multiple broad-spectrum IV antibiotics which should include a penicillin or β-lactam, often combined with a β-lactamase, and clindamycin for its antitoxin effect
- Recent reviews support the use of IVIG.

Toxic shock and toxic shock-like syndromes

Skin and soft tissue infections caused by toxin-producing strains of *S. aureus* and GAS can cause potentially TSS and toxic shock-like syndrome, respectively. A localized source of infection is more likely to be evident with streptococcal than with staphylococcal infections. Shock is a late sign of sepsis in infants and young children. A high index of suspicion is required to recognize symptoms or signs of systemic illness. Multi-organ failure results from the superantigen effect of bacterial exotoxins leading to massive cytokine release. Tachycardia, erythroderma, or diarrhoea may be indicative of toxaemia.

Investigations

- Blood culture, Gram stain, and culture of skin lesions
- FBC, CRP, serum lactate, renal, liver, and coagulation profiles
- Diagnostic imaging, ideally MRI, to detect underlying soft tissue infection and to direct drainage of underlying pus.

Treatment

- Aggressive fluid resuscitation
- Supportive care in an ICU
- Empiric treatment should include multiple broad-spectrum IV antibiotics, including a β-lactam or penicillin with potent anti-staphylococcal activity or carbapenem and clindamycin (for its antitoxin effect) which can then be rationalized to directed therapy once the aetiologic agent is confirmed
- Unlike β-lactams, clindamycin has the advantage of not being susceptible to the inoculum effect (Eagle effect)
- IVIG.

Folliculitis and furuncles (boils)

Folliculitis is a superficial infection of the hair follicles. It appears as multiple pimples or pustules at the site of hair follicles, usually caused by *S. aureus*. Treatment is often not required, though topical antibacterial cleansers, such as chlorhexidine, or topical antimicrobials may be used.

Hot tub folliculitis, caused by *P. aeruginosa*, follows exposure to contaminated water or garments. Outbreaks occur. Symptoms usually present within 48 hours of exposure and resolve spontaneously within 1–2 weeks, though areas of hyperpigmentation can persist.

Furuncles (boils) are follicular infections that extend deep into the dermis. Carbuncles are larger, deeper, contiguous infections, most commonly found on the back of the neck. *S. aureus* is again the predominant organism. Most furuncles drain spontaneously or with application of moist heat. Antimicrobial therapy is recommended if systemic signs of infection are present. Incision and drainage are recommended for larger furuncles and carbuncles.

Ecthyma

Lesions begin like impetigo but penetrate the epidermis to produce deep punched-out ulcers with a raised purplish margin. Can be 2° to infection of pre-existing breaks in the skin. Most often affect the legs. Streptococcal and staphylococcal ecthyma can complicate chickenpox. Pseudomonal lesions have a central black eschar (*Ecthyma gangrenosum*) and may be the first indication of a neutropenic state or presentation of leukaemia.

Causative organisms

- GAS
- *S. aureus*
- *Pseudomonas* or other Gram-negative bacilli.

Treatment

- IV flucloxacillin
- Anti-pseudomonal penicillin.

Animal and human bites

Cutaneous and soft tissue infections can develop after animal or human bites. Immunocompromised patients, including those who are asplenic, are at higher risk of severe infection.

Causative organisms

- *S. aureus*, anaerobic cocci, and *Bacteroides* spp
- GAS (human bites)
- *Pasteurella multocida, Capnocytophaga canimorsus,* and *Pseudomonas fluorescens* (animal bites).

Treatment

- Prophylaxis with oral co-amoxiclav for 3–5 days for cat and human bites, and severe dog bites, particularly of the face, hand, or foot, or those that cannot be adequately cleaned and irrigated or are close to bones or joints
- Cat bites are more frequently infected due to the hypodermic-like effect of their teeth resulting in deeper wounds
- Infected bites can be treated with oral co-amoxiclav
- More severe infections require IV antibiotics
- Tetanus vaccine should be administered if not received within the previous 10 years or if the vaccine schedule is incomplete.

Recurrent bacterial infection

- Recurrent abscesses at a previous site should prompt search for an underlying cause such as a pilonidal cyst or foreign body
- Swab lesions to identify the organism and to guide appropriate antimicrobial therapy
- Recurrent staphylococcal abscesses can be associated with underlying conditions, e.g. diabetes mellitus, hypothyroidism, 1° immune deficiency (CGD, leucocyte adhesion defect, etc.), but generally relate to nasal colonization and auto-innoculation of skin sites in healthy children
- In addition to management of the acute infection, decolonization regimens may be helpful to prevent recurrence, although strong evidence for their efficacy is lacking. A common regimen includes

5 days of an anti-staphylococcal nasal ointment (Naseptin® for MSSA or 2% mupirocin for MRSA), coupled with twice-weekly chlorhexidine shower/baths for 4 weeks. The nasal ointment (a pea-sized blob of cream applied once daily to the medial aspect of the anterior nares) can be reapplied for 5 days on a monthly basis over the ensuing 3–4 months in an effort to prevent re-establishment of the colonized status. Dilute bleach baths are sometimes used in the place of chlorhexidine as an equally effective, but less expensive, option. Treatment of the entire family is often required to prevent recolonization

- Dilute bleach baths are also increasingly used in atopic dermatitis to reduce *S. aureus* colonization and superinfection.

Viral infections

Chickenpox

See Chapter 53.

Chickenpox, caused by VZV, is extremely contagious; almost all individuals are infected during childhood. A prodromal illness in approximately half of patients is followed by an erythematous macular rash, which develops into vesicles. New lesions occur in crops over 3–6 days and generally number <300. *S. aureus* and GAS are the main organisms causing complicated skin infection following varicella. Signs of complications with bacterial superinfection include pyrexia for longer than 5 days, recurrence of pyrexia, and spreading erythroderma. Countries with universal childhood vaccination have seen a significant reduction in complications of chickenpox, including invasive GAS infection. VZV can be fatal in immunocompromised hosts and neonates, and IV aciclovir treatment is necessary.

Shingles

VZV persists in the dorsal root ganglia after 1° infection. Reactivation causes shingles, which classically occurs in a dermatomal distribution. It is moderately uncommon in childhood. Most children are otherwise well, and a single uncomplicated episode of shingles in a healthy child does not require further investigation. Multidermatomal involvement can be a marker of immune deficiency (see Chapter 17). Post-herpetic neuralgia is uncommon in children.

Herpes simplex virus

See Chapter 76.

1°HSV infection in children typically presents as stomatitis but can be totally asymptomatic. HSV almost always recurs in the same region as the 1° infection. Depending on the severity, frequent recurrences, e.g. more than once per month, may warrant prophylactic oral antiviral therapy. Infection of the finger and around the fingernail, termed herpetic whitlow, is acquired by auto-innoculation from concurrent oral stomatitis in 80% of children but is an occupational hazard in health-care workers. HSV infection of atopic dermatitis (eczema herpeticum) requires IV aciclovir therapy.

Molluscum contagiosum

Molluscum contagiosum caused by a poxvirus is quite common in childhood, with up to 20% of children being infected at some time. It is spread by direct contact or fomites and is moderately contagious. An individual molluscum may last for a couple of months but may persist longer. Persistent or widespread mollusca should prompt investigation for immune disorders, particularly HIV or DOCK8 deficiency (see Chapter 103).

Warts and verrucae

Warts are caused by the proliferation of HPV in the upper layers of the skin. Many over-the-counter salicylic acid-based topical treatments are available. Liquid nitrogen therapy is commonly used in general practice. Cantharidin, a blistering solution derived from the green blister beetle, is increasingly used. IV cidofovir has been used, to good effect, to treat disfiguring lesions in immunocompromised patients.

Fungal infections

See Chapter 62.

Tinea corporis (ringworm), tinea capitis (scalp ringworm), and tinea pedis (athlete's foot) are common fungal skin infections in childhood. Tinea capitis may develop into a boggy inflammatory mass known as a kerion. A kerion should not be mistaken for an abscess, as surgical debridement may result in a wound that is very slow to heal. Treatment requires prolonged systemic antifungal therapy (griseofulvin or terbinafine).

Parasites

Scabies

See Chapter 111.

Scabies is an infestation of the skin caused by the parasitic mite *Sarcoptes scabiei*. It is not uncommon in children. Scabies produces burrows and papules in the skin, classically in the interdigital spaces, wrists, and ankles, but may involve any area of the skin in young children. First-line treatment with 5% permethrin cream to the entire skin (avoiding mucous membranes) for 8 hours, repeated after 1 week, improves the cure rate. Recurrent pruritus 3–6 weeks after successful treatment is most often the result of delayed type IV hypersensitivity to the mite, mite faeces, and mite eggs, and typically responds to steroid treatment.

Head lice

See Chapter 93.

Head lice (pediculosis) is a common childhood infestation of the scalp and hair. Head lice are small arthropods that can be seen on the hair and scalp. Nits are their empty egg cases attached to the hair shafts.

Future research

- The role of cytotoxins, such as PVL, in the pathogenesis of invasive *S. aureus* infection remains to be elucidated
- Use of IV antivirals, such as cidofovir, for warts and for severe disease in immunocompromised patients
- Development of anti-staphylococcal and anti-streptococcal vaccines.

Further reading

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Chapter 34

Investigating the child with possible immunodeficiency

Introduction

An increased susceptibility to infections is the hallmark of primary immunodeficiency disorders (PIDs). This abnormal handling of infections may be characterized by:

- Unusual microbial causes of infection not generally seen in healthy individuals—e.g. opportunistic organisms such as *P. jirovecii*
- Atypical features in a common infection—e.g. severe haemorrhagic chickenpox
- Excessive frequency of normal infections—e.g. recurrent LRTIs.

Ten warning signs of PIDs, which should prompt further assessment of patients are:

- Failure to thrive
- Need for IV antibiotics to treat infections
- Family history of PIDs
- Four or more new ear infections within 1 year
- Two or more sinus infections within 1 year
- Two or more months of taking at least two antibiotics, with little benefit
- Two or more LRTIs within 3 years
- Frequent subcutaneous or organ abscesses
- Persistent (>6 months) thrush or other fungal infection
- Two or more deep-seated infections (e.g. septicaemia, OM, meningitis) within 3 years.

Other non-infective clues to the presence of immunodeficiency include:

- Lymphoid hypertrophy
- Rashes
- Enteropathy
- Autoimmune phenomena
- Malignancy (particularly haematological or unusual type)
- Haemophagocytic lymphohistiocytosis (HLH).
- Miscellaneous, e.g. delayed umbilical cord separation.

Types of immunodeficiency

Immunodeficiency disorders may affect the adaptive and innate immune systems, or both. The adaptive system can be divided into disorders affecting both T cell-mediated immunity and antibody production or just antibody-mediated immunity. Over 200 PIDs are now recognized, and over 190 monogenic defects have been identified. The pattern of infection and pathogens isolated from patients can give clues as to the component of the immune system affected and the underlying disorder. Typical clinical presentation and pathogenic organisms associated with the different types of immunodeficiency are shown in Table 34.1. Individual disorders may fall into two or more categories.

Table 34.1 Typical clinical presentations and microorganisms isolated in different types of 1° immunodeficiency

Type of PID	Clinical presentation	Typical microorganisms
T-cell deficiency*	Pneumonitis Chronic diarrhoea and failure to thrive Persistent thrush	*P. jirovecii* RSV, influenza and parainfluenza viruses, adenovirus Herpes viruses Enteropathic virus (especially vaccine strain rotavirus) BCG *Candida* spp. *Cryptosporidium*
Antibody deficiency*	Sino-pulmonary infections (LRTI, otitis media, tonsillitis, sinusitis) (commonest) Other invasive bacterial infections Chronic diarrhoea, meningitis (less common)	Capsulated bacteria (*S. pneumoniae*, *H. influenzae*) *Giardia lamblia* Enterovirus (encephalitis)
Neutropenia	Sepsis Peridontitis/gingivitis Lymphadenitis	Gram-negative bacteria, *S. aureus* *Candida* spp. *Aspergillus* spp.
Phagocyte disorders	Superficial boil and skin infections Deep-seated abscesses LRTIs Invasive infections associated with inflammatory masses Peridontitis/gingivitis Poor wound healing	*S. aureus* Gram-negative bacteria *Aspergillus* spp. *Salmonella* spp.

(*Continued*)

Table 34.1 (*Contd.*)

Type of PID	Clinical presentation	Typical microorganisms
Innate disorders	Highly disease-specific	*MSMD*: atypical mycobacteria, BCG, *Salmonella* spp. *TLR defects*: capsulated organisms, especially *Pneumococcus* spp. or HSV encephalitis *CMC*: superficial or deep-seated *Candida* infections *Others*: severe or vaccine strain viral infections
Immune dysregulation disorders	HLH Lymphoproliferation Autoimmunity (particularly blood cytopenias and eczema)	
Complement deficiency	Septicaemia Meningitis Deep-seated infections Autoimmunity/SLE	Capsulated bacteria (especially *Meningococcus*)
Asplenism	Sepsis	Capsulated bacteria, *Salmonella* spp.

* Note: children with severe combined and combined immunodeficiency present with features of both T-cell and antibody deficiencies.

CMC, chronic mucocutaneous candidiasis; MSMD, mendelian susceptibility to mycobacterial diseases; SLE, systemic lupus erythematosus; TLR, toll-like receptor.

Classification of primary immunodeficiency disorders

Tables 34.2, 34.3, 34.4, 34.5, 34.6, and 34.7, provide a framework for classifying 1° immunodeficiency disorders and list the specific features, in addition to infections suggested in Table 34.1 for specific disorders.

Table 34.2 Severe combined (T-cell and antibody) deficiency disorders

Clinical syndrome	Molecular defect and inheritance	Specific features
1: Severe combined immunodeficiency (SCID)—absent/low T cells		
B-positive	Common γ-chain (X-SCID) [XL]	Opportunistic/bacterial, viral/fungal infections. NK negative
	JAK3 [AR]	NK negative
	IL-7Rα [AR]	NK positive
	CD3γδ or ζ [AR]	NK positive
B-negative, DNA recombination defects	RAGI or II [AR]	NK positive
	Radiosensitive SCID [AR] includes artemis, ligase IV, and others	Maybe microcephaly, growth impairment. NK positive
B-negative, others	Adenosine deaminase (ADA) [AR]	SNHL, interstitial lung disease, skeletal dysplasia. NK +/–
	Reticular dysgenesis (AK2) [AR]	Absence of granulocytes and all lymphocytes
2: Less profound combined immunodeficiency (CID)		
	Potentially any SCID with a 'leaky' or hypomorphic mutation or second 'reversion' mutation	Later presentation; autoimmune features (especially intestinal and pancytopenias):
	PNP [AR]	Upper motor neuron symptoms/signs
	MHC class I [AR]	Autoimmunity, vasculitis, low CD8 cells
	MHC class II [AR]	Usually low CD4 cells
	CD8 [AR]	Reduced CD8 cells only
	ZAP70 [AR]	Very low CD8 cells
	DOCK8 [AR]	Raised IgE, severe molluscum contagiosum
	MAGT1 [XL]	Severe EBV infection/lymphoproliferation and papilloma virus infections
	ITK [AR]	
	CD40 ligand (X-linked hyper IgM) [XL]	Very low IgG and IgA; normal/high IgM with PCP and *Cryptosporidium* susceptibility
	CD40 (AR)	
3: Combined immunodeficiency with associated or syndromic features		
Thrombocytopenia	Wiskott–Aldrich syndrome (WAS) [XL]	Eczema, low platelet-volume platelets, autoimmunity, and malignancy
	WIP [AR]	

(*Continued*)

Table 34.2 (*Contd.*)

Clinical syndrome	Molecular defect and inheritance	Specific features
DNA repair defects	Ataxia telangiectasia (AT) [AR]	Ataxia, telangiectasia, ocular dyspraxia, X-ray sensitivity, malignancy
	Nijmegen breakage syndrome [AR]	Microcephaly, bird-like facies, malignancy, sensitivity to ionizing radiation
	Bloom syndrome [AR]	Short stature, bird-like facies, marrow failure, malignancies
	Immunodeficiency, centromeric instability, and facial dysmorphism [AR]	Facial dysmorphism, macroglossia, cytopenias, malignancies
Thymic defects with additional congenital anomalies	di George syndrome (DGS) (mostly 22q11 del) [spontaneous]	Facial dysmorphism, hypoparathyroidism, cardiac defects
	CHARGE syndrome (CHD7) [spontaneous]	Cardiac defects, coloboma, choanal atresia, genital, ear anomalies, deafness
	Both have a spectrum from none to complete T-cell deficiency. Complete DGS occurs in <2% cases of 22 q.11 deletion	
Immuno-osseous dysplasias	Cartilage hair hypoplasia (RMRP) [AR]	Short-limbed dwarfism, autoimmunity, malignancies
	Schimke's [AR]	
Hyper IgE syndrome (HIES)	Stat3 [AD]	Abnormal facies, pneumatoceles, fractures, hyperextensible joints, *Candida*, and *S. aureus*
Dyskeratosis congenita	Nine different genes [AR, AD, or XL]	Bone marrow failure, ↓ NKs, nail dystrophy, skin pigmentation, cerebellar hypoplasia, sparse hair
Omenn syndrome	Potentially any SCID form or complete DGS Most commonly RAG defects	Erythroderma, lymphadenopathy, hepatosplenomegaly, enteropathy

AD, autosomal dominant; AR, autosomal recessive; MHC, major histocompatibility complex; NK, natural killer cell; SNHL, sensorineural hearing loss; XL, X-linked.

Table 34.3 Major antibody deficiency disorders

Clinical syndrome	Molecular defect and inheritance	Specific features
1. Severe reduction in all immunoglobulin isotypes and absent B cells		
X-linked agammaglobulinaemia (XLA)	BTK [XL]	Severe bacterial infections, especially capsulated, giardiasis, enteroviral infections
AR agammaglobulinaemia	Several molecular types (μ heavy chain, λ5, Igα, Igβ, BLNK, PIK3 R1) [AR]	
2. Severe reduction in ≥2 immunoglobulin isotypes and low/normal B cells		
Common variable immunodeficiency disorders (CVID)	Majority (85–90%) genetically undefined. Rare genetic defects include: ICOS, CD19, CD81, CD20, CD21, TACI, LRBA, BAFF receptor [all AR]	Bacterial infections, autoimmunity, granulomatous inflammatory disease, lymphoproliferation
3. Reduced IgG and IgA, raised IgM, normal B cells		
AR hyper IgM syndromes (see Table 34.2 for XL hyper IgM)	AID [AR] UNG [AR] Protein C kinase δ [AR]	Similar to agammaglobulinaemia plus lymphadenopathy and autoimmunity
	PI3Kδ activating mutation [AD]	Severe respiratory disease, bronchiectasis, malignancy, and chronic EBV
4. Other antibody deficiencies. Normal B cell numbers		
Isolated IgG subclass deficiency	Unknown	Unknown significance. Minority may have susceptibility to viral/bacterial infection
Selective IgA deficiency	Unknown	Majority asymptomatic. Minority have poor response to polysaccharide antigens, allergies, autoimmune disease (especially coeliac disease). Rarely progress to CVID
IgA and IgG subclass deficiency	Unknown. IgA, IgG2, and IgG4 deficiency commonest pattern	Recurrent bacterial infections. May progress to CVID or be asymptomatic
Specific antibody deficiency	Unknown	Recurrent bacterial/viral infections. Reduced antibody production to specific antigens, particularly polysaccharide antigens
Transient hypogammaglobulinaemia	Unknown. Can involve all immunoglobulin isotypes	Normal vaccine responses. Not usually symptomatic. Improves with age (up to several years)

AD, autosomal dominant; AR, autosomal recessive; XL, X-linked.

Table 34.4 Disorders of immune dysregulation

Clinical syndrome	Molecular defect and inheritance	Specific features
1. Familial haemophagocytic lymphohistiocytosis syndromes		
Without hypopigmentation	Perforin [AR]	Granulomatous inflammation
	MUNC13-4 [AR]	
	Syntaxin 11 [AR]	
	MUNC 18-2 [AR]	
With hypopigmentation	Chediak–Higashi syndrome (LYST) [AR]	Partial albinism, sino-pulmonary infections, anaemia, neurological and cognitive defect
	Griscelli type 2 (RAB27A) [AR]	Partial albinism, silvery hair, infections
	Hermansky–Pudlak type 2 (AP3B1) [AR]	Partial albinism, neutropenia, interstitial lung disease, infections
Associated with susceptibility to severe EBV infection	X-linked lymphoproliferative disease 1 (XLP1) [XL]	Fulminant EBV infection, antibody deficiency, aplastic anaemia, lymphoma
	X-linked inactivator of apoptosis (XIAP) or (XLP2) [XL]	Fulminant EBV infection, colitis, inflammatory skin infections, splenomegaly. HLH can be mild
	ITK [AR]	
	CD27 [AR]	
2. T regulatory cell defects		
IPEX (immune dysregulation, polyendocrino-pathy, enteropathy, X-linked)	FOXP3 [XL]	Autoimmunity, especially IDDM, enteropathy, blood cytopenias, eczema
	CD25 (IL2Rα) [AR]	Lymphoproliferation, autoimmunity
	STAT5b [AR]	Lymphoproliferation, autoimmunity, eczema, growth hormone insensitivity
3. Autoimmunity without lymphoproliferation		
APECED (autoimmune polyendocrinopathy, candidiasis, and ectodermal dystrophia)	AIRE [AR]	Autoimmunity (IDDM, Addison's disease, hypothyroidism), alopecia, CMC

(*Continued*)

Table 34.4 (*Contd.*)

Clinical syndrome	Molecular defect and inheritance	Specific features
4. Autoimmune lymphoproliferative syndrome (ALPS)		
No increased infection susceptibility	Fas [AR or AD] Fas ligand [AR] Caspase 10 [AD]	Lymphoproliferation, autoimmunity (especially blood cytopenias), malignancy
Increased infection susceptibility	Caspase 8 [AR] FADD [AR] Protein kinase C δ [AR]	Lymphoproliferation, autoimmunity, malignancy, infections
5. Immune dysregulation with colitis		
	IL-10Rα, IL-10Rβ, IL-10 [all AR] Also NEMO deficiency (Table 34.6)	Intractable, very early-onset inflammatory bowel disease, folliculitis, malignancy

AD, autosomal dominant; AR, autosomal recessive; CMC, chronic mucocutaneous candidiasis; HLH, haemophagocytic lymphohistiocytosis; IDDM, insulin-dependent diabetes mellitus; XL, X-linked.

Table 34.5 Major neutrophil disorders

Clinical syndrome	Molecular type and inheritance	Specific features
1. Defects of neutrophil differentiation (neutropenia)		
Isolated severe congenital neutropenia (SCN)	Neutrophil elastase (ELANE) [AD]	Risk of progression to MDS/leukaemia
	GFL1 [AD]	Lymphopenia
	CSF3R [somatic mutation]	
	X-linked neutropenia (activating WAS protein mutation) [AR]	Monocytopenia, no features of WAS
	WHIM (Warts, low IgG, Infections, Myelokathexis) (CXCR4) [AD]	Lymphopenia, monocytopenia
	GATA2 [AD]	Monocytopenia, warts

(*Continued*)

Table 34.5 (*Contd.*)

Clinical syndrome	Molecular type and inheritance	Specific features
SCN with extrahaemato-poietic features	Kostmann disease (HAX1) [AR]	Cognitive/neurological defects. MDS/leukaemic transformation
	G6PC3 [AR]	Cardiac, urogenital abnormalities
	Cohen syndrome [AR]	Developmental delay, hypotonia, retinal dystrophy, hypermobility
	Barth disease [AR]	Cardiomyopathy, myopathy, growth failure
	LAMTOR [AR]	Hypogammaglobulinaemia, partial albinism
	Schwachmann Diamond syndrome [AR]	Bone marrow hypoplasia with risk of AML, pancreatic exocrine failure, growth retardation, skeletal abnormalities
Cyclical neutropenia	ELANE [AD]	Cyclical malaise, mouth ulcers, fevers
2. Defects of neutrophil function		
Chronic granulomatous disease (CGD)	Phagocyte killing defect due to mutations in the phagocyte NADPH oxidase complex	Bacterial/fungal pneumonias; non-infective granulomas, especially in intestinal and urinary tract
	gp91 [XL]—67% of CGD	
	p22, p47, p67, p40 [all AR]—33% of CGD	
Leucocyte adhesion deficiency (LAD)	LAD1: β2-integrin (CD18) [AR]	Delayed umbilical cord separation (>3 weeks); omphalitis, neutrophilia
	LAD2: GDP-fucose transporter [AR]	Short stature, cognitive and neurological abnormalities
	LAD3: KINDLIN3 [AR]	Platelet dysfunction and bleeding tendency

AD, autosomal dominant; AML, acute myeloid leukaemia; AR, autosomal recessive; MDS, myelodysplastic syndrome; WAS, Wiskott–Aldrich syndrome.

Table 34.6 Disorders of the innate immune system

Clinical syndrome	Molecular defect and inheritance	Specific features
1. Mendelian susceptibility to mycobacterial disease (MSMD)		
Isolated MSMD	IL-12Rβ1 [AR]	Susceptibility to atypical mycobacteria, BCG, and *Salmonella*
	IL-12 p40 subunit [AR]	
	IFNγR1 [AR or AD]	
	IFNγR2 [AR]	
	STAT1 [AD]	
MSMD and other features	Anhidrotic ectodermal dysplasia with immunodeficiency (NEMO) [XL]	Bacterial/viral/fungal infection susceptibility. Colitis. Autoimmunity. Skin/nail abnormalities. Hypogammaglobulinaemia
	IKBA activating mutation [AD]	
	IRF8 [AR]	Monocytopenia, absence of NK and circulating dendritic cells
2. Toll-like receptor (TLR) pathway signalling defects		
Pneumococcal susceptibility	IRAK4 [AR]	Pyogenic bacterial infection. Impaired inflammatory response
	MyD88 [AR]	
HSV encephalitis susceptibility	UNC93B1, TLR3, TRAF3, TRIF, TBK1 [AD or AR]	HSV 1 encephalitis only
3. Predisposition to severe viral infections		
	STAT2 [AR]	
	MCM4 [AR]	Short stature, adrenal failure
4. Predisposition to invasive fungal diseases		
AD hyper IgE syndrome	STAT3 [AD]	Abnormal facies , pneumatoceles, fractures, hyperextensible joints, *Candida*, and *S. aureus*
	CARD9 [AR]	Invasive *Candida*
5. Chronic mucocutaneous candidiasis (CMC)		
	STAT1 gain of function [AD]	Mouth, nail, and skin *Candida* infection, folliculitis, thyroid autoimmunity common
	IL-17RA [AR]	
	IL-17F [AD]	
	ACT1 [AR]	

AD, autosomal dominant; AR, autosomal recessive; NK, natural killer.

Table 34.7 Disorders of the complement system

Clinical syndrome	Molecular defect and inheritance	Specific features
1. Classical pathway complement deficiencies		
Early components	C1q, C1r, C1s, C2, C4 deficiencies [AR]	SLE, bacterial infections (especially capsulated organisms)
	C3 deficiency [AR or AD gain of function]	Infections, glomerulonephritis
	C3 gain of function mutation [AD]	aHUS
Late components (C5–9)	C5,C6,C7,C8α, C8γ,C8b, C9 [AR]	*Neisseria* infections
Inhibitor deficiency	C1 inhibitor [AD]	Hereditary angio-oedema
2. Alternate pathway complement deficiencies		
Inhibition of alternate pathway	Properdin [XL], factor D [AR]	Bacterial (especially *Neisseria*) infections
Activation of alternate pathway	Factor I [AR] Factor H [AR] Factor H-related protein [AR] Thrombomodulin [AD] Factor B gain of function [AD] CD46 [AD]	Bacterial (especially *Neisseria*) infections aHUS
3. Mannose-binding lectin (MBL) deficiency		
	MASP1 or MASP2 deficiency [AR]	General increased infection susceptibility—mainly to bacteria, including *Meningococcus*. Usually only problematic in young children or older individuals who become immunosuppressed

AD, autosomal dominant; aHUS, atypical haemolytic–uraemic syndrome; AR, autosomal recessive; SLE, systemic lupus erythematosus; XL, X-linked.

When to suspect primary immunodeficiency

PIDs are rare, and consequently the diagnosis is often delayed. This can have major consequences for the child. The more severe disorders generally present in infancy.

- Table 34.8 lists some common clinical presentations and the most likely diagnoses to consider.
- Table 34.9 lists common clinical presentations for which immunodeficiency is unlikely to be the cause.

Table 34.8 Common presenting features of 1° immunodeficiency

Clinical feature	Diagnoses to consider
Interstitial pneumonitis caused by *P. jirovecii* or viruses	Combined immunodeficiencies (especially SCID), CD40 ligand deficiency, MHC II deficiency, complete DGS
Chronic diarrhoea; either persistent enteric viral infection(s) or immune-mediated gut inflammation	Combined immunodeficiencies, IPEX syndrome, IL-10/IL-10R deficiency
Persistent superficial candidiasis	Combined immunodeficiencies, neutrophil disorders, CMC
≥2 episodes of invasive bacterial disease. Staphylococcal or Gram-negative bacillary (including bacteraemia)	Neutrophil disorders, antibody deficiencies, combined immunodeficiencies (especially Omenn syndrome)
≥2 episodes of invasive capsulated bacterial infections (including bacteraemia)	Combined immunodeficiencies, antibody deficiencies
Pneumonia (≥2 episodes)	Antibody deficiency, combined immunodeficiency, innate disorders, neutrophil disorder (especially if staphylococcal or fungal)
≥4 episodes of otitis media, sinusitis, or LRTIs in a year	Antibody deficiency, combined immunodeficiency, complement or MBL deficiency
Chest and ear infections with unsteady gait	AT
Invasive fungal disease (excluding catheter-associated *Candida* infection)	Neutrophil disorders (especially CGD if *Aspergillus* infection), combined immunodeficiencies
Disseminated atypical mycobacterial infection or invasive non-typhoidal *Salmonella* infection (in infant over 6 months of age)	MSMD, combined immunodeficiency, NEMO deficiency, CGD
Failure to thrive in infancy (with infection susceptibility)	Combined immunodeficiencies, antibody deficiencies
Severe generalized erythroderma (± lymphadenopathy, hepatosplenomegaly)	SCID/complete DGS with Omenn syndrome or GVHD (maternal engraftment or transfusion acquired)

(*Continued*)

Table 34.8 (*Contd.*)

Clinical feature	Diagnoses to consider
Severe eczema and susceptibility to infection	SCID with Omenn syndrome, IPEX, STAT3 deficiency, DOCK 8 deficiency, WAS (with thrombocytopenia)
Granulomatous rash	CVID, AT, perforin deficiency, LAD
Facial dysmorphism and susceptibility to infection	DGS (22 q.11 deletion), CHARGE syndrome, DNA repair defects, STAT3 deficiency, ICF syndrome
Other congenital abnormalities, e.g. cardiac, hypoparathyroidism, colobomata, choanal atresia, short limbs	DGS (22 q.11 deletion), CHARGE syndrome, cartilage hair hypoplasia
Multiple autoimmunity phenomena: multi-lineage cytopenias; polyendocrinopathy; atypical SLE	ALPS, combined immunodeficiencies, CVID, APECED, IPEX, complement deficiencies
Unexplained lymphadenopathy and splenomegaly	ALPS, combined immunodeficiencies; AR hyper IgM
HLH	XLP, XLAP, perforin deficiency, Munc13-4 or 18-2, syntaxin
HLH with hair pigment abnormalities	Chediak–Higashi syndrome, Griscelli's syndrome

ALPS, autoimmune lymphoproliferative syndrome; AT, ataxia telangiectasia; CGD, chronic granulomatous disease; CMC, chronic mucoctaneous candidiasis; CVID, common variable immunodeficiency disorder; DGS, di George syndrome; GVHD, graft-versus-host disease; HLH, haemophagocytic lymphohistiocytosis; ICF, immunodeficiency, centromere instability, and facial anomalies; LAD, leucocyte adhesion deficiency; MBL, mannose-binding lectin; MHC, major histocompatibility complex; MSMD, mendelian susceptibility to mycobacterial disease; SLE, systemic lupus erythematosus; WAS, Wiskott–Aldrich syndrome.

Table 34.9 Common scenarios not usually associated with 1° immunodeficiency

Clinical scenario	Comments
Recurrent upper respiratory 'viral' infections without bacterial complications	Most likely related to social/schooling circumstances
Recurrent septic spots/boils in absence of other infections	Exclude IDDM; most likely colonization with a troublesome strain of *S. aureus*
Recurrent tonsillitis	Consider chronic streptococcal infection; periodic fever syndrome such as PFAPA
Recurrent central line sepsis in absence of other infections	Consider treating for *S. aureus* colonization; possible MBL deficiency
Recurrent regular fevers	Periodic fever syndrome such as PFAPA, possible cyclical neutropenia
Idiopathic thrombocytopenia without other autoimmunity, infections, or lymphadenopathy/splenomegaly	Most are idiopathic; consider X-linked thrombocytopenia (WAS variant without immunodeficiency)—look for small platelet volume

IDDM, insulin-dependent diabetes mellitus; MBL, mannose-binding lectin; PFAPA, periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis; WAS, Wiskott–Aldrich syndrome.

Laboratory investigations

Laboratory tests used to diagnose PIDs can be grouped as follows:

1. *Descriptive tests*: quantification of individual components of the immune system (e.g. immunoglobulin levels, lymphocyte subsets)
2. *Functional tests*: testing the function of a component of the immune system (e.g. mitogen-stimulated T proliferative responses, vaccine responses)
3. Specific protein expression or function: by flow cytometry or Western blot
4. *Genetic testing*: to confirm a pathological mutation.

Laboratory testing is targeted to the type of immunodeficiency suspected from the history. Initial investigation involves confirming the presence of a real deficiency (first-line tests). This is followed by more specific tests to try to establish a precise diagnosis (second-line tests). In some instances, very specific clinical features may allow focused investigation for individual conditions, e.g. Wiskott–Aldrich syndrome or ataxia telangiectasia.

Discussion with the laboratory and/or a clinical immunologist prior to testing will usually help focus investigations and maximize the information gained. The interpretation of immunological assessments can be affected by:

- Age of the child
- Gestation at birth (if an infant)
- Recent administration of blood products/immunoglobulin
- Recent/current use of immunosuppressive agents, including corticosteroids.

First-line immunodeficiency investigations should exclude 2° causes of immunodeficiency (e.g. HIV infection). Typical targeted investigation schemes for each group of immunodeficiency disorders are shown in Table 34.10.

Genetic testing

The diagnosis of a PID is confirmed by the combination of defective protein expression or function and the identification of an explanatory pathogenic genetic mutation. There are several approaches to identifying a genetic diagnosis:

- Direct Sanger sequencing of specific genes—fastest and most efficient when a specific diagnosis is suspected
- Next-generation sequencing of targeted DNA enrichment—cost-effective sequencing of multiple (>90) known PID genes
- Whole exome or genome next-generation sequencing—potential to identify novel genetic disorders, but slowest and most expensive.

All genetic testing requires robust bioinformatics to predict whether DNA sequence variants are likely to be significant and disease-causing. Genetic results suggesting a novel defect must be corroborated with protein or functional assays.

Storage of DNA from a child dying of an unusual infection (either EDTA blood or skin fibroblast culture) is important, as it may enable a posthumous genetic diagnosis to be made, with subsequent genetic counselling.

Table 34.10 Tests for immunodeficiency

Type of immunodeficiency suspected	First line	Second line
Combined immunodeficiency	FBC Immunoglobulin levels (IgG, IgA, IgM, IgE) Lymphocyte subsets Mitogen proliferative response (e.g. phytohaemagglutinin, PHA)	Naive/memory T-cell subsets Other lymphoid markers (MHC classes I and II, CD25, CD40L) T-cell receptor repertoire studies (TCR Vβ families, spectra typing) TRECs Anti-CD3 or antigen specific (*Candida*, tetanus) T-cell proliferative responses Functional molecular assays, e.g. phosphorylation of components of signalling pathways (e.g. STAT5) Specific protein assays by flow cytometry or Western blot (e.g. WAS protein) ADA and PNP enzyme levels Comparative genomic hybridization array Radiation sensitivity testing (skin fibroblast culture) α-fetoprotein screen for AT (after infancy)
Antibody deficiency	FBC Immunoglobulins levels (IgG, IgA, IgM) Vaccine response antibodies (tetanus, *Pneumococcus*) Lymphocyte subsets	Memory B cell subsets Antibody levels post-revaccination IgG subclasses Isohaemagglutinins Specific protein assays (e.g. Btk for XLA)
HLH	Granule release assay (CD107 expression on cytotoxic cells following stimulation) Perforin expression SAP and XIAP protein expression	Protein expression for other proteins involved in granule release
ALPS	Lymphocyte subsets assessing double negative α/β T cells ($CD4^-$, $CD8^-$)	Apoptosis assays Fas expression Biomarkers in blood (IL-10, soluble FasL, vitamin B_{12})

(*Continued*)

Table 34.10 (*Contd.*)

Type of immunodeficiency suspected	First line	Second line
Neutrophil disorders	FBC Nitroblue tetrazolium (NBT) test Expression of LFA-1 (CD11/18)	Sequential FBCs (cyclical neutropenia) Bone marrow aspiration and trephine DHR assay (oxidative burst by flow cytometry) Neutrophil activation (CD62L shedding) Assays of migration, phagocytosis, bacterial killing Specific protein assays, e.g. gp91 (XL CGD)
Innate disorders	Exclusion of other types of disorder. No first-line tests	Cytokine release assay Neutrophil activation (CD62L shedding) Specific protein assays
Complement disorders	MBL levels C3 and C4 levels Classical and alternate pathway function	Individual complement component assays

Prenatal testing and newborn screening

Families should be counselled about the risk of recurrence of serious immunodeficiencies in the family. Prenatal testing can be performed as follows:

- Chorionic villous sampling from 12 weeks (where a genetic mutation has been identified)
- Amniocentesis at 14–16 weeks—enzyme assays for ADA- and PNP-deficient SCID
- Fetal blood sampling from 19–20 weeks—for complete SCID with absent T cells.

Where families choose not to have these procedures, cord blood should be collected for testing when the infant is born, and appropriate prophylactic measures initiated.

It is also important to save cord blood as a potential source of stem cells for possible future affected babies in the family.

Newborn screening for SCID, using PCR for T-cell receptor excision circles (TRECs) on dried blood spot samples, has been introduced in a number of countries, including the US. This technique is highly sensitive at identifying babies with severe T-cell disorders, allowing diagnosis prior to the development of life-threatening infections.

Management while investigating for suspected immunodeficiency

If a diagnosis of 1° immunodeficiency is strongly suspected, consider the following treatment.

Severe combined immunodeficiency

- Commence PCP prophylaxis with co-trimoxazole.
- Commence antifungal prophylaxis with fluconazole.
- All blood products to be CMV-negative and irradiated.
- Stop breastfeeding until mother's CMV status established (if negative, can restart).
- No live vaccines to be given (BCG, rotavirus).

Antibody deficiency

- Commence prophylactic antibiotics to cover capsulated bacterial pathogens, e.g. azithromycin.

Complement factor deficiency

- Commence penicillin prophylaxis.

Further reading

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Chapter 35

Invasive fungal infection

See also Chapters 2, 17, 23, 47, 51, 95.

Introduction

The management of IFI is hampered by poor diagnostics and limited antifungal drugs, while the incidence of IFI in children is rising due to an increasing number of immunocompromised children. Children particularly at risk are those born prematurely or requiring intensive care, children undergoing intensive chemotherapy or HSCT for the treatment of malignancies, children with 1° immune disorders, children receiving extensive immunosuppressive treatment, including the use of monoclonal antibodies for the prevention and treatment of GVHD and for the treatment of rheumatological, auto-inflammatory, and autoimmune conditions.

Aspergillus spp. and *Candida* spp. have been the commonest pathogens isolated, but, over the past few decades there has been an emergence of invasive infections caused by *Cryptococcus* spp., *Mucorales, Fusarium*, and *Scedosporium* spp. among other filamentous fungi (moulds). The mortality related to IFI remains high, despite the development of new management strategies, and depends strongly on the reversal of the underlying immune dysfunction.

Epidemiology

Candida spp.

- *Candida* spp. are the commonest cause of IFI. *C. albicans* is still the most frequent species causing invasive candidiasis, although 25% is caused by *C. parapsilosis,* while *C. glabrata* is rarely seen as a causative species in children (opposite from the epidemiology in adults).
- *Candida* is a yeast that multiplies in the bloodstream by budding and forms pseudohyphae in solid tissues. Being a commensal of the GI and urogenital tract, infections are mainly endogenous in origin but may also be transmitted by the hands of health-care workers or during delivery (vaginal colonization). *Candida* spp. cause BSIs, with or without dissemination, single-organ infections, or chronic disseminated (hepatosplenic) candidiasis.
- Reported incidences of invasive candidiasis in extremely low-birthweight (ELBW) infants (<1000g) ranges between 5% and 25%, in haemato-oncology patients between 4% and 10%, and in children admitted to the ICU 9–18% of all nosocomial infections.

Aspergillus spp.

- *Aspergillus* is a filamentous fungus that is ubiquitous in our environment and grows on decaying vegetation. Over 100 *Aspergillus* spp. are known,

but *Aspergillus fumigatus* is the most frequent species causing infections. Construction and renovation works, and contaminated air systems and water sources have been associated with invasive aspergillosis in immunocompromised children.
- The hydrophobic conidia of the *Aspergillus* spp. are easily dispersed by air, and inhalation of conidia is the commonest route of infection, leading to respiratory tract disease (lungs, sinuses). After infection, the conidium will germinate and form hyphae, the tissue-invasive form. Dissemination can occur, especially to the CNS.
- *A. fumigatus* is the commonest spp. isolated, with *Aspergillus flavus, Aspergillus terreus, Aspergillus niger*, and *Aspergillus nidulans* less frequent. *A. nidulans* preferentially causes disease in patients with CGD, with a predisposition to bone infection next to pulmonary disease.
- Incidences of invasive aspergillosis in immunocompromised children are similar to adults and depend on the degree of immunosuppression. Children with acute leukaemias and treated with HSCT have the highest risk (≥10%) among patients with malignancies and organ transplants, while patients with CGD have a lifetime incidence of 25–40%.

Other fungi

Cryptococcus spp.
- *Cryptococcus* spp. are encapsulated yeasts and live in soil and organic matter containing high concentrations of bird excreta.
- Infection is acquired by inhalation of contaminated air.
- *C. neoformans* is the commonest species causing disease and is characterized by its neurotropism, leading to predominantly CNS infection.
- Cryptococcosis is an AIDS-defining illness but is also observed in other patients with compromised cellular immune function (e.g. lymphoma, prolonged steroid use). The introduction of combination ART has reduced its incidence to almost zero in those areas of the world where ART is available.
- There has been an increasing incidence of non-*neoformans Cryptococcus* spp. causing invasive disease in the past few decades, especially *Cryptococcus laurentii* and *Cryptococcus albidus*.

Mucorales
- These filamentous fungi include, among others, *Rhizopus* spp, *Mucor* spp, *Rhizomucor* spp, *Lichtheimia* spp, and *Cunninghamella* spp.
- Transmission is mainly airborne, and common sites of infection include the sinuses and the lungs.
- *Mucorales* have, even more than the *Aspergillus* spp. and other filamentous fungi, a predilection for the invasion of blood vessels, causing extensive thrombosis, infarction, and bleeding.
- They tend to be resistant to most azoles and echinocandins.

Fusarium and Scedosporium spp.
- Filamentous fungi similar to *Aspergillus* with respect to their presence in the environment and route of transmission, but are able to sporulate *in vivo* and cause fungaemia presenting with skin lesions.
- Often resistant to amphotericin and the echinocandins.

Risk factors and mortality rates

- Neutropenia is the most significant risk factor for IFI, especially significant neutropenia for prolonged periods (≤500/microlitre for ≥10 days). Moderate neutropenia of 0.1–0.5 × 10^9/L for <1 week carries considerably less risk.
- Table 35.1 shows the individual risk factors associated with either invasive yeast or mould infections.
- The mortality rate of invasive candidiasis in children ranges between 10% and 25% and can be up to 50% in ELBW infants.
- The overall mortality of invasive aspergillosis in children is as high as 50%, and even higher for invasive infections caused by other moulds.

Table 35.1 Individual risk factors for the development of invasive yeast (*Candida*) and mould (*Aspergillus* and other moulds) infections

Invasive yeast infections	Invasive mould infections
Prolonged/severe neutropenia	Prolonged/severe neutropenia
Prolonged use of steroids (>0.3mg/kg/day of prednisolone)	Prolonged use of steroids (>0.3mg/kg/day of prednisolone)
Severe congenital neutropenia	CGD
Leucocyte adhesion deficiency	Severe congenital neutropenia
CARD9 deficiency (only CNS)	AD-HIES (STAT3 mutations)
Colonization	Leucocyte adhesion deficiency
Mucosal disruption	
Presence of indwelling catheters	Accidental exposure (construction sites, compost, hay barn, contaminated ventilation systems)
Total parenteral nutrition (TPN)	Severe influenza virus pneumonia
Abdominal surgery	GVHD (grades III/IV > grades I/II)
Broad-spectrum antibiotic use	
Elevated serum glucose levels	
H2 blockers	
Neonatal risk factors:	
Extreme prematurity (<28 weeks of gestation)	
ELBW (<1000g)	

Risk stratification

Risk stratification allows patient groups to be identified as low-, intermediate-, or high-risk for developing IFI. Based on reported incidences, it is possible to categorize paediatric patients with cancer and is summarized in Box 35.1. Risk stratification allows for specific management strategies and the use of particular screening and diagnostic measures. Among premature neonates, those born below 28 weeks of gestation and/or <1000g birthweight (ELBW) have the highest risk of developing invasive candidiasis, while the risk is minimal in neonates born after 32 weeks of gestation and/or >1500g birthweight. For children with PIDs, those with phagocytic disorders have the highest risk (e.g. children with CGD).

Box 35.1 Stratified risk of invasive fungal infection in children treated for cancer*

- Sporadic
  - Solid tumours
  - Brain tumours
  - Hodgkin's lymphoma.
- Low risk (below and close to 5%)
  - Autologous HSCT
  - Acute lymphoblastic leukaemia
  - Non-Hodgkin's lymphoma.
- High risk (close to and above 10%)
  - Acute myeloblastic leukaemia
  - Acute recurrent lymphoblastic leukaemia
  - Allogeneic HSCT (moderate to severe GVHD will increase risk)
  - High-risk acute lymphoblastic leukaemia.

* Source data from Groll AH, Castagnola E, Cesaro S, *et al*. Fourth European Conference on Infections in Leukaemia (ECIL-4): Guidelines for Diagnosis, Prevention and Treatment of Invasive Fungal Diseases in Paediatric Patients with Cancer or Allogeneic Haematopoietic Stem Cell Transplantation *Lancet Oncol* 2014, **15**(8):e327-e340 doi: 10.1016/S1470-2045(14)70017-8.[1]

Management strategies

Due to the current poor diagnostic tests available, the need of performing invasive diagnostics to isolate the causative fungus, and the dismal outcome of IFI in children, several management strategies have been developed.

- Antifungal prophylaxis may be indicated in those patients with a high risk (>10%) of developing IFI. Based on the local epidemiology, a choice needs to be made between an antifungal with activity against yeasts (fluconazole or micafungin, or nystatin in neonates) or a mould-active antifungal like itraconazole, voriconazole, or posaconazole. The development of resistance or changes in the epidemiology is a concern when antifungal prophylaxis is used.
- Empirical antifungal therapy has been common practice in neutropenic patients with persistent fever for >4 days despite broad-spectrum antibiotics. Although empiric antifungal therapy was shown to reduce the incidence of IFI, no effect on overall mortality could be observed. Both liposomal amphotericin and caspofungin can be used in an empiric treatment setting.
- A pre-emptive strategy aims to detect IFI in an early phase by non-culture-based screening methods and an extensive work-up if an IFI is suspected. This strategy is only feasible if rapid performance of imaging and bronchoscopies and/or biopsies are available. It has been shown to reduce the consumption of antifungal drugs.
- In very premature neonates presenting with fever or signs of infection after the second week of life, with the presence of two or more additional risk factors, initiation of empiric antifungal treatment might be considered, in addition to broad-spectrum antibiotics, while awaiting results of cultures (blood, CSF, urine).[2]

- In children with CGD, every effort should be undertaken to make a causative diagnosis due to the wide range of fungi causing disease in this particular host. Invasive diagnostic measurements are, in general, more feasible to perform, when compared with children with haemato-oncological diseases (e.g. thrombocytopenia, marginal clinical condition).
- In addition to these management strategies, targeting specific risk factors, and thereby lowering the risk of developing an IFI, should be part of each management strategy. One should consider the following measures: prevention of exposure to moulds; reduction of the duration of neutropenia by G-CSF; a rational antibiotic policy and avoidance of prolonged broad-spectrum antibiotics; daily assessment of the need for indwelling catheters; and the need for prescribing H2 blockers.

Diagnostic measures

Microbiology/histopathology

- Microscopy and culture, along with histopathology, has traditionally been the gold standard for diagnosing IFI. Testing can be performed on blood (for yeasts and certain moulds sporulation *in vivo*), CSF, BAL fluid, urine, fluid from normally sterile sites, and tissue specimens.
- Microscopy has a higher yield than culture alone, especially in BAL samples. The use of fluorescent brighteners (e.g. calcofluor white, blankophor) can improve the sensitivity, allowing septate (*Aspergillus, Fusarium, Scedosporium*) and non-septate (*Mucorales*) moulds to be distinguished and appropriate antifungal therapy to be initiated in a timely manner.
- All fungi cultured from normally sterile sites, including blood, urine, CSF, peritoneal dialysis fluid, and CVC tips, should be identified to the species level by referring them to a specialist laboratory, and drug susceptibility testing should be carried out.
- Recovery of moulds and *Cryptococcus* spp. from BAL fluid should be identified to the species level as well, including susceptibility testing.
- In the absence of an alternative diagnosis in an appropriate host, the CSF should be tested for cryptococcal antigen if neurological signs and/or symptoms are present.
- All histology samples for suspected IFI should be stained with a fungal stain, such as silver stain, concurrently with conventional haematoxylin and eosin stain.

Major advances, in particular the early detection of invasive mould infections, have been made by the development of non-culture assays for fungal antigens or nucleic acids and by high-resolution CT (HRCT)-chest imaging. Although these diagnostic tools have been included in the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) definitions of IFI,[3] their validity and usefulness in children have not been fully assessed.

Non-culture-based diagnostics

Galactomannan

- Galactomannan[4] is a cell wall component of the *Aspergillus* spp. (and a few other moulds like the *Fusarium* spp.) secreted during invasive growth and can be analysed by galactomannan enzyme-linked immunosorbent assay (ELISA) (Platelia®).
- The test has predominantly been validated as a screening tool in the serum of neutropenic patients with a high risk of developing invasive aspergillosis, but studies support its diagnostic use in BAL fluid and CSF as well.
- Two or more positive results (index ≥0.5) from consecutive serum samples are indicative of a probable invasive aspergillosis, and further diagnostic procedures (e.g. HRCT-thorax, BAL) are required to make a diagnosis.
- Paediatric studies have shown a combined sensitivity of 76% and specificity of 86%, which is consistent with adult studies.
- Prospective monitoring of galactomannan twice weekly is recommended for neutropenic children at high risk for IFI.
- Cross-reactivity has been observed with β-lactam antibiotics, Bifidobacteria abundantly present in infantile gut microflora and several foods, such as rice and pasta, by translocation across damaged gut mucosa.
- False negative results may occur when mould-active antifungal prophylaxis is used.
- The test is not validated in the serum of non-neutropenic patients (e.g. CGD patients, solid organ transplant recipients) as a screening or early detection measure.

Mannan

- The detection of mannan, a candidal antigen, in combination with the detection of anti-mannan antibodies, is a method to detect the *Candida* spp. in serum samples.
- Studies in adults with candidaemia showed sensitivity and specificity rates of around 80% and 85%, respectively, which means an accuracy of 50–70%.
- The test has not been validated in children, and studies are lacking.

1,3-β-D-glucan

- This assay detects 1,3-β-D-glucan (BDG) (Fungitell®), which is present in most opportunistic fungi (not in *Cryptococcus* spp. and *Mucorales*).
- It has a reported sensitivity of >65% (cut-off value 80pg/mL) and specificity of >80% for diagnosing candidaemia in adults.
- The test has not been validated in children, and it has been shown that BDG baseline levels are higher in non-infected children, compared to adults.

Fungal DNA

- The use of PCR technology to diagnose IFI still remains unvalidated but will potentially enable the routine screening of high-risk patients and enhance the diagnosis of IFI.

- While many data are published regarding in-house PCR techniques, external validation and harmonization should be made before clinical recommendations can be made.

Imaging

- In adults with haematological malignancies, the use of serial HRCTs of the chest has allowed invasive aspergillosis to be diagnosed earlier. Characteristic radiological features include the halo sign (an area of ground glass opacity around a nodule seen early in the infection) and the air crescent sign (in a later phase of the infection due to lung tissue destruction). It is recommended to perform an HRCT-thorax in high-risk children with persistent neutropenic fever not responding to broad-spectrum antibiotics or if galactomannan in the serum tests positive in two consecutive samples. HRCT abnormalities may be surprisingly advanced, even when the child has a normal CXR!
- Unfortunately, the characteristic radiological features, as seen in adults, are found far less commonly in children. Non-specific lobar changes are more often seen and may represent invasive aspergillosis. Every new pulmonary infiltrate in a high-risk patient presenting with persistent fever, despite broad-spectrum antibiotics, should give rise to the suspicion of invasive aspergillosis or other invasive mould infection.
- Abnormalities on the HRCT-thorax are not specific for invasive aspergillosis but can be caused by any filamentous fungus. A BAL or biopsy has to be performed to identify the causative fungus. The *Candida* spp. might rarely give invasive lung disease, but more commonly it will spread to the lungs by persistent candidaemia.
- If a diagnosis of invasive aspergillosis has been made, an MRI cerebrum should be considered, due to the fact that up to 15% of patients will also have CNS disease, and neurological symptoms will only become apparent at a later stage of infection. CNS aspergillosis might require a different therapeutic approach (e.g. choice of antifungal and dose).
- In neonates and children with candidaemia, imaging of the heart (ultrasound), eye (fundoscopy), and abdominal organs (ultrasound) should be performed due to the prevalence of metastatic infectious foci.
- In children with haematological malignancies with persistent fever, despite broad-spectrum antibiotics, and with/without recovery of neutropenia and negative blood cultures for *Candida* spp., one should consider chronic disseminated candidiasis, also called hepatosplenic candidiasis. Ultrasound of the liver and spleen will detect multiple small lesions in those organs, although, very early in the course, imaging might be normal. Ultrasound changes are more marked when neutrophil recovery has occurred. Persistent or worsening fever on recovery of neutropenia should prompt an abdominal ultrasound.
- Further imaging in the course of any IFI depends on clinical signs and symptoms.

Key references

1 Groll AH, Castagnola E, Cesaro S, *et al*. Fourth European Conference on Infections in Leukaemia (ECIL-4): guidelines for diagnosis, prevention, and treatment of invasive fungal diseases in paediatric patients with cancer or allogeneic haemopoietic stem-cell transplantation. *Lancet Oncol* 2014;**15**:e327–40.

2 Hope WW, Castagnola E, Groll AH, *et al*. ESCMID guideline for the diagnosis and management of *Candida* disease 2012: prevention and management of invasive infections in neonates and children caused by *Candida* species. *Clin Microbiol Infect* 2012;**18**(S7):38–52.

3 De Pauw B, Walsh TJ, Donnelly JP, *et al*. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis* 2008;**46**:1813–21.

4 Cuenca-Estrella M, Verweij PE, Arendrup MC, *et al*. ESCMID guideline for the diagnosis and management of Candida disease 2012: diagnostic procedures. *Clin Microbiol Infect* 2012;**18**(S7):9–18.

Chapter 36

Toxic shock syndrome

See also Chapters 36, 40, 104, 105.

Toxic shock syndrome

- TSS is an acute febrile illness caused by Gram-positive bacteria (*S. aureus, S. pyogenes* (*GAS*), and occasionally groups C and G) that rapidly progresses to shock with multi-organ failure.
- The capillary leak that underlies the disease results from intense T-cell proliferation and cytokine release that is part of an inflammatory response initiated by bacterial protein exotoxins that act as superantigens.

Pathophysiology

- Superantigens are potent immunomodulatory proteins that stimulate T cells by directly binding class II molecules on antigen-presenting cells to the T-cell receptor (Fig. 36.1).
- Unlike conventional antigens, superantigen stimulation is not major histocompatibility complex (MHC) class II-restricted but is constrained in only a limited fashion by the specificity of the T-cell receptor 'Vβ family', defined by the variable portion of the B chain of the T-cell receptor (TCRVB).
- Superantigens stimulate a large proportion (up to 20%, versus normally 0.01%) of T cells, resulting in intense immune activation and the release of cytokines, including TNF-α, IL-1, IL-2, and IFN-γ, which lead to the clinical features of TSS.
- Nearly all *S. aureus* strains and many GAS strains have the capability to produce one or more superantigens. Recently also some CoNS and groups C and G streptococci have been shown to produce superantigens.
- In addition, GAS M protein form complexes with fibrinogen. These complexes stimulate integrins on polynuclear neutrophils, resulting in oxidative burst and endothelial damage. This, in turn, leads to vascular leak and stimulates coagulation.

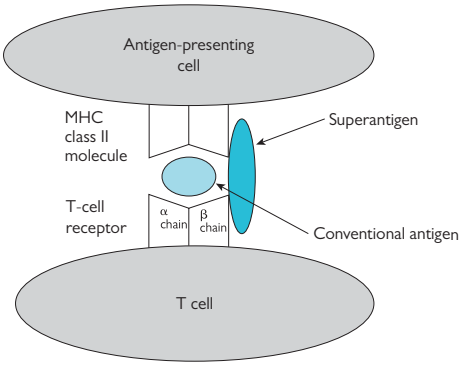

Fig. 36.1 Composite diagram contrasting T-cell stimulation by a conventional antigen and a superantigen.

Incidence and aetiology

Streptococcal toxic shock syndrome

- GAS:
  - Gram-positive cocci
  - Form chains
  - Catalase-negative
  - β-haemolytic colonies on blood agar
  - Lancefield typing (typing of the carbohydrate in the cell wall) identifies the organisms as GAS
  - M1 and M3 protein types are associated with TSS and necrotizing fasciitis.
- Streptococcal TSS occurs in association with invasive *S. pyogenes* infections (isolation of the organism from a normally sterile site).
- Since the mid 1980s, there have been increasing reports of streptococcal TSS around the world.
- The incidence of invasive GAS infection in industrialized countries is ~2–4 cases per 100 000, 10–15% of which are TSS.
  - The incidence in resource-poor countries appears to be at least three times higher.
- Streptococcal TSS can affect any age group:
  - Infants, pregnant women, and the elderly are most at risk
  - ~20% of all cases of invasive *S. pyogenes* infections occur in children.

Staphylococcal toxic shock syndrome

- *S. aureus*:
  - Gram-positive cocci
  - Form clusters
  - Catalase-positive
  - Coagulase-positive.
- There are two types of staphylococcal TSS: menstrual and non-menstrual.

Menstrual staphylococcal toxic shock

- Accounts for 50–60% of adult cases of staphylococcal TSS.
- First described in 1980 in the US in menstruating women using hyperabsorbable tampons.
- Incidence rates were as high as 12.3 per 100 000 in women of menstruating age.
- Incidence rates fell to 1 per 100 000 within 6 years of the removal of these tampons from the market, and continues at this rate today.
- Almost always associated with the superantigen 'TSS toxin-1' (TSST-1).

Non-menstrual staphylococcal toxic shock

- Accounts for nearly 50% of all cases of staphylococcal TSS.
- Surgical procedures and burns are important risk factors.

The overall incidence rate for staphylococcal TSS currently is about 3.4 per 100 000.

Clinical features

- Streptococcal TSS and staphylococcal TSS share similar clinical features, including:
  - Fever
  - Diffuse, macular, erythematous, blanching ('sunburn') type rash, followed by desquamation after ~2 weeks (often as early as a few days in staphylococcal TSS)
  - Rapid progression to shock and multi-organ failure
  - Mucosal hyperaemia: non-purulent conjunctivitis; oropharyngeal changes, including swollen lips or strawberry tongue; vaginal hyperaemia in the case of staphylococcal TSS.
- Approximately half of patients have hypotension at presentation, and nearly all develop hypotension over the following 4 hours; subacute presentations, in which patients deteriorate over days, are rare.
- Other early signs suggesting capillary leak include postural hypotension, tachycardia, and increased capillary refill time.
- While it is not possible to reliably distinguish streptococcal from staphylococcal TSS from the clinical features alone, particularly early in the disease, there are some differences between the two syndromes (Table 36.1).

Table 36.1 Characteristic features of streptococcal and staphylococcal TSS

	Streptococcal TSS	Staphylococcal TSS
Mortality rate	30–60%	<3%
Positive blood cultures	60–80%	Low
Typical rash	Less common	Very common
Associations	Soft tissue infection	Tampon use
	Varicella infection	Surgical procedures
	NSAID	NSAID
		Burns
		Influenza infection

Streptococcal toxic shock syndrome

- Patients with streptococcal TSS may initially present with a flu-like prodromal illness with fever, myalgia, vomiting, and diarrhoea.
- Soft tissue infection is the commonest associated focus of infection (>60% of cases).
  - Up to 75% of these soft tissue infections may progress to necrotizing fasciitis.
  - Other associated clinical infections include empyema, SA, peritonitis, meningitis, tracheitis, endophthalmitis, and perihepatitis.
  - Presents with bacteraemia alone, without a clear focus, in ~15% of cases.
- Neonatal streptococcal TSS is well described.
  - In 75% of cases, there is documented maternal vaginal carriage of GAS.

Necrotizing fasciitis

See Chapter 33.

- Thirty to 50% of patients with GAS-associated necrotizing fasciitis develop streptococcal TSS.
- In children, most cases of necrotizing fasciitis occur without an apparent preceding factor.
- When a precipitating factor is present, the commonest factor is varicella infection.
  - Persistent fever or a new fever on day 3 or 4 of chickenpox should alert the clinician to the possibility of invasive GAS infection.
  - Blunt trauma is another risk factor in children.

Staphylococcal toxic shock syndrome

Menstrual staphylococcal toxic shock syndrome

- Starts during or within 2 days of the end of menses.
- Up to 30% of cases are recurrent.

Non-menstrual staphylococcal toxic shock syndrome

- Occurs in any age group and affects both sexes.
- Patients may only have a trivial cutaneous or subcutaneous (or undetected) infection as the focus of infection.
- In children, the skin is the commonest site of infection.
  - Other clinical syndromes include visceral abscesses, endocarditis, OM, pyomyositis, mastitis, and peritonitis.
- Staphylococcal TSS has been associated with:
  - Surgical procedures: especially ear, nose, and throat surgery, and nasal packing
  - Post-operative wound infection and colonization; there may be no evidence of obvious inflammation of the wound
  - Burns: children are at particularly high risk; if TSS occurs, it is usually in the first few days following the burn
  - Influenza infection: TSS occurring in children with influenza carries a high mortality rate
  - AIDS: recalcitrant desquamative syndrome
  - Chronic peritoneal dialysis
  - Childbirth.

Differential diagnosis, depending on geographical area

- Gram-negative septic shock.
- Meningococcal sepsis.
- Myocarditis.
- Kawasaki disease.
- Severe influenza.
- Rocky Mountain spotted fever and other rickettsial infections.
- Leptospirosis.
- Measles.
- Hantavirus.

Investigations and diagnosis

- Case definitions for both staphylococcal TSS and streptococcal TSS have been developed (Boxes 36.1 and 36.2).
  - The diagnostic criteria for TSS were designed as research criteria.
  - They have high specificity to identify established cases, but poor sensitivity, particularly early in the disease course.
  - Failure to meet these criteria should not delay a provisional diagnosis and the management strategies described.

Box 36.1 Diagnostic criteria for streptococcal TSS

Streptococcal TSS—case definition

1. Isolation of GAS:
   A. From a sterile site (definite case)
   B. From a non-sterile site (probable case).
2. Clinical signs of severity:
   a. Hypotension

   AND
   b. Two or more of the following clinical and laboratory abnormalities:
      i. Fever (>38.5°C)
      ii. Rash (diffuse macular erythema with subsequent desquamation)
      iii. Renal impairment
      iv. Coagulopathy (platelets <100 × 10^9/L or DIC)
      v. Liver enzyme abnormalities
      vi. ARDS
      vii. Extensive tissue necrosis (including necrotizing fasciitis)
      viii. GI symptoms.

Box 36.2 Diagnostic criteria for staphylococcal TSS

Staphylococcal TSS—case definition

1. Fever (38.9°C).
2. Hypotension.
3. Rash (diffuse macular rash with subsequent desquamation).
4. Involvement of three of the following organ systems:
   a. Liver (elevated transaminases)
   b. Blood (platelets $<100 \times 10^9$/L)
   c. Renal (raised creatinine/urea or pyuria in absence of UTI)
   d. Mucous membranes (vaginal, conjunctival, or oropharyngeal hyperaemia)
   e. GI (vomiting and profuse diarrhoea)
   f. Muscular (severe myalgia or raised creatinine phosphokinase)
   g. CNS (disorientation or alteration in consciousness without focal neurological signs)
   h. Respiratory distress.
5. Exclusion of the following illnesses by negative serology:
   a. Measles
   b. Leptospirosis in endemic areas
   c. Rocky Mountain spotted fever in endemic areas.
6. Negative blood or CSF cultures for organisms other than *S. aureus*.

Probable case: 5/6 features; confirmed 6/6, including desquamation.

Investigations

- Patients with suspected TSS need adequate microbiological investigations, including:
  - Blood cultures
  - Culture of any obviously infected sites, as clinically indicated, such as joint aspiration, pleural fluid aspiration
  - Culture of tampon and high vaginal swab in menstrual TSS.
- Patients with suspected TSS need investigating for the potential development of multi-organ failure, including the following (these tests often need to be repeated):
  - Arterial blood gas (ABG)
  - FBC
  - Creatinine, U&Es
  - CRP
  - Liver enzymes
  - Clotting profile, including fibrinogen, D-dimers
  - Serum albumin
  - Creatinine phosphokinase
  - CXR.
- Later in the course of the illness, anti-streptolysin O titre, anti-DNase, and anti-staphylolysin can be determined.
- Routinely establishing the presence of a tampon (and its prompt removal) is a crucial part of the examination and investigation of all post-menarche ♀ patients with TSS.

- If the diagnosis of necrotizing fasciitis is not clear, several investigations may be useful. including:
  - MRI
  - Frozen section biopsy specimens of suspected areas of tissue.
- However, if there is a strong suspicion of necrotizing fasciitis, surgery should not be delayed.

Management

There are four elements to the management of TSS:

- Supportive care
- Surgical intervention
- Correct antibiotic choice
- Adjunctive treatments:
  - IVIG
  - Clindamycin.

Supportive care

- As one of the defining features of TSS is the profound hypotension caused by toxin-mediated capillary leak, aggressive fluid replacement and the early use of inotropes is crucial.
- Renal support may also be required early; renal failure often precedes hypotension.
- Patients often require endotracheal intubation and ventilation, particularly when ARDS develops.

Surgical intervention

- Surgical intervention is particularly important in streptococcal TSS when there is soft tissue infection.
  - In necrotizing fasciitis, wide debridement of non-viable tissue is critical and substantially improves outcome, although more recent reports question the evidence behind this widely adopted management.
  - Surgical intervention is also important in establishing the diagnosis of necrotizing fasciitis.
- Surgical intervention is required less often in staphylococcal TSS.

Antibiotic therapy

- Empiric broad-spectrum antibiotics are required until a streptococcal or staphylococcal aetiology is confirmed.
- β-lactams are the first-line antibiotic of choice for streptococcal TSS.
- A β-lactamase-resistant antibiotic, such as flucloxacillin, is the first choice for staphylococcal TSS.
- Flucloxacillin is also an effective anti-streptococcal antibiotic and should therefore be used when the aetiology is uncertain.
- Clindamycin is often also added, acting as a protein synthesis inhibitor. Theoretical advantages of clindamycin include:
  - Inhibitory action on toxin production
  - Ability to potentiate phagocytosis
  - Post-antibiotic effect
  - Superior tissue penetration.

- Clindamycin should be added to the above standard treatment regimens, rather than replace them, because not all *S. aureus* and GAS strains are sensitive to clindamycin.
  - Clindamycin is a bacteriostatic (not bactericidal) antibiotic.
- Vancomycin, or alternatively daptomycin or linezolid, may replace flucloxacillin as empiric therapy if there is a significant likelihood of MRSA:
  - Hospital-acquired infection
  - In regions where susceptibility patterns suggest that there is a relatively high risk of community-acquired MRSA
  - Patients from communities with high rates of community-acquired MRSA infections.

Intravenous immunoglobulin therapy

- Studies suggest that streptococcal TSS may be a subgroup of systemic disease where IVIG has a beneficial role.
  - There is only one RCT of IVIG in streptococcal TSS. The trial was ceased prematurely because of slow patient enrolment.
  - The study found a trend toward improved survival at 28 days but did not find a significant difference in mortality.
  - An earlier observational historically controlled cohort study showed a significant difference in mortality at 30 days.
  - It is unlikely that another RCT of IVIG will take place in either staphylococcal or streptococcal TSS.
  - Most experts recommend the use of IVIG in streptococcal TSS.
  - Some experts state that early IVIG administration might prevent the need for extensive surgical debridement and would allow for a more conservative approach.
- The role of IVIG in staphylococcal TSS has been studied in even less detail.
  - Generally, IVIG is not indicated because of the low mortality rate of staphylococcal TSS.
  - However, given that the pathogenesis of staphylococcal and streptococcal TSS is similar and that the superantigens produced by *S. aureus* and *S. pyogenes* share a common three-dimensional structure and mode of action, it seems likely that IVIG will also be beneficial in severe cases.
- There is no consensus on the dose of IVIG that should be given in TSS.
  - Suggested doses included in Table 36.2 are based on doses used in the RCT of IVIG in streptococcal TSS and the higher single-dose regimen proven of value in Kawasaki disease.

Table 36.2 Two suggested dosing regimens for IVIG in TSS

Regimen	Day 1	Day 2	Day 3
1	2g/kg	–	Repeat 2g/kg if patient remains unstable
2	1g/kg	0.5g/kg	0.5g/kg

Outcome

- The case fatality rate for streptococcal TSS ranges between 30% and 60%.
- There is high morbidity with streptococcal TSS, especially in cases of necrotizing fasciitis, in which wide debridement, potentially with amputation, is performed.
- The case fatality rate for non-menstrual staphylococcal TSS is ~6%, while that of menstrual TSS is <3%.

Prevention

- Some studies have noted an association between the use of NSAIDs, necrotizing fasciitis, and streptococcal TSS.
- The underlying cause for this association may be:
  - NSAIDs mask fever and reduce pain and may therefore lead to delayed presentation
  - Inhibition of the normal feedback loop of prostaglandin on the production of TNF-α by macrophages leads to an excess of cytokines that predisposes to TSS.
- NSAIDs should be avoided in patients with TSS.
- Some experts recommend generally avoiding NSAIDs in patients without a known source for their fever, and particularly in children with varicella (which is a predisposing factor for TSS).

Contact prophylaxis in streptococcal toxic shock syndrome

- The attack rate of streptococcal TSS in close contacts of patients with streptococcal TSS is higher than the attack rate in the general population:
  - Data from Canada: 2° attack rate 294 per 100 000
  - Data from the US: 2° attack rate 66 per 100 000.
- There is no evidence to suggest that contact prophylaxis is effective in preventing disease in contacts.
- The advantages of contact prophylaxis are potentially preventing disease in contacts and preventing transmission of virulent strains.
- The disadvantages of contact prophylaxis include the unnecessary use of antibiotics in most contacts and the risk of serious side effects, including anaphylaxis.
- Expert opinion varies on the use of contact prophylaxis.

Prevention of recurrent menstrual staphylococcal toxic shock syndrome

- Patients who have had a first episode of staphylococcal TSS are at risk of recurrent episodes. Risk factors include:
  - Menstrual TSS, particularly in the first 6 months after the episode of TSS
  - Inadequate anti-staphylococcal antibiotic therapy
  - Inadequate antibody response to staphylococcal toxin.

Future research

- The changing epidemiology of both staphylococcal and streptococcal TSS is the subject of ongoing surveillance in many centres.
  - The problem of MRSA, both hospital- and community-acquired, is increasing.
  - Despite the increasing rates of community-acquired MRSA and their association with severe soft tissue infections, there is currently no evidence to suggest that these organisms are more likely to cause TSS.
- Improved knowledge of the immunopathogenesis of superantigen-mediated disease may lead to the development of new therapeutic agents.

Further reading

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Chapter 37

Trauma, bites, and burns

See also Chapters 38, 39, 48, 104, 105.

Bites

- The majority of bites are due to dogs (80–90%), cats (5–15%), humans (3–20%), and rats (under 2%), with other animals contributing a small percentage of the cases.
- Dog bites tend to be on the limbs, particularly on the arms, with up to 25% of bites being on the head and neck. Preschool children tend to have bites on their heads, as this part of the body is closer to the biting reach of the animal than in older children.
- The main locations of cat bites in about 60% of cases are on the arms, ~28% on the head and neck, and the rest mostly on the lower limbs.
- Human bites are found on the hand, arm, shoulder, and leg in ♂ victims, and, in addition, in ♀, bites may occur on the breast or genitalia. Many people bitten manage the bite without further consequences; this applies to an estimated five out of six people who are bitten.
- In over 70% of cases, people are bitten by animals known to them; children are at high risk on injury, with children <5 years of age being at highest risk.

Incidence

- US data show that over 4.5 million Americans are bitten every year; 400 000 require treatment, and about 20 die from their injuries, mostly by exsanguination. They account for 1% of visits to emergency departments in the UK, with young ♂ being more often bitten by dogs.
- Infectious complications can occur from all types of bites. Infection is usually polymicrobial, with up to 173 types of bacteria being found in the oral cavity. Bites usually contain aerobic and anaerobic bacteria, with *Pasteurella, Streptococcus, S. aureus*, and the anaerobes *Fusobacterium* and *Bacteroides* most commonly identified from animal bites.
- Cat bites and hand wounds are more likely to become infected.
- Blood-borne viral infections may also be transmitted via a bite, including hepatitis viruses and HIV.

Principles of management of bites

- The following features should be documented:
  - How and when did it occur? Is there any delay in presentation?
  - When did it happen and in what circumstances?
- Assessment of the wound.
- Cleaning and debriding the wound.
- Consideration of prophylactic antibiotics.
- Treatment of any infections.
- Appropriate pre-emptive tetanus measures.

History

A history must be taken that includes any bleeding tendency, underlying immunosuppression, or deficiency in making a competent immune response. This includes a history of diabetes or steroid therapy, liver disease, or functional asplenia.

Immunization status, including the tetanus status, must be documented, and, if required, booster vaccines administered. The mechanism must be determined, and the possibility of non-accidental injury considered; if there is concern, safeguarding procedures should be activated.

Examination

The location of the bite, its appearance, and if there is any associated damage to structures at the bite site, e.g. tendons, nerves, joints, blood vessels, or involvement of any organs such as the eye, must be documented and acted upon.

The clenched fist also has the potential for the metacarpophalangeal space to be breached by a bite which can lead to OM, SA, or tracking infections within synovial sheaths.

Cleaning the wound

Wound cleaning is mandatory in the management of any bite. The wound should be irrigated with water, pain relief given, and the bite examined.

The risk of infection is estimated to be >1 in ten cases if any of the following apply:

- Full-thickness puncture
- Deep penetration
- Injury occurred over 24 hours ago
- Devitalized or dead tissues
- Hand or foot wounds
- Medical predisposing conditions
- Underlying injury to other structures other than skin.

Penetrating wounds on the distal aspects of limbs, such as the foot or hand, are at higher risk of infection, especially if the wound comprises puncture-like lacerations, which inoculate organisms into deeper tissues.

Dirty wounds, i.e. those with debris or faecal material contaminating the wound, are also at higher risk of infection and may require surgical debridement, along with wounds with extensive devitalized tissues.

Avoid 1° closure in:

- Deep puncture wounds
- Infected wounds
- Dirty wounds
- Bites to the feet or hands (consult with the recognized expert in your area)
- Wounds >24 hours of age.

Prophylactic antibiotics

- The use of antibiotics is controversial.
- Suggested sites for the use of prophylactic antibiotic use include:
  - Joints, bone, or tendons
  - Hand or foot bites

- Cat bites
- Devitalized or dead tissue, or heavily contaminated tissues
- Deep puncture wounds
- Immunosuppression.

- Erythromycin should NOT be used, as *Pasteurella* is resistant to this antibiotic.
- Co-amoxiclav is the commonest antibiotic advised to be given—give for 3 days as prophylaxis, 7 days for established 2° infection.

Insect bites

Incidence

Up to 100% of the population gets bitten by an insect every year, but the number of fatalities are very small, comprising on average about four deaths per annum.

UK insects

The very few harmful arthropods of the UK comprise:

- *Hymenoptera*—bees (including bumblebees and honeybees), wasps (including hornets and yellow jackets)
- *Diptera*—mosquitoes, horseflies, stable flies, blackflies
- *Siphoneptra*—fleas (human, cat, dog)
- Scabies
- Bedbugs
- *Phthiraptera*—lice.

Management

The child should be assessed for any life-threatening conditions such as an anaphylactic reaction.

Small local reactions

- If a sting is in place, remove without squeezing it.
- If bitten by a tick, remove it with tweezers (do not burn it off, as otherwise the skin may be burnt!). Consider sending for identification.
- Thoroughly wash the site with water, and cold compresses can be applied (never put ice directly on a wound, as otherwise cold thermal injury can take place), along with mild analgesia such as paracetamol.
- A mild-potency hydrocortisone cream can be applied, such as 1% strength, but a lesser dose should be used on facial bites.
- Antihistamines may have a place to reduce swelling and irritation, especially a sedating one, should the irritation be disturbing sleep.

Large reactions

These are defined as extending beyond the site of the bite.

- Offer pain relief—usually simple analgesia is sufficient.
- A short course of antihistamines—non-sedating for daytime use and a sedating one for night-time may be helpful to the patient.

Systemic reactions

Anaphylaxis is likely if there are features of these three categories:

- Sudden onset and rapid evolution of signs and symptoms
- An impact on airway (A) and/or breathing (B) and/or circulation (C)
- Cutaneous features and/or mucosal involvement (e.g. flushing, angio-oedema, urticaria).

Cutaneous features alone are not indicative of anaphylaxis; however, up to 20% of patients with anaphylactic reactions do NOT have a cutaneous manifestation.

Hence, consider if the reaction is a systemic one, especially if there are any of the following:

- Signs of airway difficulty or obstruction
- Increased respiratory effort
- Hypotension, marked pallor, collapse, chest pain.

Burns

The skin acts a barrier, having a role in the regulation of temperature and water loss from the body. Once breached, these functions may be reduced, and heat loss accompanied by fluid loss can occur. The tissues deeper to the skin may become accessible to colonization by cutaneous commensals, as well as pathogenic bacteria.

Prophylactic antibiotics are not routinely recommended, as the normal flora may be disturbed and lead to infection with other pathogens, including fungal infection. Burns commonly occur in children, varying from superficial scalds to full-thickness and life-threatening conditions.

Initial management of a child with a burn

- The initial approach is A (airway), B (breathing), and C (circulation), D (disability), and E (exposure), as in the management of any potentially life-threatening condition.
- Heat that may cause inhalation injury, such as upper airway obstruction, is life-threatening; hence a child whose voice has changed pitch or is unable to speak properly should be considered for emergency intubation.
- The majority of burns do not fall into this life-threatening group; however, a full history and explanation is required in all cases, as a small number of cases are due to non-accidental injury and must be managed appropriately.
- The assessment of pain and its relief at the earliest stage possible is mandatory.
- Tetanus status must be assessed, and appropriate treatment given accordingly (see Chapter 117).

Assessment of the burn

The depth, location, and size of the burn are important features, as these have a bearing on the healing process and the need for involvement of specialists such as plastic burns surgeons and their teams.

Depth

Superficial burns (formerly known as first-degree burns) only affects the epidermis but are nonetheless painful, as cellular contents reach pain fibres in the dermis. An example of superficial burn is sunburn.

Partial-thickness burns (formerly called second-degree burns) do extend into the dermis but do not obliterate structures such as hair follicles or sebaceous glands, whose lining within the dermis is epithelial tissue. Hence, regeneration of the burnt area comes from marginal growth and growth from the epithelial structures that go into the dermal tissues. This means that there may not necessarily be scarring, as the whole burn area can be regenerated from epithelial cells.

Blisters may appear with this type of burn and are painful, for the same reasons as seen in superficial burns.

Full-thickness burns (formerly called third-degree burns) involves the dermis, so that structures, such as the hair follicles and sebaceous glands, are destroyed. As the pain receptors are also destroyed, this lesion tends to be painless in the affected area (note that there may be gradients of burns, so that surrounding tissues may show partial-thickness or superficial-thickness burns).

Full-thickness burns are associated with scarring and a poor cosmetic result, unless plastic expertise is sought, as the deeper regenerative epithelial layers have been destroyed.

Location and size

Full-thickness burns, fire injuries, and burns over 30% of the surface area are more likely to become infected. Large burns—over 30%—also cause significant immunosuppression. Humoral, T-cell, and neutrophil immune deficits have been reported.

For all ages, the following surface areas apply:

- The anterior and posterior aspects of trunk = 26%
- The neck circumference = 2%
- The upper arm (humeral part) = 4%
- The forearm = 3%
- The dorsum of the hand = 1.5%
- The plantar aspect = 1.5%
- The dorsum of the feet = 1.75%
- The plantar aspect of the foot = 1.75%
- The genital area = 1%
- Each buttock = 2.5%.

Management

As noted, attention is first paid to ABC and pain relief. Then use simple measures such as cooling the burns with tepid water (very cold water can cause hypothermia).

A simple non-adherent covering can be applied, such as cling film, in the first instance, so that the wound can be observed.

Complications

Infection is often a difficult diagnosis in children with burns, as they usually have a high WCC and CRP. Nearly all children with a serious burn have a high fever, often for a week or longer.

The classical signs of a burn wound infection are local signs of inflammation or a purulent exudate, with or without clinical signs of sepsis syndrome. A skin biopsy may be helpful in confirming the diagnosis and for culture. Early infection in the first 2 days is usually due to skin organisms, including GAS and *S. aureus*.

By around 1 week, most burns are colonized by Gram-negative organisms, including *Pseudomonas* and other *Enterobacteriaceae*. Later infections include those caused by *Candida, Aspergillus*, and other fungi. Later infections of nosocomial organisms have been reported. Inhalation pneumonitis can be complicated by severe pneumonia.

TSS is an uncommon complication but can be lethal if it is not recognized. It may occur in any size of burns, including small burns. There will often not be the appearance of infection at the wound site, but the symptoms of being unwell, with the signs of erythema, vasodilation, tachycardia, tachypnoea, diarrhoea, and 'toxic' appearance, should raise the suspicion of this disorder.

Management

- Routine prophylactic systemic antibiotics are no longer used in burns units, or for burns treated and sent home.
- Careful dressing and use of topical antimicrobial agents are often used.
- Replacement immunoglobulin is now also no longer used.
- Systemic antibiotics are given only for clinical or proven sepsis. Use as narrow-spectrum as possible, with short treatment duration. Very narrow-spectrum penicillin-based antibiotics may be used in the first 2 days, but an agent active against *Pseudomonas* should be used after the first few days (e.g. piperacillin, tazobactam).
- Note that the pharmacokinetics of antibiotics may be altered in burns patients. Renal impairment is also common.

Future research

- Further studies to define the optimal topical antimicrobial agent and regimen.
- Improved clinical and laboratory tests to diagnose serious infections.

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Chapter 38

Travelling abroad with children

See also Chapters 33, 34, 42.

Introduction

When adults take children on trips, they can worry too much, or they can be so relaxed as to overlook the dangers—it is tricky being a parent! The travel industry frequently underplays the risks; indeed the whole idea of travel is often sold as an escape to a health-giving environment.

The medical outcome of a family trip overseas depends on:

- Destination and style of travel
- Pre-existing medical conditions
- Parental experience and knowledge
- Availability of safe equipment and safety equipment
- Parental willingness to consent to immunization and also, if appropriate, to comply with malaria prophylaxis
- Parental willingness to follow other precautions, including bite prevention and sun protection.

Causes of ill health

It is difficult to study outcomes in travelling children. Broadly, patterns of disease in travelling families parallel those in the home environment, but with additional hazards and infection risks (such as swimming in *Schistosoma*-infected lakes and rivers). Travelling children, like other children, commonly ingest undesirable substances. In low-income countries, ingestion is made more likely when, for example, fuel is stored in old cola bottles.

Trauma is also more likely where safety standards are different from those at home, especially where conditions are less familiar and traffic is on the 'wrong' side of the road. Toddlers may fall off flat roofs or through insecure balustrades, or hazards may be highlighted in a language unfamiliar to the caring adults. Drowning is also a common cause of death. Adventure travel probably comes with increased risks of trauma; parents are well advised to book with companies with experience of child clients so that safety equipment is age-appropriate. Heatstroke is a significant risk in small infants—especially in cars.

Motion sickness

This can be a huge challenge to travelling families. It is rare below the age of 2 years, and the peak age is between 3 and 12 years. ♀ are almost twice as susceptible as ♂ (1.7:1). Hyoscine is effective and the fastest acting in preventing travel sickness, but, if >1 dose is given, it causes dry mouth and drowsiness. The skin patches that release hyoscine over 72 hours are not recommended for children under 10 years. Antihistamines

(cinnarizine, meclozine, and cyclizine) are better for multiple dosing but need to be started before the onset of symptoms; dosing starting the night before travel can work well. Ginger is also an effective antiemetic, even in the form of ginger biscuits.

Immunization and prophylaxis

- Travel immunizations are given, in addition to routine childhood vaccines; yet some parents resist immunization, even when travelling into regions where vaccine-preventable diseases are common. Routine childhood immunizations are especially important in travellers to regions where vaccine delivery or health infrastructure is poor.
- Information on which vaccines are needed for travelling from Europe is available on the National Health Service (NHS) 'fitfortravel' website (🔗 <http://www.fitfortravel.nhs.uk>).
- Those visiting friends and relations are at increased risk of infection, compared with tourists. Children raised in industrialized nations may be immunologically naive, compared with family members raised overseas; yet relatives may not see the need for bed nets or malaria prophylaxis.
- Commonly, parents assume that vaccines provided free by the NHS are the most important ones; thus hepatitis A and typhoid are accepted, whereas Japanese encephalitis may not be.
- There are some challenges in immunizing the very young. For example, there is a poor immune response to typhoid in children <18 months. Yellow fever vaccine is contraindicated in children <6 months and should be used with caution in those <9 months of age. It is probably wise to defer to a specialist travel practitioner if the family is travelling to a high-risk or remote destination or going on an extended trip.
- The BCG vaccine is recommended for those <16 years of age who are going to live or work with local people for >3 months in a country where the annual incidence of TB is 40/100 000 or greater.

Malaria

- Small children and also pregnant women are most likely to die if they contract malaria, so families may need to be encouraged to rebook for safer destinations—until children are capable of reporting early symptoms. About 300 children are treated for malaria in Britain annually, which represents around half of the total paediatric reports for Europe. There is concern that prescribing antimalarials to small children may appear to sanction an unwise and risky trip into a highly malarious region.
- Malaria prevention means firstly avoidance of bites:
  - Permethrin impregnation of cover-all clothes
  - An effective repellent applied frequently to any exposed skin
  - Permethrin-impregnated bed nets.
- Bite prevention precautions may be difficult to apply in young children, and a curfew—retiring to screened accommodation—at 6 p.m. when mosquitoes are most voracious may be necessary, yet difficult, to enforce.

- Bite prevention is crucial, and coverall clothes (which can be proofed with permethrin) and 30–50% DEET applied to any skin that is left exposed are protective. Children should sleep under a permethrin-impregnated bed net if the bedroom is not mosquito-free. Applying DEET repeatedly to extensive areas of skin in infants is undesirable and unnecessary. Babies can be protected by cot nets and coverall clothes.
- If parents are prepared to take adequate preventive measures, and there are good reasons to travel into regions where there is a high risk of contracting malaria (i.e. much of sub-Saharan Africa), then a prescriber may offer mefloquine or proguanil/atovaquone prophylaxis. Details of prophylaxis is given in the *BNFC* (🖱 <http://www.bnfc.org>).
- Advice on malaria areas and specific drugs is also given by the National Travel Health Network and Centre (🖱 <http://www.nathnac.org) or the 'fitfortravel' website (🖱 <http://www.fitfortravel.nhs.uk>).
- Mefloquine can be given (crushed or chopped) to any child weighing >5kg; it does not seem to cause the neuropsychiatric side effects that are reported in some adults. Weight is a better guide to dosing than age.
- Proguanil/atovaquone paediatric tablets can be given for prophylaxis daily to children over 10kg, and these tablets may also be crushed or mixed with food, jam, or a milky drink.
- Homeopathic prophylaxis and immunization are contrary to homeopathy theory and is not promoted by competent homoeopaths, nor should it be endorsed by paediatricians.
- Reminding parents about the prompt reporting of fever, especially within 3 months of leaving a malarious region, can also be lifesaving.

Diarrhoeal disease

The commonest cause of morbidity in travelling children is diarrhoeal disease. Travel—or more specifically eating in restaurants and hotels—increases the risk of diarrhoea, even in northern Europe and North America (the attack rate in adults is in excess of 5%). During any trip to the Indian subcontinent and tropical Latin America, the attack rate is probably >50% per trip. The risks in children, especially in the under 3s, are high, and the consequences potentially graver. It is essential that parents understand oral rehydration (and local alternatives to ORS, e.g. fresh coconut water) and can recognize the clinical signs of dehydration. Some cautious advisers say travel to high-risk regions of diarrhoeal disease is foolhardy with young children, but risks depend on the preparedness of the parents.

Peel it, boil it, cook it, or forget it is a useful guide to safe food. Ice cream and hotel buffets are risky in regions where electricity is intermittent or hygiene standards are poor. Parents may find it helpful to know that a few minutes of a 'rolling boil' will kill most organisms, including amoebic cysts. Iodination is an effective backup and is unlikely to cause upset over a brief trip, but will not kill *Cyclospora*.

Any persisting GI symptoms on return home should be investigated by sending stools on 3 different days, with a request for microscopy for cysts and ova and stool culture.

Skin infections

In hot climates, *young skin* needs sun protection, even when swimming.

- There is a good range of clothes/swimwear and beach 'pods' with ultraviolet protection factor ratings.
- Any insect repellent should be applied 30–60min after sunscreen.
- Beach shoes protect the feet from coral, sea urchin spines, broken glass, and used hypodermics.
- Long, loose 100% cotton clothes protect from sunburn, biters, scratches, and stings.
- There is a strong association between sunburn in childhood and skin cancer later.
- Prickly heat or miliaria rubra is common, especially in young infants; vitamin C is no help, and antihistamines do not relieve symptoms since the mechanism is not histamine-mediated. It settles when sweating is reduced by a few hours per day in an air-conditioned environment or by cooling under a fan. 2° infection is common.
- Mobile youngsters sustain innumerable grazes, and it is important, especially in warm climates, for any wounds to be cleaned and covered to prevent sepsis. Creams tend to promote infection. Potassium permanganate, a good drying antiseptic, is available in many regions.
- Scratching mosquito bites is also a problem.

Atopic conditions

Atopic conditions can be unpredictable during travel. Often hay fever and asthma improve, but stress and dry aircraft air may precipitate an asthma attack. Eczema should get no worse as long as moisturizers are applied liberally and there is no sensitivity to sunscreens. DEET repellent is unsuitable on broken skin. Acne may worsen or improve in increased sun exposure.

High-risk travellers

Immunocompromised children may need or choose to travel; their increased risks and issues include the following:

- Live vaccines: these should be avoided in immunocompromised children (except HIV-infected children with CD4 counts >15%). Otherwise full immunization, as per travel schedules, should be encouraged (including influenza and hepatitis B)
- Emergency antibiotic course prescription: all immune-suppressed travellers to resource-poor countries should be prescribed a supply of an antibiotic such as azithromycin. They should be advised to have a low threshold for taking antibiotics for any diarrhoeal illness, other than mild watery diarrhoea.

HIV-infected children

- Families of HIV-infected children will need advice on the safe transport and storage of antiretrovirals during trips. They may also need advice about possible drug interactions with other medication.
- HIV-infected children can be given most travel vaccines (namely inactivated typhoid, hepatitis B, rabies, hepatitis A, and meningococcal ACYW) when needed, except when the CD4 T-cell counts are very low.
- However, there is insufficient evidence as to the safety of yellow fever vaccine in HIV-positive people.

Children with cancer

- Families should be strongly discouraged from travelling with immunocompromised children during the immediate *post-chemotherapy* or *radiotherapy* period, at least until the treatment course is complete, neutrophil counts have returned to normal, and the patient is not requiring transfusions.

Transplant recipients

- Traveller's diarrhoea may be associated with greater risk in a transplant recipient for reasons over and above the increased susceptibility to infection such as increased risk of compromised renal function from dehydration and altered absorption of post-transplantation immunosuppressants.

Post-splenectomy patients

- Prior to travel, parents should ensure that splenectomized children are up-to-date with pneumococcal, Hib, and meningococcal ACWY vaccines, according to prevailing guidelines. A 'standby' course of a broad-spectrum antibiotic therapy (such as co-amoxiclav) should be considered for children who may have limited access to emergency medical care during their travel.
- Asplenic children have a high risk of severe malaria. If travel to regions of high malaria transmission is unavoidable, then asplenic travellers and those with thalassaemia and sickle-cell disease should seek expert advice regarding malaria risk and prevention before travel. They must pay meticulous attention to bite prevention, and adequate malaria prophylaxis must be taken.
- Parents of asplenic children should have a low threshold for seeking urgent medical advice if there is unexplained fever, whether or not presumptive antimicrobial therapy has been started.

Antibody-deficient children

- In travelling children who require replacement immunoglobulin for a congenital or acquired humoral immune deficiency, protection against travel-acquired infection is optimized by scheduling their dose close to departure. Vaccine efficacy is likely to be poor in children with immunoglobulin deficiency.

Drug interactions

- Antimalarials may interact with some antiretrovirals and transplant-related immunosuppressives. Chloroquine can increase serum levels of ciclosporin, and perhaps sirolimus and tacrolimus. Data are limited regarding other possible interactions between travel-associated drugs and anti-rejection drugs. The effect on ciclosporin levels of short courses of ciprofloxacin or azithromycin for traveller's diarrhoea is thought not to be a significant risk.

Less familiar 'tropical' infections reported to be of heightened risk to the immunocompromised are:

- Helminth infections: these may become overwhelming in the immunocompromised. *Strongyloides* infection may be especially disastrous, so children should be advised against walking barefoot in tropical areas that might be contaminated with excreta
- Leishmaniasis (both cutaneous and visceral) in atypical forms: this may be more frequently encountered in immunosuppressed patients. The most important personal protective measure in endemic regions is excluding minute biting sandflies by sleeping under an insecticide-treated bed or cot net
- *Cyclospora* and *Cryptosporidium* infections can also be severe in the immunocompromised, so, in endemic regions, water should be boiled before drinking.

First-aid kits

Large medical kits are seldom necessary; most drugs are available overseas, but paediatric preparations may be unpalatable, unobtainable, or unsafe (there have been deaths from contaminated paracetamol syrup in Bangladesh and Haiti); colourful dressings (which have 'magical' analgesic properties) may be difficult to find. Over-the-counter remedies may contain pharmaceutical mixtures or even counterfeit medicines. Parents might be encouraged to travel with a health guide.

Suggested minimal kit

- Insect repellent—up to 30% DEET can be used on children, but use with long clothes reduces the amount that needs to be applied. Concerns about DEET toxicity are now largely discounted, with most reports due to accidental ingestion; sensible family advice therefore is to recommend wipes or a roll-on preparation and to avoid prolonged use and application onto broken skin. If the travelling infant is too young for the parents to feel happy about using DEET, they possibly should not be taking the child to a high malaria risk setting.
- Sunscreen: test for sensitivity before travel; so-called sunblocks reduce wavelengths causing sunburn, without completely protecting from cancer-causing wavelengths. It is probably better to apply sun protection factor (SPF) 15–25 and reapply frequently. Sun products need to be replenished annually too.

- Paracetamol and/or ibuprofen syrup: pleasant, melt-in-the-mouth paracetamol (= acetaminophen) is available in the US.
- Motion sickness preparation.
- Digital thermometer.
- Skin closure strips.
- Colourful pictorial sticking plasters.
- Drying antiseptic.
- Mild to medium-strength steroid cream for itching bites, jellyfish stings, and exacerbations of eczema
- Sometimes a broad-spectrum antibiotic such as amoxicillin.

Probably the most challenging time for children to travel is between the onset of independent mobility (often at 8–9 months) and the start of the age of reason with the onset of the ability to describe symptoms (from perhaps 3 years). With intelligent preparation, appropriate immunization, prophylaxis, and plenty of time, family travel need not have health implications. However, sometimes it is the duty of a doctor to point out that certain trips are perhaps just too hazardous to particular children and/or individuals of certain ages.

Future research

A systematic investigation of child illness among returning visitors to friends and family would form a useful addition to the literature.

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Chapter 39

Urinary tract infection

See also Chapters 37, 69.

Introduction

Definition: UTI is defined as significant bacteriuria in the presence of symptoms.

- UTI is a common bacterial infection, affecting around 10% of girls and 4% of boys by the age of 16 years.
- In most children, UTI is an isolated acute infection from which they recover quickly.
- Clinical presentation ranges from mild localized complaints to systemic symptoms. Infants often present with non-specific symptoms and can be severely ill.
- Because fever is often the only symptom at younger ages, UTI is a frequent differential diagnosis in children presenting in 1° care and in the hospital setting with unexplained fever.
- The presence of fever increases the probability of renal involvement and is associated with increased likelihood of underlying congenital abnormalities of kidneys and urinary tract (CAKUT) such as vesicoureteral reflux (VUR), hydronephrosis, or renal dysplasia.
- However, infection associated permanent renal scarring and anatomical abnormalities requiring surgical attention occur only in a minority of children with UTI.
- In recent years, there has been a less aggressive approach to the management and invasive investigations of children with uncomplicated UTI.

Causative organisms

- The bacteria that cause UTIs originate from the gut flora.
- The ability of bacteria to cause urinary infections depends on host factors, as well as bacterial virulence factors.
- Uropathogenic *E. coli* (UPEC), due to their specific virulence properties, account for 70–90% of community-acquired infections.
- UPEC may possess P-fimbriae that facilitate uroepithelial attachment and express adhesins, haemolysins, and other molecules, which trigger innate inflammatory response of the uroepithelium through multiple pathways.
- Other bacteria, referred to as 'non-*E. coli*', can also cause UTI.
  - Examples are: *Klebsiella* spp., *P. mirabilis, P. aeruginosa*, CoNS, streptococci (e.g. GBS), enterococci, *S. aureus*, or even 'fastidious' organisms like *H. influenzae*.

- Non-*E. coli* organisms often do not possess the virulence factors seen in UPEC. Their ability to cause UTI depends heavily on host factors—CAKUT leading to reduced urine flow, renal calculi, urinary catheters, or certain host immunological characteristics.
- Therefore, non-*E. coli* UTI is one of the indications for investigating the urinary tract of affected children.

Epidemiology

- The risk of UTI has been estimated to be 11.3% for girls and 3.6% for boys during the first 16 years of life.
- The incidence of UTI in children <3 months of age is higher in boys, reflecting probably a higher incidence of obstructive CAKUT in ♂, e.g. posterior urethral valves. After this age, girls prevail. UTI affects 2.1% of girls and 2.2% of boys <2 years of age, and 6.6% of girls and 1.8% of boys 2–5 years of age.
- Children with UTI and CAKUT are more likely to present with severe systemic illness and tend to present in infancy.
- Recurrences:
  - Children presenting in infancy have a higher rate of recurrence than those presenting later
  - Girls are more likely to have recurrences of UTI
  - The presence of a dysfunctional bladder and/or chronic constipation increases the risk of recurrence of UTI.

Clinical presentation and differential diagnosis

Severity of illness varies, and the clinical spectrum can be classified into:

- '*Cystitis*' or lower tract infection. The infection is confined to the bladder, and a typical clinical presentation includes dysuria, frequency, incontinence, urgency, sometimes accompanied by haematuria
- '*Acute pyelonephritis*' or upper tract infection. The infection involves the kidneys, and the clinical presentation includes fever (≥38°C) or other systemic symptoms: loin pain, vomiting, failure to thrive, or persistent irritability
- More severe forms of UTI affect mostly children with urological history and include:
  - '*Renal abscess*', which is characterized by focal purulent destruction of the renal parenchyma
  - '*Acute focal bacterial nephritis*' (*AFBN*), which is a severe form of pyelonephritis involving large renal parenchymal areas and is considered the midpoint between acute pyelonephritis and an abscess
  - These entities are clinically indistinguishable from pyelonephritis
- '*Asymptomatic bacteriuria*' is the presence of significant bacterial growth in the urine of a child who is entirely well. This condition represents rather colonization than true infection and needs no treatment or investigation.

Clinical presentation

- Clinical presentation suggestive of UTI is only seen in older children.
- In infants and young children, the commonest form of presentation of UTI is non-specific fever (≥38°C) and vomiting.
- It is often not possible to localize the level of infection in infants. It is advisable to assume that all UTIs in infants are upper tract.
- Infants <3 months of age can occasionally present with dehydration, hyponatraemia, and hyperkalaemia, mimicking the findings in congenital adrenal hyperplasia.

In practice:

- Infants and children presenting with unexplained fever >38°C should have a urine sample tested after 24 hours at the latest
- The evaluation of infants and children with symptoms and signs suggestive of UTI should include a urine culture.

Urine collection and testing

- Urine culture is the standard for the diagnosis of UTI. Because the culture result is expected to take at least 18 hours, rapid diagnostic urine tests are very useful.
- Rapid diagnostic urine testing:
  - In children ≥3 years, urine dipsticks with reagent strips for nitrite and leucocyte esterase can be used
  - Children <3 years should have urgent microscopy for the detection of pyuria and bacteriuria, rather than urine dipstick
  - Table 39.1 shows guidance on the interpretation of urine dipstick and urgent microscopy results.

Table 39.1 Interpretation of rapid urine testing

Result	Interpretation	Further management
Dipstick		
LE (+) Nitrite (+)	UTI very likely	Urine culture and antibiotics
LE (−) Nitrite (+)	UTI very likely	Urine culture and antibiotics
LE (+) Nitrite (−)	UTI likely	Urine culture. Antibiotics in suggestive clinical presentation
LE (−) Nitrite (−)	UTI unlikely	Search for alternative diagnosis, no culture or antibiotics required
Microscopy[a]		
WBC (+) Bact (+)	UTI very likely	Urine culture and antibiotics
WBC (−) Bact (+)	UTI likely	Urine culture. Antibiotics in suggestive clinical presentation
WBC (+) Bact (−)	UTI very likely	Urine culture and antibiotics
WBC (−) Bact (−)	UTI unlikely	Search for alternative diagnosis, no culture or antibiotics required

Bact, bacteriuria; LE, leucocyte esterase; WBC, white blood cells.

[a] Pyuria on microscopy is defined as ≥5 white cells/high power field.

- Recently, the combination of culture-proven significant bacteriuria, together with an infection-suggestive urinalysis has been proposed for the establishment of diagnosis.
- Collecting an uncontaminated urine sample is one of the greatest challenges in diagnosing UTI in young children, and indeed in clinical paediatrics.
- Suprapubic aspiration and transurethral bladder catheterization are least likely to yield a contaminated growth in non-toilet-trained children, but these methods are not routinely feasible in 1° care.
- Clean catch is a reliable and 'parent-friendly' alternative.
  - If a clean-catch sample is unobtainable, a urine pad or bag can be used. Both methods run the major risk of contamination, which can be minimized by changing the bag/pad every 30 minutes.
- Interpretation of culture results depends on the method of urine sample collection. Different positivity cut-offs have been defined for suprapubic aspiration, catheterization, and bag/clean-catch/midstream samples on the basis of contamination risk.
  - Table 39.2 shows guidance on the interpretation of urine culture results in samples obtained by different methods.

Table 39.2 Interpretation of urine culture results

Method	Colony count (CFU/mL)
Suprapubic aspiration	Gram-negative: any number
Transurethral catheterization	10^3–5×10^4
Midstream/clean-catch/bag	$>5 \times 10^4$–10^5

The evidence for culture positivity threshold is weak, and the range given reflects different proposals. The most recent one from American Academy of Pediatrics (AAP) reduces the threshold to 5×10^4 and includes a suggestive urinalysis for a definite UTI diagnosis.

CFU, colony-forming unit.

Clinical assessment

- Infants <3 months with a suspected diagnosis of a UTI should be assessed by an experienced physician for this age group.
- The history and examination of all children with confirmed UTI should be recorded and include the following:
  - Temperature
  - Hydration
  - BP
  - Growth
  - Enlarged bladder
  - Abdominal mass
  - Evidence of any spinal lesion
  - History of previous UTI or recurrent fever of uncertain origin
  - Antenatally diagnosed renal abnormality
  - Family history of UTI, VUR, or other renal disease
  - Constipation or dysfunctional voiding.

- Children >3 months who are clinically well and able to retain fluids can be treated orally.
- Hospital admission should be considered in the following conditions:
  - Infants <3 months
  - Severely ill children
  - Intolerance to oral intake
  - Uncertain compliance
  - Non-response to oral therapy.

Management

Antibiotics

- Initial empiric antibiotic choice should be guided by local sensitivity data.
- The resistance of *E. coli* to amoxicillin is currently too high in many countries for this antibiotic to be recommended as a first-line antibacterial.
- Children with cystitis can be treated with a 3- to 5-day course of oral antibiotics. Trimethoprim alone or co-amoxiclav, co-trimoxazole, nitrofurantoin, and cephalexin, are other antibiotics of choice.
- Children with acute pyelonephritis should be treated with around a 7-day course of antibiotics, which can be given orally in most cases. For children who require hospitalization, the available evidence suggests that IV antibiotics given for 2–3 days until clinical improvement, followed by a week's oral course of antibiotics, has the same outcome as a 10-day IV antibiotic course. Second- and third-generation cephalosporins and co-amoxiclav are adequate in most cases.
- Neonates and children with more severe forms of upper UTI, such as AFBN and renal abscess, may require prolonged parenteral antibiotic courses. A combination of ampicillin with gentamicin, or a third-generation cephalosporin is commonly used.
- There is no need to check a post-treatment urine sample if the child is asymptomatic.
- Asymptomatic bacteriuria needs no treatment.
- There is no indication for the routine use of antibiotic prophylaxis after treatment of the acute infection.

Subsequent management

- Decisions for subsequent management have for long been based on the assumption that there is a causal relationship between VUR, UTI, and major renal damage with long-term consequences.
- This approach has recently been questioned on the basis of the following evidence:
  - *Renal parenchymal defects* are found in ~5–15% of children after their first UTI
  - Studies on prenatal scanning and post-natal follow-up showed that many of these defects, especially in boys, are more likely to be congenital, representing renal dysplasia

- *VUR* is present in approximately a third of children with UTI:
  - —There is a positive association of VUR and febrile UTI
  - —Although VUR is associated with renal parenchymal defects, it appears to be only a weak indicator
  - —These defects may also be present in the absence of VUR
  - —Interventions in VUR, either surgery or long-term antibiotic prophylaxis, have not been shown to alter outcome in terms of both scarring and recurrences prevention
  - —VUR tends to resolve spontaneously over time
  - —Bladder dysfunction plays a key role in UTIs of older children, and VUR can be a 2° effect
- *Long-term sequelae*:
  - —The risk of hypertension in children after UTI appears to be very small and associated with severe or bilateral scarring
  - —The main cause for high BP in late adolescence and adulthood in those who have a history of childhood UTI seems to be essential hypertension
  - —Lifestyle factors probably represent a much larger risk, compared to UTI, in the development of hypertension
  - —Similarly, the effect on renal function is more likely to be seen in cases where there has been a reduction of renal mass such as in severe bilateral renal scarring, which is rare.

Investigation of the renal tract after urinary tract infection

- Current recommendations have moved away from investigating every child with a first UTI. There has also been a shift away from focusing on identifying VUR. Although there is still much controversy, the current approach is to try to identify children with risk factors for severe renal scarring.
- The NICE CG54 guideline on UTI (🔗 <http://www.nice.org.uk/CG54>)[1] that is followed in the UK and the recent AAP guideline[2] have been influential all over Europe; however, there are different guidelines in different countries, like the one from Italian Society of Pediatric Nephrology,[3] and local policies should be followed.
- The recommendations vary, depending on age, clinical features, and recurrences.
- The main form of investigation is ultrasound.
- Further imaging, including micturating cystourethrogram (MCUG) for VUR detection and dimercaptosuccinic acid (DMSA) scan for renal parenchymal defect detection, is recommended for children with specific clinical characteristics or risk factors.

Who needs investigation?

Children who will need investigation after a *first UTI* according to current recommendations are summarized in Table 39.3.

Table 39.3 Current recommendations for urinary tract imaging for infants and children with first febrile UTI

Test!	NICE CG54[1]	AAP Practice Parameter[2]	Italian Society of Pediatric Nephrology[3]
US within 6 weeks	Infants <6 months	All children <24 months	All children <3 years
	Children >6 months with atypical UTI		
[a]US during acute infection	[b]Atypical or recurrent UTI, no improvement within 48 hours	No improvement within 48 hours, severe presentation	No improvement within 48 hours
MCUG	Infants <6 months with atypical or recurrent UTI Children <3 years with atypical UTI, severe dilatation, abnormal DMSA, or family history of VUR	Children <24 months with abnormal US	Children <3 years with abnormal US, recurrent UTI, or [c]risk factors
DMSA 4–6 months following the acute infection	Children <3 years with atypical or recurrent UTI Children >3 years with recurrent febrile UTI	Not necessary in any case	Children <3 years with VUR

[a] AAP points out that an unnecessary early US could be misleading and show acute changes that will resolve spontaneously.

[b] Atypical UTI: seriously ill, poor urine flow, abdominal or bladder mass, raised creatinine, septicaemia, failure to respond to treatment within 48 hours, infection with non-*E. coli* organisms.

[c] Risk factors: abnormal prenatal US, family history of VUR, septicaemia, chronic kidney disease, age <6 months, non-compliance of the family, abnormal bladder emptying, non-response to appropriate antibiotic within 72 hours, infection with non-*E. coli* organisms.

MCUG, micturating cystourethrogram; US, ultrasound.

Follow-up and outcome

The indications for follow-up are:

- Recurrent UTI
- Renal parenchymal defects (unless unilateral and minor, provided no recurrent UTI or at risk of hypertension because of lifestyle factors or family history of hypertension, or chronic kidney disease)
- Bilateral renal abnormalities, impaired kidney function, hypertension, and/or proteinuria (in liaison with a paediatric nephrologist)
- Obstructive renal tract abnormalities (in liaison with a paediatric urologist).

Antibiotic prophylaxis

- Although antibiotic prophylaxis after the acute episode is no longer routinely recommended, it can be considered in infants and children:
  - With recurrent febrile UTI
  - With reflux grade ≥ III
- Co-trimoxazole and co-amoxiclav are the most commonly used prophylactic agents.
- Asymptomatic bacteriuria requires neither prophylaxis nor follow-up.

Vesicoureteric management

- Surgical referral for VUR is not routinely recommended.

Advice to parents/carers or to young people

Parents of children who have had a UTI and young people themselves should be advised on:

- Prompt recognition of symptoms
- Urine collection, storage, and testing
- Preventive measures such as good fluid intake, avoiding constipation, and addressing any issues around bladder function
- The nature and reason for any urinary tract investigations
- Treatment options and reasons for long-term management, if required.

Advice leaflets with pictures can be helpful, e.g. the UTI information sheet at the Medicines for Children website (🔗 <http://www.medicinesforchildren.org.uk>).

What's new?

- New criteria for UTI diagnosis in children <2 years have been proposed, which, in combination with the reduction of culture positivity cut-off and the inclusion of pyuria, aim to differentiate a true UTI from asymptomatic bacteriuria.
- A less aggressive management of children with UTI has been recommended in recent guidelines.
- The issue of antibiotic prophylaxis remains controversial, and, until results of well-designed studies are published, there is some evidence for its beneficial effect in selected patients

What's next?

- Implementation of new simple, rapid diagnostic tools and biomarkers such as rapid urine tests for cytokines or other inflammatory molecules that could identify high-risk patients.
- Further studies with the use of non-antibiotic adjunct therapies such as short courses of steroids and vitamin A in acute UTI and cranberry juice and probiotics for recurrence prevention.
- Improved evidence-based management of high-risk children with UTI, who are usually excluded from large-scale studies, such as neonates, children with grade V reflux, and children with complicated forms of pyelonephritis.

Key references

1 National Institute for Health and Care Excellence. *Urinary tract infection in children: diagnosis, treatment and long-term management. Clinical guidance 54*. London: National Institute for Health and Care Excellence, 2007. Available at: ℒ <http://www.nice.org.uk/CG54>.
2 Roberts KB; Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics* 2011;**128**: 595–610.
3 Ammenti A, Cataldi L, Chimenz R, *et al*.; Italian Society of Pediatric Nephrology. Febrile urinary tract infections in young children: recommendations for the diagnosis, treatment and follow-up. *Acta Paediatr* 2012;**101**:451–7.

Further reading

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Chapter 40

Upper respiratory tract infections

See also Chapters 28, 40, 65, 70, 79, 88, 98, 105, 107.

Introduction

- *Definition*: URTIs are infectious diseases anatomically restricted to the upper respiratory tract, including the nose, sinuses, ears, pharynx, and larynx.
- This chapter focuses on acute URTIs, including the common cold, rhinosinusitis, otitis media, pharyngitis/tonsillitis, and laryngitis/laryngotracheitis.
- URTIs are generally uncomplicated, self-limiting diseases and, in the great majority of cases, do not require antibiotic treatment.
- Unusual organisms should be considered in children from abroad.
- Immune deficiency should be considered in children with:
  - Severe disease
  - Recurrent severe purulent URTIs (e.g. otitis media, rhinosinusitis)
  - Serious complications.

Common cold

Causative organisms

- Most (95%) of episodes are caused by one of over 200 different viruses; the most frequent viruses involved are:
  - Rhinovirus
  - RSV
  - Adenovirus
  - Influenza virus
  - Parainfluenza virus
  - Coronavirus
  - Human Metapneumovirus (hMPV)
  - Bocavirus.
- Up to 2% are complicated by bacterial superinfection.

Epidemiology

- URTIs constitute a large number of 1° care visits, with a peak during the winter months.
- The frequency of episodes varies by age, the number of siblings, and the degree of day-care exposure.

- Between one and ten episodes/year of URTIs is usual, with a peak between 6 months and 6 years of age. Thereafter, the frequency gradually decreases, with 1–2 episodes/year in older children and adolescents, occurring mainly during the winter months.

Transmission and incubation period

- Viruses affecting the respiratory tract are primarily transmitted by droplets from human to human. Alternatively, infectious secretions can be spread by direct contact, especially via contaminated hands and fomites.
- The incubation period varies between:
  - One and 4 days (influenza virus, rhinovirus, coronavirus)
  - Three and 6 days (RSV, parainfluenza virus, hMPV)
  - Two and 10 days (adenovirus).

Clinical features and sequelae

- A common cold is characterized by varying combinations of the following signs and symptoms:
  - Nasal congestion due to mucosal hyperaemia and oedema
  - Clear, watery to viscous or purulent nasal discharge
  - Breathing or feeding difficulties, especially in young infants
  - Sore throat, cough
  - Fever, malaise, fatigue, loss of appetite, muscle aches, headache
  - Conjunctivitis.
- Within 7–14 days, the patient gradually recovers without sequelae.

Diagnosis

- Is based on clinical findings, and no further investigations are necessary in uncomplicated cases.
- If indicated, NPAs or swabs for various rapid antigen tests, culture, or PCR for both viral and bacterial organisms are used
- The diagnostic value of bacterial organisms identified in nasopharyngeal secretions is limited due to the high rate of bacterial colonization of the respiratory mucosa.

Management and treatment

- Antibiotics are not indicated.
- Consider nasal vasoconstrictive decongestants (e.g. xylometazoline hydrochloride, oxymetazoline) to facilitate breathing and feeding, especially in infants. They should not be prolonged beyond 5 days to avoid the ‘rebound phenomenon’.
- Locally administered isotonic saline is sufficient, especially when the mucosa is dry or with limited secretions.
- Antipyretics/analgesics (e.g. paracetamol, ibuprofen) to reduce fever.
- There is little evidence for benefit of ‘immune system-stimulating or enhancing’ bacterial or herbal therapies, or vitamins or minerals.
- There is little evidence, and even less plausibility, for hot steam.
- Etheric oils or creams (e.g. mint, eucalyptus) may provide symptom relief but should be used with caution due to potential irritability of the skin and eyes, and drying of mucous membranes.

Prevention

- Hand hygiene, in particular in health-care institutions, to prevent nosocomial transmission.
- Respiratory hygiene, e.g. single-use tissues for sneezing and removal of nasal secretions.
- Social distancing may reduce the spread of respiratory tract viruses.
- Disinfection of the patient's environment is not of proven benefit in the outpatient setting.
- Influenza vaccines are effective in preventing seasonal or pandemic influenza. They are primarily indicated for children at risk of severe or complicated disease (e.g. patients with significant heart, lung, renal, liver, or neuromuscular disease, immune suppression, cystic fibrosis, and prematurely born infants).
- Some European countries (e.g. the UK, Finland) have introduced universal influenza immunization for healthy young children (6 months or older).

Acute rhinosinusitis

Rhinitis is an infection of the nasal mucosa potentially associated with sinusitis, an infection of either maxillary, frontal, ethmoidal, or sphenoid mucosa, with accumulation of (purulent) secretions in the respective cavities.

Causative organisms

- Rhinitis is caused by common cold viruses, primarily rhinoviruses.
- Bacterial superinfection occurs in <5%. Frequent causative bacterial organisms for sinusitis are:
  - *S. pneumoniae, H. influenzae* (mainly non-typeable), *Moraxella catarrhalis* (together 70–90%)
  - *S. pyogenes, S. aureus*, anaerobic bacteria.

Epidemiology

The epidemiology of rhinosinusitis is identical to that of the common cold. Maxillary and ethmoidal sinuses are present from birth. The sphenoid and frontal sinuses are developed by the age of 3–7 and 7–12 years, respectively.

Transmission and incubation period

- Identical with the common cold.

Clinical features and sequelae

- Acute rhinosinusitis is generally a self-limiting disease, with a duration of about 2–3 weeks. In addition to nasal symptoms:
  - Tracking of purulent nasopharyngeal secretions at the back of the throat in patients with sinusitis may cause persistent cough (*syndrome descendant*)
  - Increasing pressure of trapped pus in sinusitis may cause toothache or frontal or temporal headache.

- Potential important complications are:
  - (Peri)orbital cellulitis
  - Dental abscesses
  - Cavernous sinus thrombosis
  - Frontal abscess, Pott's puffy tumour
  - Meningitis, intracranial empyema.

Diagnosis

- The diagnosis of rhinitis is based on its clinical features. Acute sinusitis may be diagnosed in patients with:
  - High fever, pronounced malaise, and purulent nasal secretions for >3 days.
- Worsening nasal secretions and/or cough after 5–7 days.
- Persisting nasal secretions and/or cough for >10 days.
- Conventional sinus radiographs demonstrate poor sensitivity, specificity, and PPVs and are generally not recommended.
- The radiological method of choice is CT or MRI which may be indicated when complications are suspected.
- Detection of the causative organism is best done on sinus aspirates but is rarely needed.

Management and treatment

- There is limited evidence for any added value of antibiotics in the treatment of acute rhinosinusitis, unless the patient:
  - Is systemically very unwell
  - Has symptoms and signs suggestive of serious illness and/or complications
  - Is at high risk of serious complications due to pre-existing illness (e.g. patients with significant heart, lung, renal, liver or neuromuscular disease, immunosuppression, cystic fibrosis, and prematurely born infants).
- Bacterial superinfection cannot be inferred from:
  - The colour of nasal secretions
  - A duration of symptoms for longer than 7–14 days.
- Patients should be actively reassured that antibiotics:
  - Are not needed immediately
  - Are not expected to make a difference to symptoms
  - May have side effects (e.g. diarrhoea, vomiting, or rash).
- If indicated, oral antibiotics of choice for 7 days are:
  - Amoxicillin for uncomplicated illness. Consider the following for severe infection or if no improvement on amoxicillin after 48 hours:
    —Co-amoxiclav, *or*
    —Cefuroxime, *or*
    —Clindamycin.
- Unless clinical improvement is observed within 48 hours, the diagnosis and selected antibiotic should be reviewed.
- In purulent rhinitis, especially when unilateral, a nasal foreign body should be excluded by local inspection and be removed, if present.

Prevention

- Identical with the common cold.

Acute otitis media

Acute otitis media (AOM) is an infection of the middle ear mucosa, including the tympanic membrane, mostly in combination with a common cold. The great majority of AOM cases are due to viral infections, especially influenza, RSV, and adenovirus.

Causative bacterial organisms

- ~90%: *S. pneumoniae, H. influenzae*.
- ~10%: *M. catarrhalis, S. pyogenes* (Lancefield group A β-haemolytic *Streptococcus* (GABHS))

In addition to pneumococci and *Haemophilus* spp., *S. aureus* and *P. aeruginosa* are found in suppurative complications of AOM such as mastoiditis.

Epidemiology

- AOM is a frequent cause of paediatric 1° care visits for sick children.
- By 3 years of age, over 80% of children have had at least one episode of AOM. By 7 years of age, 40% have six or more recurrences.

Transmission and incubation period

- Similar to the common cold for viral causes. Bacterial AOM arises from the proliferation of colonizing bacteria during viral disease.
- Risk factors for colonization with oto-pathogens are young age, crowding, attendance of day-care centres, viral URTIs, and siblings. Colonization is decreased by sanitation, specific conjugate vaccines, and breastfeeding.

Clinical features and sequelae

- AOM typically presents during or after a common cold with acute onset of fever, earache, irritability, vomiting, or acute otorrhoea not caused by external otitis.
- AOM is a self-limiting disease in 80% of children after 4 days.
- Potential complications are perforation of the tympanic membrane, and rarely mastoiditis, hearing loss, and meningitis.

Diagnosis

- Clinical diagnosis of AOM relies on visualization (otoscopy) and functional testing (pneumatic otoscopy, tympanometry, acoustic reflectometry) of patients with the signs and symptoms listed.
- Otoscopy of AOM shows a highly inflamed, entirely red, undifferentiated, bulging tympanic membrane as an expression of a sometimes visible middle ear effusion, or a perforation with middle ear secretions in the ear canal. Functional testing demonstrates tympanic immobility.
- In contrast, acute otitis with effusion (AOE) will show an essentially non-inflamed eardrum with a visible middle ear effusion as a result of reduced middle ear ventilation via the Eustachian tube.
- While there is some degree of clinical overlap, paediatricians should make all efforts to distinguish the two entities, as diagnostic uncertainty is a major reason for unnecessary antibiotic prescribing in developed

countries where infants and toddlers spend a mean of between 40 and 50 days per year on antibiotics for the first 2 years of their life (detailed instructions available at the following websites: PedsEd (🖱 <http://pedsed.pitt.edu/>) and UTMB (🖱 <http://www.utmb.edu/pedi_ed/AOM-otitis/default.htm>).

Management and treatment

- No or delayed antibiotic prescribing strategies are now generally recommended in children, except very young infants. Rather, immediate symptomatic therapy with regular antipyretics/analgesics, followed by clinical review 48–72 hours later with re-evaluation regarding potential antibiotic treatment are recommended.
- **The theoretical aims of antibiotic treatment may be a reduction in pain and clinical infection, prevention of complications, and eradication of oto-pathogens.**
- **But antibiotics *do not*:**
  - Reduce pain on day 1; a reduction of pain is observed on days 2–7. However, appropriate treatment with antipyretics/analgesic/anti-inflammatory controls pain without antibiotics
  - Prevent the development of contralateral AOM
  - Accelerate the resolution of middle ear fluid
  - Have a beneficial effect on hearing
  - Appear to be justified as an immediate treatment strategy for the prevention of suppurative complications—this is because the number needed to treat to prevent one case of mastoiditis is over 4000, and the course of treated mastoiditis in developed countries is most commonly now benign
  - Reduce substantially the overall number of signs or symptoms and do cause side effects
  - Contribute to reduce the detrimental effects of increasing antibiotic resistance, if prescribed unnecessarily.
- Immediate antibiotic prescribing should still be considered for children:
  - <2 years with bilateral AOM
  - With marked otorrhoea, not caused by external otitis
  - Who are systemically very unwell
  - With symptoms and signs suggestive of serious illness and/or complications (mastoiditis, abscess, intracranial complications) (but refer immediately to the hospital!)
  - At high risk of serious complications because of pre-existing illness (e.g. significant heart, lung, renal, liver, or neuromuscular disease, immunosuppression, cystic fibrosis, prematurely born infants and toddlers)
  - Recurrent AOM.
- If indicated, the oral antibiotic of choice is amoxicillin. High-dose amoxicillin should be used in areas with high rates of penicillin-resistant pneumococci. Because of the improved effectiveness against *H. influenzae* and *M. catarrhalis*, co-amoxiclav, or cefuroxime axetil, may be used after 48 hours of treatment failure with amoxicillin (see local guidelines).

- Duration of antibiotic treatment for AOM is 5 (children ≥2 years) or 7–10 (children <2 years) days.
- In children with difficulties in oral antibiotic uptake, ceftriaxone once daily for 1–3 days IM or IV is an effective alternative.

Prevention

- Immunization with conjugated pneumococcal vaccines is the most effective strategy to prevent AOM—in spite of the relatively weak effect (10–30%) in preventing it.
- Recurrent episodes may be best prevented by early immunization in infancy. Once recurrent disease is established, tympanostomy tube placement is another treatment option.
- Other preventive measures, such as reduction of risk factors of colonization and decrease of continuous use of pacifiers, may be considered but contribute comparatively little to preventing disease overall.

Tonsillopharyngitis

Tonsillopharyngitis (TP) is an infection of the tonsils and pharyngeal mucosa mostly during a common cold.

Causative organisms

- Viral causes are similar to the common cold, apart from EBV and Coxsackie herpangina, both of which may cause severe pharyngitis.
- The major bacterial cause of TP is *S. pyogenes* (GABHS). In adolescents, *Fusobacterium necrophorum* (angina Plaut–Vincent) appears to be increasing.
- Other causes of acute pharyngitis include group C and G streptococci, *Corynebacterium diphtheriae*, *M. pneumoniae*, and *Chlamydia pneumoniae*.

Epidemiology

- GABHS TP may occur at any age. However, it is rare in children <3 years and is primarily a disease of children 5–15 years of age.
- GABHS tonsillitis usually occurs in winter and early spring.
- The incidence rate of post-streptococcal rheumatic fever is <0.5 cases per 100 000 in resource-rich countries, and 100–200 cases per 100 000 in resource-poor countries.

Transmission and incubation period

- GABHS is transmitted by droplets from human to human during acute pharyngitis.
- The incubation period is 2–4 days.
- Pharyngeal carriage does not appear to be infectious interestingly.

Clinical features and sequelae

- Features suggestive of GABHS as a causative agent are:
  - Sudden-onset sore throat
  - Pain on swallowing

- Fever
- Scarlet fever rash
- Headache
- Nausea, vomiting, and abdominal pain
- Tonsillopharyngeal erythema (dark red)
- Tonsillopharyngeal exudates
- Soft palate petechiae ('doughnut' lesions)
- Beefy, red, swollen uvula
- Tender, enlarged anterior cervical nodes
- Patient 5–15 years of age
- Presentation in winter or early spring (in temperate climates)
- History of exposure.

- Features suggestive of a viral origin are:
  - Conjunctivitis
  - Rhinitis
  - Hoarseness
  - Cough
  - Diarrhoea
  - Characteristic exanthems.
- Duration of the disease is on average 1 week.
- Purulent complications of bacterial pharyngitis (<1%) include:
  - Retropharyngeal abscess
  - Peritonsillar abscess (quinsy)
  - Lemierre's syndrome (peritonsillar abscess, jugular vein thrombosis, and septic PEs in *Fusobacterium* infection).
- Non-purulent complications:
  - Scarlet fever: a rash caused by exotoxins released by GABHS appears 12–48 hours after the onset of fever and lasts about 3–5 days. In contrast to the rash potentially caused by penicillins, it does not involve the perioral area and spares the palms and soles
  - Acute PSGN may occur ~10 days after the onset of streptococcal pharyngitis; most cases remain asymptomatic. If symptomatic, oedema, haematuria, proteinuria, and arterial hypertension prevail
  - Rheumatic fever is a well-described inflammatory disease following GABHS pharyngitis. Cross-reactive antibodies are hypothesized to involve the heart, skin, joints, and brain. First-time attacks tend to occur 2–3 weeks after the onset of GABHS pharyngitis
  - Post-streptococcal reactive arthritis tends to occur about 10 days after an episode of GABHS pharyngitis, does not respond well to acetylsalicylic acid, and may involve any joint in a persistent manner. Arthritis of rheumatic fever occurs later (14–21 days), responds well to acetylsalicylic acid, and only involves large joints in a migratory manner. However, it is not yet fully understood whether both entities are part of the same spectrum of disease
  - PANDAS should currently be considered as a hypothesis in need of verification.

Diagnosis

- Several scoring systems have been developed to predict bacterial TP. The four Centor criteria are probably the most widely used:
  - Fever, *and*
  - Tonsillar exudate, *and*
  - Tender anterior cervical lymphadenopathy or lymphadenitis, *and*
  - Absence of acute cough.
- A positive throat culture for GABHS in unwell patients 3–15 years of age confirms the diagnosis; the presence of 3–4 Centor criteria and the absence of signs and symptoms of viral disease increase the pre-test probability for GABHS as an aetiological agent, rather than colonization.
- Many GABHS rapid tests are commercially available. However, the specificity and sensitivity of these tests vary widely and should be locally compared with the results of blood agar plate cultures to estimate the PPVs and NPVs pertinent to the local population.
- In patients with features of viral disease (e.g. cough, rhinitis, almost normalized well-being following antipyretics), testing for GABHS should not be performed or, if done, the finding of GABHS on rapid test or culture should be interpreted with considerable caution as regards to an aetiological role of concurrent disease.
- Urine tests to detect asymptomatic acute PSGN are not recommended.

Management and treatment

- Effects of antibiotic treatment for GABHS TP are:
  - Reduction of duration of symptoms by only 16 hours
  - Reduction of the rate of quinsy. However, given the small absolute risk, over 4000 children with tonsillitis have to be treated to prevent one case of quinsy
  - Reduction of inflammatory complications with the same efficacy after several days (up to 9 days) of TP, as compared with immediate treatment. These complications are now extremely rare in developed countries and are *not* a reason to prescribe antibiotics, as the absolute risk reduction is also extremely small
  - Reduction of the contagiousness from 6–14 days to 24 hours.
- *No or delayed* antibiotic treatment is generally recommended for TP.
- Immediate treatment may be considered if all four Centor criteria are present.
- A 10-day course of oral phenoxymethylpenicillin still remains the treatment of choice in view of rheumatic fever prevention. However, compliance is known to be very low. Alternative regimens with similar effectiveness regarding bacterial eradication are high-dose amoxicillin twice daily or narrow-spectrum oral cephalosporins for 5 days. Erythromycin and clarithromycin are the macrolides of choice for patients with penicillin intolerance or allergy.
- Azithromycin is now recognized as a major driver of macrolide resistance due to its very long half-life and should not be used.
- A follow-up throat culture is not indicated.

Prevention

- A causal prevention is not available.
- Children may return to day care or school after 24 hours of antibiotic treatment.
- GABHS rapid antigen tests of throat cultures or antibiotic prophylaxis are not indicated in asymptomatic contact persons.

Laryngotracheitis

Laryngotracheitis (croup syndrome) is a viral infection of the laryngeal and tracheal mucosa.

Causative organisms

- Identical to the common cold. The most frequent are parainfluenza 3 and influenza viruses.

Epidemiology

- In the winter months, children between 6 months to 6 years are commonly affected. Most are <3 years of age.

Transmission and incubation period

- Identical to the common cold.

Clinical features and sequelae

- Fever.
- Sudden onset of hoarse voice, often at night.
- Pathognomonic 'seal-like' barking cough.
- Potentially rapid progression to stridor and sometimes pronounced dyspnoea.

Diagnosis

- Based on clinical features alone.
- Important differential diagnoses should be considered:
  - Foreign body aspiration (no fever, little improvement on croup treatment)
  - Diphtheria
  - Epiglottitis (severely ill child with muffled, rather than hoarse, voice)
  - Bacterial tracheitis (rare in children).

Management and treatment

- Close monitoring, as progression to life-threatening disease may be rapid.
- Anti-inflammatory antipyretics.
- Oral corticosteroids (e.g. dexamethasone 0.5 mg/kg single dose).
- Adrenaline nebulizer for severe dyspnoea (monitor for at least 4 hours for potential relapse—most within 1–2 hours).

Prevention

- Identical to the common cold.

Further reading

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Chapter 41

Zoonoses

Introduction

Zoonoses are infections that are naturally transmitted from vertebrate animals to humans. Some zoonotic infections can be acquired from other humans, as well as from other animals. For others, humans represent a dead-end host from whom ongoing transmission cannot occur. With the exception of a few infections in the former group, most zoonoses are uncommon in children. There are around 2000 cases/year of notified zoonoses in adults and children in the UK. The European Food Safety Authority and the European Centre for Disease Prevention and Control analysed the occurrence of zoonoses across the 27 EU members in 2011. Food-borne infections accounted for the vast majority of zoonoses. Campylobacteriosis was the most commonly reported zoonosis, with 220 209 human cases. Cases of salmonellosis and listeriosis decreased, but an increase in verotoxigenic *E. coli* (VTEC) was reported, compared with previous years.

Careful consideration of the likelihood of exposure should be done when assessing children in whom the differential diagnosis might include zoonoses. The possibility of a zoonotic infection must not be overlooked, but, at the same time, care must be taken not to over-investigate children for rare infections.

This chapter considers the commonest and/or important zoonotic infections that might be seen in the UK and Western Europe; specialist advice or texts should be consulted where a diagnosis of a rare zoonosis acquired overseas is being considered. To make a diagnosis of zoonotic infection requires:

- Knowledge of the clinical manifestations of the diseases
- Understanding of the local epidemiology of zoonoses
- Identification of a detailed exposure history for the individual patient.

Causative organisms

The pattern of infections seen in different areas of the world depends on the types of animal to which humans may be exposed. Table 41.1 summarizes common and/or important zoonoses. In western countries, most zoonoses are acquired from pets or other domesticated animals.

For a zoonosis to occur, there has to be indirect or direct contact between the animal and child. Routes of transmission are:

- Direct skin contact, including via bites and scratches
- Ingestion of contaminated material in food or water
- Inhalation of contaminated material
- Transmission via an insect vector.

Clinical presentation

Descriptions of individual zoonotic infections are provided in the relevant disease-specific chapters in this book. However, a brief description of the main clinical features of individual infections is provided in Table 41.1.

The commonest presentations of zoonotic infections are:

- Localized skin and soft tissue infections
- GI infections.

These infections are:

- Generally easy to diagnose, because the onset is acute, the incubation period is short, and the symptoms and signs are easy to identify
- Often commoner in young children, because their curiosity and lack of understanding of hygiene place them at greater risk of exposure.

Less common presentations are:

- Multisystem disease with non-specific signs
- Pneumonia.

These infections are often more uncommon in children than adults, because children are less likely to have been exposed. Infections are more difficult to diagnose, because the possible clinical manifestations are protean, and there may be no clear exposure history to prompt consideration of the diagnosis.

Careful history-taking is required to ensure that clues as to the possibility of a zoonotic infection are not missed. Key points are:

- Pets—especially unusual pets
- History of any other contact with animals or their environment within the likely incubation period. This may require careful questioning around leisure pursuits, e.g. animal petting farms (and in the case of older children, possible occupational exposure)
- Travel history
- Ingestion of unusual foods
- Time of year may also be important, especially where insect vectors are involved.

Management and treatment

The management and treatment of zoonoses is disease-specific and is considered in individual chapters in this book. Guidance on the recognition, investigation, and management of zoonoses produced by Public Health England (PHE) may also be useful.

It is important to remember that some zoonoses may be statutorily notifiable under national veterinary and/or human legislation. The primary purpose of the notification system is to identify possible outbreaks and epidemics and initiate appropriate action as soon as possible. Continuing outbreaks of *E. coli* O157 disease in children associated with visiting an animal petting farm are a salutary reminder of the potential for zoonotic infections to occur as large and/or serious outbreaks. It is recommended that any serious zoonotic infection that may be of public health importance should be notified via appropriate authorities, even if it is not statutorily notifiable.

Table 41.1 Key features of common and/or important zoonotic infections

Infection	Microorganisms	Animal source	Route(s) of transmission	Incubation period	Clinical presentation
Animal bites, bacterial infections	*Pasteurella multocida* Capnocytophaga Staphylococci, anaerobes, etc. Infections are frequently polymicrobial	Dogs, cats (most commonly)	Inoculation via bite	1–3 days	Skin and/or soft tissue infection
Anthrax	*B. anthracis*	Livestock, wild animals	Usually by direct contact; inhalation or ingestion may occur	2 days to several weeks	Characteristic black-centred skin ulcer; systemic illness; pneumonia
Arboviruses, e.g. West Nile virus	West Nile virus (a flavivirus)	Birds	Mosquito bites	3–14 days	Asymptomatic (80%) systemic illness which may be severe
Avian influenza	Animal influenza viruses, e.g. avian H5N1	Poultry, water fowl	Direct contact	3–5 days	Influenza: may be severe
Bovine TB	*M. bovis*	Cattle	Ingestion of unpasteurized milk	Months to years	Indistinguishable from infection with *M. tuberculosis*
Brucellosis	*Brucella* spp.	Cattle, goats, sheep, pigs	Usually by ingestion of unpasteurized milk or dairy products	5–30 days	Systemic illness

(*Continued*)

Table 41.1 (*Contd.*)

Infection	Microorganisms	Animal source	Route(s) of transmission	Incubation period	Clinical presentation
Cat scratch disease	*B. henselae*	Cats and other animals	Inoculation via scratch or bite	3–10 days	Lymphadenopathy, fever
Cowpox	Cowpox virus	Wild rodents	Direct contact	9–10 days	Pustules, typically on the hands and arms
Cysticercosis	*T. solium* (pork tapeworm) *T. saginata* (beef tapeworm)	Cattle, pigs	Ingestion of meat	Around 10 days to establishment of intestinal infection	Intestinal tapeworm infection neurocysticercosis (following *T. solium)*
Dermatophytes	Wide variety of species, especially *Microsporum* spp., *Trichophyton* spp.	Various, mainly dogs, cats	Skin contact	1–2 weeks	Skin and hair infections (e.g. ringworm)
Fish tank granuloma	*M. marinum*	Fish	Direct contact with water from aquariums	At least 2–3 weeks	Granuloma at the site of entry; further granulomas may occur later along the path of lymphatic drainage
GI infections	*Campylobacter* spp. *S. enterica* *Y. enterocolitica* *E. coli* O157 *Cryptosporidium* *G. lamblia*	Wide range of animals and birds	Ingestion through direct contact with infected animals or consumption of contaminated food or water	Usually 2–5 days	Diarrhoea: may be complicated by systemic illness (especially in the very young or immunocompromised)

Hantavirus infection	Hantaviruses	Rodents	Direct or indirect contact with domesticated or wild rodents	Usually 2–4 weeks	Disease characterized by fever, headache, GI symptoms, and renal dysfunction; haemorrhagic manifestations in the more severe forms
Hepatitis E	Hepatitis E virus	Not yet fully delineated, but pigs appear to be an important human reservoir	Not fully delineated	15–64 days	Clinical course similar to hepatitis A
Hydatid disease	*Echinococcus granulosus*	Dogs	Ingestion of eggs in dog faeces	Months to years	Hydatid cyst—liver is the most commonly affected organ
Leptospirosis	*B. burgdorferi*	Deer, sheep, other animals	Contact with contaminated water, e.g. via mucous membranes or damaged skin	3–21 days	Systemic flu-like illness; bleeding, liver and kidney failure may follow 7–10 days later
Lyme disease	*Leptospira* spp.	Rodents, ruminants	Tick bites	1–4 weeks	Cutaneous lesions (erythema migrans), systemic illness
Orf	Orf virus	Sheep	Direct contact	3–6 days	One or more pustular skin lesions, typically on the hands and arms

(*Continued*)

Table 41.1 (*Contd.*)

Infection	Microorganisms	Animal source	Route(s) of transmission	Incubation period	Clinical presentation
Psittacosis	*Chlamydophila psittaci*	Birds (usually)	Inhalation	5–14 days	Atypical pneumonia
Q fever	*C. burnetii*	Livestock, especially sheep, goats, and cattle	Inhalation	9–40 days	Atypical pneumonia, hepatitis
Rabies	Rabies virus	Any infected animal, especially cats, dogs, foxes, bats	Animal bite	1–4 weeks	Cutaneous lesions (erythema migrans), systemic illness
Streptococcus suis	*Streptococcus suis*	Pigs	Direct contact, meat	A few hours up to 14 days	Meningitis and septicaemia are the commonest clinical manifestations
Tick-borne encephalitis	Tick-borne encephalitis virus (a flavivirus)	Small rodents	Tick bite	7–14 days	Biphasic: initial viraemic illness, followed in 20–30% of patients by CNS system disease 7–9 days later
Trichinellosis	*Trichinella spiralis*	Pigs, wild boar	Consumption of pork products	8–15 days	Muscle soreness; pain and swelling of upper eyelids, marked eosinophilia
Toxocariasis	*Toxocara canis, Toxocara cati*	Dogs, cats	Ingestion of worm eggs excreted in dog and cat faeces	Variable: larvae remain viable indefinitely	Asymptomatic (commonest); visceral larva migrans; ocular toxocariasis

Toxoplasmosis	*T. gondii*	Cats, sheep, pigs, cattle	Ingestion of oocysts in cat faeces Ingestion of tissue cysts in raw or undercooked meat	5–25 days	Asymptomatic (commonest); glandular fever-like illness; severe disseminated infection in immunocompromised patients
Viral haemorrhage, fevers	Ebola, Crimean–Congo haemorrhagic fever, Lassa, and Marburg	Rodents, ticks, livestock, primates, bats	Direct contact, inoculation, ticks	6–21 days	Malaise, fever, headache; multisystem disease with thrombocytopenia
Zoonotic diphtheria	*Corynebacterium ulcerans*	Cattle, farm animals, dogs	Direct contact, milk	2–5 days	Non-healing skin ulcers with grey membranes

Prevention

General preventative measures

- Good personal hygiene.
- Avoid children having unsupervised contact with animals or their environment.
- Ensure that pet cats and dogs are regularly de-wormed.
- Protect damaged skin when having contact with animals or their environment.
- Ensure that food is thoroughly cooked.
- Avoid consuming unpasteurized milk or dairy products.
- Avoid drinking water that may be contaminated with animal faeces.

Specific preventive measures will depend on the individual disease but may include:

- Immunization (rabies; TBE)
- Antimicrobial prophylaxis (bites)
- Use of insect repellent (insect-borne infections).

What's new?

- Successful implementation of controls across EU member states has led to a Europe-wide reduction in cases of salmonellosis and listeriosis in humans in recent years.
- In the UK, badgers have been identified as a reservoir of bovine TB, and a badger control policy is now being evaluated in England. Bovine TB can also infect domestic pets, although the risk to humans from this route remains very low.
- Changes in human activities can have a direct impact on the risk of zoonoses: the growth in the popularity of petting farms and zoos is an important risk factor for paediatric zoonotic infections, especially VTEC.

What's next?

- It is likely that there will be new national or EU action targeting the prevention of campylobacteriosis, which is now by far the commonest zoonosis in Europe.
- Global warming and growing international travel and cross-border trade in live animals and foodstuffs is likely to change the epidemiology of zoonoses.
- A study is currently under way in England to determine hantavirus seroprevalence rates in persons who have contact with wild and domesticated rats.

Further reading

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Section 2

Specific infections

Chapter 42

Adenovirus

See also Chapters 11, 20, 27, 31, 44.

Name and nature of organism

- Adenoviruses, so named because they were first isolated from adenoidal tissue surgically removed from children in 1953, infect most mammals, birds, and reptiles.
- Human adenoviruses (HAdV) are medium-sized (80–100nm), non-enveloped viruses with icosahedral symmetry, and easily visible on negative staining EM.
- The nucleocapsid is composed of 252 capsomers, with 12 vertices and seven surface proteins. The genome is a linear, non-segmented double-stranded DNA, encoding about 30 proteins.
- HAdV (family *Adenoviridae*, genus *Mastadenovirus*) are classified into seven subgenera (A–G).
- There are at least 54 immunologically distinct serotypes, differentiated by quantitative neutralization with hyperimmune sera.

Epidemiology

- Initially recognized as a cause of acute respiratory disease (ARD) in children and young adults, HAdV are associated with a wide variety of clinical syndromes, from asymptomatic or mild infection, typical self-limiting respiratory, GI, or ophthalmological illnesses, through to rarer severe and occasionally fatal disease.
- There is striking concordance between disease syndrome and serotype, although this is not absolute, and there is some inconsistency between the serotype associations reported in the literature.
- HAdV are present all year round; respiratory infections show typical seasonality, while GI disease does not.
- Infection occurs at any age in children, typically from infancy to school age. Most children have had one form of HAdV infection by age 10 years.
- HAdV usually cause localized infections; generalized infection is commoner in immunocompromised patients.
- Outbreaks occur in young adults in institutions such as the army.

Transmission and incubation period

- HAdV are relatively stable to chemical or physical agents and adverse pH conditions, allowing prolonged survival outside the body, in water, and on fomites (such as doorknobs, hard surfaces, toys) for many hours.

- HAdV are highly contagious; there are very high levels of viral particles in secretions of infected individuals (10^5–10^6/mL in sputum or oral secretions), coupled with a very low infective dose (e.g. the inhalation of as few as five virions in droplet nuclei).
- Acquisition is via one of several routes: respiratory droplets, ingestion via the faecal–oral route, contact—especially hand-to-eye transfer, water, e.g. inadequately chlorinated pools, and venereal.
- Route of acquisition can determine the disease syndrome caused, e.g. HAdV 7 can cause severe LRTI if inhaled, but mild GI disease when introduced orally.
- Incubation period is also affected by the route of acquisition, ranging from 2 to 14 days between inhalation and the onset of respiratory illness, and 3–8 days between ingestion and GI symptoms.
- Infections are lytic; the adenovirus enters epithelial cells, and the replication cycle results in cytolysis, cytokine production, and induction of the host inflammatory response. Some HAdV serotypes cause cellular cytopathic effect with rounded, swollen cells.
- Chronic or latent infection frequently occurs, but the exact mechanism is unknown. After recovery of illness or following asymptomatic infection, HAdV maintain latent persistent infections in the tonsils, adenoids, and other lymphoid tissues, and can shed from the respiratory tract, stool, and urine for months to years. Shedding is especially prolonged in children and immunocompromised individuals.

Clinical features and sequelae

- HAdV infections are very common, and most are asymptomatic. Symptomatic HAdV disease includes a wide variety of clinical syndromes, the majority of which involve the respiratory tract. There is a striking, but not absolute, association between the HAdV serotype and clinical syndrome (Table 42.1).

Respiratory

- Respiratory HAdV serotypes account for an estimated 5% of respiratory infections across all ages, and about 10% of LRTIs in childhood. ARD typically presents with fever, non-specific upper respiratory symptoms of rhinorrhoea, cough, and pharyngitis (may be exudative), usually lasting 3–5 days.
- LRTIs, including tracheobronchitis, bronchiolitis, and pneumonia, may mimic RSV infection or influenza, although associated conjunctivitis is a clue to an adenoviral aetiology. Pulmonary infiltrates are often diffuse and reticulonodular, but may be lobar.
- HAdV has been isolated from children with a whooping cough-like syndrome in the absence of *B. pertussis* infection; however, whether HAdV are the aetiological agent remains unclear.
- Sporadically, severe disease, such as necrotizing HAdV bronchiolitis, occurs in previously healthy immunocompetent infants; bronchiolitis obliterans may then ensue. Fatal HAdV pneumonia, although rare, can occur in neonates infected by virulent serotypes.

Table 42.1 Clinical syndromes of HAdV disease

Clinical syndrome	At risk	Associated serotypes
Pharyngitis	Infants	1, 2, 3, 5, 7
Pharyngoconjunctival fever	All	3, 4, 7
Acute respiratory disease	Boarding schools	4, 7, 14, 21
Pneumonia	Infants	1, 2, 3, 7, 14, 21, 30
Follicular conjunctivitis	All	3, 4, 11
Epidemic keratoconjunctivitis	All	8, 19, 37
Pertussis-like syndrome	Infants	5
Acute haemorrhagic cystitis	Infants, older children	11, 21
Acute infantile gastroenteritis	Infants	12, 18, 31, 40, 41
Mesenteric adenitis, intussusception	Infants	1, 2, 3, 5, 6
Hepatitis and multi-organ disease in immunocompromised patients	Any	5, 34, 35
Meningitis		3, 7

- Non-pulmonary complications of respiratory HAdV infection include meningo-encephalitis.
- Clusters of severe and occasionally fatal disease were seen in a number of US states in 2006–7, largely due to a new variant of HAdV 14 little seen before in children.

Gastrointestinal

- Ingested HAdV can cause gastroenteritis that is clinically indistinguishable from other causes such as rotavirus. HAdV serotypes are responsible for an estimated 10% of infantile gastroenteritis, typically in the second year of life when maternally derived humoral immunity has waned. Watery, non-bloody diarrhoea typically precedes vomiting, and the infant can be symptomatic for 1–2 weeks.
- However, enteric HAdV serotypes replicate readily in human intestine and can be detected from asymptomatic individuals, so their role in the setting of a diarrhoeal syndrome may not always be causal. Conversely, some serotypes (40, 41) are fastidious in culture and were termed 'non-cultivatable' and evaded detection before newer methods became available.
- Intussusception can complicate HAdV gastroenteritis. Interestingly, up to 40% of infants with intussusception are positive for non-enteric serotypes from stool or mesenteric lymph nodes, and most have no evidence of infection with enteric strains (i.e. 40, 41).
- Mesenteric lymphadenitis or hyperirritable small bowel associated with non-enteric adenoviral infection has been postulated as a precursor

to intussusception; the role of HAdV in this setting is unclear, and, as most patients with intussusception have no evidence of HAdV infection, intussusception probably has multiple aetiologies.

Ocular

- Pharyngoconjunctival fever syndrome most often affects school-aged children and is highly contagious via respiratory secretions and contact with ocular secretions.
- Sporadic outbreaks occur in small groups, especially in the setting of inadequately chlorinated water such as private swimming pools or lakes, although confirming the water source of HAdV is often difficult.
- Fever, sore throat, coryza, and acute conjunctivitis are seen, with or without pharyngitis or a respiratory syndrome, and these may precede the eye signs: follicles in bulbar and/or palpebral conjunctivae, typically with a mild granular appearance.
- Unilateral, before progression to bilateral, redness is typical, associated with mild (rarely severe) pain (indicating corneal involvement), photophobia, tearing, pruritus, and morning crusting for up to 5 days.
- In epidemic keratoconjunctivitis, severe follicular keratoconjunctivitis and palpebral oedema are typically granular, and haemorrhagic conjunctivitis can develop.
- Visual haziness or impairment indicates keratitis or corneal inflammation and may persist for months to years.
- Preauricular lymphadenopathy (Parinaud's syndrome) is not common in ocular HAdV disease but, when present, is highly suggestive of HAdV.

Renal

- Haematuria may occur in the setting of nephritis (usually febrile) or haemorrhagic cystitis (typically not).
- Acute haemorrhagic cystitis usually affects children >5 years, especially immunosuppressed individuals (e.g. kidney or bone marrow transplant recipients, HIV-infected).
- Boys are affected more often than girls.
- Grossly bloody urine usually lasts 3 days or so, although associated dysuria and frequency can be prolonged, especially in haematopoietic stem cell recipients.

Other

- Symptoms of HAdV in otherwise healthy individuals also include rash, malaise, headache or frank encephalitis, hepatitis (sometimes with dramatically elevated transaminases), and myocarditis.

Immunocompromised patients

- Transplant recipients and those with 1° and acquired immunodeficiency states are especially at risk of severe HAdV disease.
- T-cell immunodeficiency related to HIV infection has been associated with adenoviral infections, particularly in infants and children infected with HIV. Most often seen are pneumonitis and haemorrhagic cystitis, cholecystitis, and severe hepatitis.

- Pre-existing latent HAdV are reactivated during immunosuppression in paediatric recipients of solid organ transplants, with diffuse adenoviral infection of the allograft itself, and this is a major problem in the rejection of transplanted hearts and lungs. Use of newer, more potent immunosuppressive regimens has increased the frequency of severe adenovirus infections.
- HSCT recipients are also prone to severe HAdV disease, with risk factors including allogeneic stem cell transplantation, T-cell depletion and non-myeloablative conditioning regimens, lymphopenia, young age, and GVHD.
- Manifestations may vary, but features include dyspnoea, dry cough, focal pulmonary signs of pneumonitis, haemorrhagic cystitis (usually uncomplicated haematuria), nephritis (fever, haematuria, flank pain, and worsening renal function), hepatitis/liver failure.
- Risk is highest during the acute post-transplantation period.
- Transplant outcomes include both allograft loss and recovery.
- Mortality rates associated with adenovirus infections among transplant recipients can be high.

Clusters of fatal disease in young adults

- Fatal disease may occur, especially from HAdV 7, also 3 and 4.
- HAdV 14 has caused rare outbreaks of ARD since 1955; a notable cluster in certain US states over 14 months from May 2006 involved over 14 cases, of which 40% of affected persons were hospitalized, almost half in intensive care, with a 5% overall mortality.

Diagnosis

- Diagnostic tests are now predominantly by molecular detection methods, being specific, sensitive, and fast.
- PCR methods can be used on a variety of specimens (e.g. respiratory, tissue, urine, blood). Options include locally developed methods with broad or all subtype specificity, or commercial PCR kits with defined, narrower subtypes detected. Real-time PCR assays permit virus quantification, which is especially important in longitudinal monitoring of the immunocompromised.
- HAdV from stool are detectable through non-serotype-specific enzyme immunoassay. Immunofluorescence techniques still have utility, especially for rapid diagnosis out of hours and for direct examination of tissue specimens. These methods have superseded virus isolation in cell culture.
- Serology is rarely useful, because seroreactivity to HAdV is common; by age 4 years, around half of all children have detectable titres.

Management and treatment

- Most adenoviral infections in the immunocompetent host are self-limiting and do not warrant specific therapy. However, HAdV keratitis is treated to preserve vision with early topical steroids administered under specialist ophthalmologic care. Severe adenoviral disease, especially in immunocompromised hosts, drives the search for effective therapies.
- Absence of T-cell-specific immunity appears to be a poor prognostic sign for recovery, regardless of antiviral therapy.
- Antiviral agents inhibiting viral DNA and protein synthesis have generally been ineffective against HAdV infection. Several drugs, such as ribavirin (which inhibits viral replication by inhibiting DNA and RNA synthesis in RSV) and cidofovir (a nucleotide analogue that selectively inhibits viral DNA production in CMV), have been used to treat HAdV infections, especially the immunocompromised, with variable success.
- Benefit of dual therapy with ribavirin and cidofovir has been documented in case series. Cidofovir therapy may result in complete clinical resolution in haematopoietic stem cell recipients, where the virus can become undetectable, without severe nephrotoxicity.
- Anecdotal reports of success with intravesical cidofovir against HAdV haemorrhagic cystitis may reduce the systemic toxicity. However, HAdV disease in immunosuppressed hosts are more likely to be disseminated, rather than localized.
- Anecdotal success with IV antivirals combined with pooled IVIG is also reported.
- No available studies adequately address issues such as which syndromes are most likely to respond to treatment or which patients develop limiting haematological toxicity from ribavirin or nephrotoxicity from cidofovir.
- The development of improved adenovirus therapy still remains a challenge.

Prevention

- Infection control measures: in health-care settings, effective isolation procedures, handwashing, and sterilization of instruments prevent nosocomial infection. This is particularly important in ophthalmology practice where contact precautions must be robust. Hospitalized patients with HAdV pneumonia require both droplet and contact precautions. Any HAdV syndrome in a health-care worker warrants exclusion from work until symptoms resolve.
- Vaccine: a live enteric-coated adenovirus vaccine against serotypes 4 and 7 was in production for two decades; it was limited to military use, but with notable effect. When given orally, these serotypes induce effective humoral immunity without producing disease. No HAdV vaccines have since been developed.

Future research

- HAdV have great potential as vectors for vaccination and for gene therapy, because they can be genetically altered *in vitro* without producing infectious, pathogenic viral offspring.
- The potential for gene therapy is based on a DNA segment that codes for an enzyme or protein product that corrects a human genetic defect being delivered to the host by an adenovirus vector.

Further reading

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Chapter 43

Amoebiasis

See also Chapters 22, 42.

Name and nature of organism

Amoebiasis, caused by the protozoa *Entamoeba histolytica*, only occurs in humans and primates. *E. histolytica* is indistinguishable from the non-pathogenic *Entamoeba dispar* (described in 1978) and *Entamoeba moshkovskii* (described in 1941), using conventional microscopy.

Recent molecular techniques have demonstrated that, of these three species, only *E. histolytica* definitely causes disease; *E. moshkovskii* possibly causes clinical disease. Numerous other protozoa have been identified in human faecal samples; the majority are non-pathogenic but, if identified, are generally indicative of high rates of faecal contamination. Experienced laboratories can separate the majority of cysts of *E. histolytica/dispar* by light microscopy.

Epidemiology

- *E. histolytica/dispar/moshkovskii* occur worldwide, but the majority of cases are in developing countries or in travellers returning from these countries. The greatest disease burden occurs in Central America and western South America, West and South Africa, parts of the Middle East, and the Indian subcontinent.
- Worldwide, ~500 million people are infected with *E. histolytica/dispar*. The true incidence of asymptomatic carriage of *E. histolytica* is unclear, and it is therefore difficult to determine an accurate incidence of true *E. histolytica* infections. Best estimates are that only 10% of infections are caused by *E. histolytica* (50 million cases), the rest by *E. dispar*.
- The incidence of paediatric amoebiasis is poorly documented. In the UK, between 1992 and 2006, <10% of all cases reported in the UK occurred in children <14 years. While uncommon in children under 5 years in Europe, this is not necessarily mirrored in resource-poor countries, from where case reports of colitis and amoebic liver abscesses (ALAs) in neonates have been reported.
- *E. histolytica*, spread by the faecal–oral route, occurs most frequently where human waste is used as a fertilizer or contaminates water sources. Cysts can persist in damp environments, such as soil, for months and are resistant to conventional chlorination as well as gastric acid. Ingested cysts develop into trophozoites in the small intestine and then pass to the colon where they feed on luminal bacteria and partially digested food. The trophozoites divide by binary fission and form cysts that are passed in the stool, completing the cycle. Trophozoites cannot survive outside the body.

Clinical features

Asymptomatic carriage

Asymptomatic carriage rates are lower than previously reported. In patients identified carrying *E. histolytica*, probably 90% will remain asymptomatic and eliminate the organism without any treatment. In children, arginine polymorphisms (223R) in the leptin receptor gene increases invasive disease, while the presence of the HLA-DQB1*0601 allele protects.

Intestinal disease

In follow-up studies of asymptomatic carriers over 1 year, 4–10% develop colitis when the intestinal mucosa is breached. This can occur months, or even years, after infection. Usually there is a 1- to 3-week history of worsening diarrhea, progressing to dysentery. In 80% of patients, this lasts for <4 weeks, while, in ~10%, GI symptoms may persist for longer than a year (a third in some studies). Pain is common, occurring in up to 80%, but constitutional symptoms are uncommon: weight loss <50% and fever 10–30%.

Fulminant colitis with perforation is rare, occurring in 0.5% of cases, most frequently affecting the caecum and ascending colon. Those at most risk include the very young and old, the malnourished, pregnant women, and those receiving corticosteroids. Mortality from fulminant colitis with perforation was 40% but, with early diagnosis and intervention, has fallen to <3%. Abdominal pain, distension, and tenderness occur in the majority.

Systemic disease

The commonest systemic manifestation in amoebiasis is ALA, occurring in 0.5–1.5% of patients infected with *E. histolytica*; equal sex predominance in children, in comparison with adults where 90% occurs in men.

The proportion of patients with ALA and concurrent or prior intestinal disease, including dysentery, is variable; quoted rates range from 30% to 60%. ALA can occur months to years after travel to an endemic area. In the majority of ALA cases, the right lobe of the liver is involved (drainage of the ascending colon and caecum), and 70% are single abscesses. ALA patients have:

- Fever and pain: 85–90%
- Weight loss: 30–50%
- Diarrhoea: 20–30%
- Cough: 10–30%
- Hepatomegaly: 30–50%
- Jaundice: 6–10%.

Symptoms are present for <10 days in 80% of patients. Reactive pleural effusions and a raised right hemidiaphragm are common but can signify rupture of the ALA through the diaphragm into the pleural space.

Very rarely, disease disseminates further, either by rupture of the ALA or during intestinal perforation and peritonitis to the pericardium, genitourinary system, and brain.

Differential diagnosis

Intestinal disease

- 'Traveller's' diarrhoea.
- Shigellosis, salmonellosis, *Campylobacter enteritis*.
- Entero-invasive and entero-haemorrhagic *E. coli*.
- Coeliac disease, tropical sprue.
- Inflammatory bowel disease.

Amoebic liver abscess

- Bacterial liver abscess.
- Echinococcal cyst.
- 1° or 2° liver malignancy.

Investigation

A detailed travel history, often going back a number of years, is vital to suspect *E. histolytica* infections. The results of investigations need to be considered in the context of a patient's history.

Light microscopy

- Stool microscopy is the mainstay of diagnosis and screening of patients with intestinal disease. Detection of protozoal cysts in saline or Lugol's iodine-stained faeces is relatively straightforward; however, the differentiation between *Entamoeba* spp. and other intestinal flagellates species requires experience.
- If dysentery is present, then fresh warm stool needs to be sent urgently for microscopy to look for trophozoites with ingested red blood cells, diagnostic of *E. histolytica*. If the sample is allowed to cool, then *E. histolytica* trophozoites lose red blood cells and are impossible to separate from the trophozoites of *E. dispar/moshkovskii* and difficult to separate from cysts of *E. hartmanni* and *E. coli*.
- Microscopy of ALA fluid, if available, rarely identifies trophozoites, but antigen detection has a high sensitivity and specificity.

Antigen detection

Possible on frozen stool or ALA abscess fluid samples <24 hours old. An ELISA-based assay using a monoclonal antibody against the Gal/GalNAC-lectin specific to *E. histolytica*, developed by TECH LAB USA, is available in the UK and has a sensitivity and specificity exceeding 96% in amoebic dysentery and ALA (Figs. 43.1 and 43.2). PCR technology, far more sensitive than antigen detection, is now being used to differentiate *E. histolytica/dispar/moshkovskii* but is not clinically available in the UK.

Serology

More than 90% of patients who have had amoebiasis develop antibodies to *E. histolytica*, possibly lower in asymptomatic carriers. The serological tests available remain negative in *E. dispar/moshkovskii* carriers. In amoebic dysentery and ALA, serology is positive in 88% and 90–100% of patients,

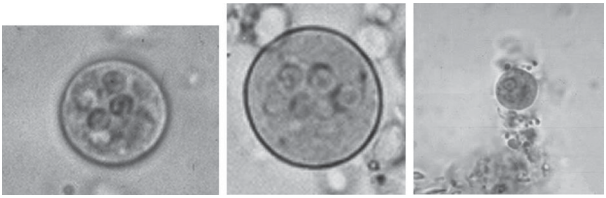

Fig. 43.1 Cysts of (A) *E. histolytica/dispar* (size range 10–15 microns); (B) *E. coli* (size range 10–35 microns); (C) *E. hartmanni* (size range 5–10 microns). (℞ <http://www.cdc.gov/index.htm>.)

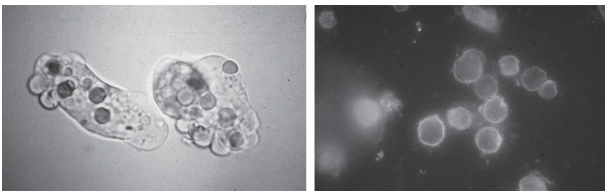

Fig. 43.2 *E. histolytica* trophozoites. (A) Ingested red blood cells; (B) fluorescein isothiocyanate (FITC) immunofluorescent antibody (IFA) staining.
(Courtesy: Wendy Bailey, Liverpool School of Tropical Medicine.)

respectively. In acute ALA, serology may be initially negative if there is a very short history but becomes positive 2–4 weeks later. Antibody titres remain elevated for years, even after successful treatment, and therefore they have limited application in endemic countries where up to 30% of the population may be seropositive.

Endoscopy

Endoscopy in amoebic colitis may demonstrate non-specific findings, but occasionally the pathognomonic finding of a flask-shaped ulcer can be seen. Endoscopy needs to be combined with histology and antigen detection methods.

Imaging

Plain chest and abdominal radiographs may reveal a raised hemidiaphragm or pleural effusion. Ultrasound, CT, and MRI can characterize liver lesions. Gallium scans can potentially differentiate between cold ALA and hot bacterial abscesses. Repeat scanning is sometimes useful to demonstrate resolution of liver lesions, but complete resolution, even with cure, does not always occur or may be delayed.

Treatment

E. dispar, and probably *E. moshkovskii*, infections do not require treatment. All *E. histolytica* infections require intestinal luminal clearage, with or without treatment for systemic/invasive disease. Where identification of *E. histolytica* from *E. dispar* and *E. moshkovskii* is not possible, luminal cidal treatments without confirmation are sometimes used, with the risk of increasing drug resistance.

Luminal amebicide therapy for asymptomatic intestinal disease

Paromomycin

Side effects: nausea and stomach cramps.

Diloxanide furoate

Side effects: flatulence, vomiting, urticaria, pruritus.

Iodoquinol

Side effects: diarrhoea, dizziness, headache, nausea, vomiting, rectal itch, and stomach cramps.

Invasive bowel and systemic disease

Only rarely do patients with ALA require drainage, as this carries a risk of perforation, systemic dissemination, and sepsis syndrome. Resolution of fever usually occurs within 3–4 days after starting treatment. Perforation, peritonitis, and septicaemia are managed as in routine practice, with the addition of metronidazole for 5 days.

Important: if the patient is critically unwell, they need coverage for 2° sepsis from bowel flora.

Metronidazole

Side effects: GI disturbances (including nausea and vomiting), taste disturbances, furred tongue, oral mucositis, anorexia.

Tinidazole

Side effects: same as metronidazole, but fewer.

A recent Cochrane review concluded that tinidazole was superior to metronidazole; fewer treatment failures and side effects were noted, but the quality of the studies was poor.

If treatment failure, alternative drugs used include nitazoxanide, dehydroemetine, and chloroquine phosphate with metronidazole. In rare cases surgical drainage of liver abscesses may be required.

Metronidazole is not effective therapy to remove luminal carriage; 50% fail to eliminate after a 10-day course. Therefore need to follow with luminal amebicide therapy, see above.

Probiotics

Recent small studies have demonstrated that the use of the probiotic *Saccharomyces boulardii* in resource-poor countries reduced the length of diarrhoea and cyst excretion in children. Large, better-quality studies are required before probiotics are routinely added to treatment regimens.

Prevention

- Interruption of the faecal–oral route.
- Improved sanitation.
- *E. histolytica* only occurs in primates, including humans. Vaccines, if available, would prevent disease—an area of ongoing, but early, research.

Further reading

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Chapter 44

Anaerobic infections

See also Chapters 22, 28, 38, 40, 44.

Introduction

Anaerobic organisms are those which replicate preferentially at reduced oxygen tension. Most clinical anaerobic infections in humans are caused by commensal bacteria from the skin and mucous membranes. These can cause serious infections in children in all body sites but are often related to the entry of organisms from mucous membranes or the gut, especially in chronic infection or immunocompromise. They are commonly found with other aerobic or anaerobic organisms in polymicrobial infections.

Nearly all anaerobic infections originate inside the host, except for infections following bites or penetrating trauma and those caused by *Clostridium* spp.

When to suspect anaerobic infection

- Infection at sites of anaerobic colonization, e.g. head and neck, abdomen, ♀ genital tract.
- Possible spread from such sites, e.g. CNS infection from the head and neck, aspiration pneumonia.
- Entry of external anaerobes, e.g. surgery, penetrating injury, including human or animal bites, indwelling devices, e.g. shunts, tracheostomy.
- Host susceptibility, e.g. after splenectomy.

Mixed infections of aerobic and anaerobic organisms are commoner than isolated anaerobic infections.

Microbiology

Definitions

- *Strict anaerobes* only survive in conditions of reduced oxygen levels.
- *Microaerophilic organisms* require small amounts of oxygen to replicate.
- *Facultative anaerobes* can replicate in the presence or absence of oxygen.
- *Strict aerobes* replicate only if oxygen is present.

Classification

The clinically important obligate anaerobic bacteria are listed.

Gram-positive cocci

- *Peptostreptococcus* spp.

Gram-positive bacilli

- Spore-forming and non-spore-forming.

Spore-forming

- *Clostridium*. spp.—the most important being *C. tetani, C. difficile, C. botulinum, C. perfringens*.

Non-spore-forming

- *Actinomyces* spp., *Propionibacterium acnes, Propionibacterium propionicus, Bifidobacterium eriksoni, Bifidobacterium dentium*.

Gram-negative cocci

- *Veillonella* spp.

Gram-negative rods

- *Bacteroides fragilis* group
- Other *Bacteroides: B. gracilis, B. ureolyticus*.
- Pigmented *Prevotella* spp.
- Other *Prevotella* spp.
- *Fusobacterium* spp., including *F. nucleatum, F. necrophorum*.

Clinical infections

Specific anaerobic conditions

Clostridial infection

For *C. tetani, C. difficile*, and *C. botulinum*, see Chapters 117, 58, and 48, respectively.

Actinomycosis

- *Actinomyces* spp. (most commonly *A. israelii*) may be part of the normal flora of the mouth, GI tract, or vagina. *Actinomycosis* is a rare cause of subacute or chronic infection in children, which presents as lymphadenopathy that develops into 'woody' abscesses, which may form sinuses. Classically, the sinuses drain yellow sulfur granules which are pathognomonic. The child is usually afebrile and well, but with a chronic induration in the affected area that crosses tissue planes. Lesions may mimic chronic abscesses or malignancy, and the organism may resemble *Nocardia* spp.
- Abscesses may develop following the extraction of carious teeth (cervical), an oesophageal disruption (thoracic), or the use of intrauterine devices (pelvic); they may also occur in the brain after bites. Treatment often involves surgical debridement, but prolonged antibiotic therapy is essential (6–12 months of IV, then oral, penicillin is usual, or alternatively clindamycin or tetracyclines).

Anaerobic infections by body system

Central nervous system infections

- Anaerobes can cause brain abscesses, subdural empyemas, epidural abscesses, and meningitis; they may also complicate intraventricular shunt infections. The usual sources of bacteria are head and neck infections originating in the adjacent ears, mastoids, sinuses, oropharynx, or teeth.

- *Shunt infections* can be caused by anaerobes. *P. acnes*, a skin commensal, is a recognized organism. Shunts ending in the peritoneum may be infected by GI organisms such as *B. fragilis*. Anaerobic shunt infections commonly result in milder fever and lower CSF WCCs than aerobic infections.
- *Brain abscesses* are more likely to have an anaerobic component if they are 2° to sinusitis, acute or chronic otitis media, or mastoiditis. Anaerobes can also complicate the intracranial infection associated with Potts puffy tumour (severe frontal sinus abscess with osteomyelitis). Treatment of a brain abscess is prolonged and difficult, requiring neurosurgical input and medical management with long courses of antibiotics with good blood–brain barrier penetration. Bacteria generally grown from abscesses include the pigmented *Prevotella* spp., *Porphyromonas* spp., *Bacteroides* spp., *Fusobacterium* spp., *Peptostreptococcus* spp., and the microaerophilic *Streptococcus* spp.
- *Meningitis* is rarely caused by anaerobic bacteria in children. It should always prompt the careful clinical examination of the child for a dermal sinus. There are case reports of anaerobic meningitis most commonly complicating an underlying head or neck infection—*B. fragilis* has been isolated from the CSF in children with a history of chronic otitis media, infected ventriculoperitoneal shunt, abdominal sepsis, and an infected pilonidal sinus or midline dermoid cyst. *B. fragilis* meningitis carries high mortality and morbidity, with premature infants and neonates at particularly high risk. In children with associated risk factors, CSF and blood should be sent for anaerobic and aerobic culture.

Head and neck infections

Anaerobic organisms form part of the normal oropharyngeal flora and are often isolated in chronic infections of the head and neck.

- *Teeth*—anaerobic bacteria colonize the mouths of infants within the first few months of life and greatly increase in numbers once teeth erupt. Bacteria in root canals of necrotic pulp and periapical lesions are predominantly anaerobic. It is common to find transient low-level bacteraemia following tooth extraction in children (up to 65%), of which half the strains are anaerobes or microaerophilic streptococci. Organisms that predominate include *Prevotella* spp., *Porphyromonas* spp., *Fusobacterium* spp., and *Peptostreptococcus* spp.
- *Ears*—anaerobes are cultured in up to 10% of patients with AOM, and 42% of those with effusions. Predominant species include Gram-positive cocci (*Peptostreptococcus* spp.) and anaerobic Gram-negative rods (*Prevotella* spp., *Porphyromonas* spp., *Bacteroides* spp., and *Fusobacterium* spp.).
- *Lemierre's disease* is the most severe manifestation of infection with *F. necrophorum*. This Gram-negative rod is found in the oropharynx, as well as the GI and ♀ genital tracts. It can cause purulent and necrotic infections at various sites. Head and neck infections include pharyngitis, sinusitis, parotitis, dental, and middle ear infections. Lemierre's disease comprises local septic thrombophlebitis of the jugular vein, bacteraemia, and possible distal septic metastases. Meningitis and osteolysis of the temporal bone or other long bones may also occur. The initial focus

is usually the middle ear but may be the pharynx or teeth. Anaerobic bacteraemia may also complicate thrombophlebitis of other veins.
  - Diagnosis may prove difficult, as the disease is fairly rare, and cultures may be sterile or polymicrobial. The key is finding septic thrombophlebitis on ultrasound. Molecular analysis by PCR and sequencing may be necessary to identify *F. necrophorum* from samples, e.g. middle ear fluid, pus from abscess formation, or CSF.
  - Treatment is with antibiotics. In a recent review of 25 cases of Lemierre's, children were treated with a combination of high-dose co-amoxiclav, metronidazole, and clindamycin, and all made good recovery. Antibiotics should be given for 2–6 weeks minimum but may be needed for months if severe mastoiditis is present with slow recovery. Oral therapy can be given after clinical improvement and normalization of inflammatory markers. Mastoidectomy and anticoagulant therapy should also be considered. Mortality was >90% in the pre-antibiotic era, but deaths are uncommon with good microbiological diagnosis, appropriate antibiotics, and intensive care.
- *Tonsils*—acute bacterial tonsillitis is usually caused by aerobic *Streptococcus* spp., but there is increasing evidence for the involvement of anaerobes in chronic tonsillitis and complications such as peritonsillar and retropharyngeal abscess and Vincent's angina—*Fusobacterium* spp., Gram-negative anaerobic bacilli, and *Peptostreptococcus* spp. have been isolated. Children who undergo tonsillectomy for recurrent chronic tonsillitis show a significant drop in the number of anaerobic bacteria in the oropharyngeal flora post-tonsillectomy.

Pleuropulmonary infections

- *Aspiration pneumonia*—aspiration of oropharyngeal secretions or gastric contents, and severe periodontal disease or abscess are the highest risk factors for developing anaerobic pleuropulmonary infections in children; tracheostomies also increase the risk of anaerobic infection. Complications include lung abscess or empyema. Predominant organisms include *Peptostreptococcus* spp., *Fusobacterium* spp., pigmented *Prevotella* spp., *Porphyromonas* spp., and *B. fragilis*. Microbiological diagnosis may be complicated by contamination of sputum samples by oropharyngeal organisms.

Intra-abdominal

- Anaerobic bacteria are part of the normal GI flora. Peritonitis and abscess formation are the result of entry of enteric bacteria into the peritoneal cavity. Perforated appendicitis, resulting in peritonitis or periappendicular abscess, is the commonest cause in children. The commonest organism isolated is *E. coli*, but mixed cultures and anaerobes are frequently present, especially once an abscess has formed. *B. fragilis* is the commonest anaerobe isolated, followed by *Peptostreptococcus* spp. and *Clostridium* spp.
- Therapy consists of surgical management and an antibiotic combination that covers both aerobes and anaerobes. Cefotaxime and metronidazole, or ampicillin with metronidazole and an aminoglycoside, have been shown to be effective.

Female genital tract

- Anaerobes are common in the genital tract in sexually active ♀. Infections that may be polymicrobial include bacterial vaginosis, soft tissue perineal and vulval abscesses, pelvic collections, intrauterine device-associated infections, and post-operative obstetric and gynaecological infections. Predominant bacteria include *Prevotella* spp., *Peptostreptococcus* spp., *Porphyromonas* spp., *Clostridium* spp., and *Actinomyces* spp.

Skin and soft tissue

- *Bite wounds* often contain anaerobic oral flora, including microaerophilic *Eikenella* spp. in human bites and *P. multocida* in animal bites.
- *Gas gangrene* is a deep-seated infection of the muscle caused by *C. perfringens* or *C. septicum*. It is extremely rare in children and is associated with underlying neutrophil dysfunction, bowel ischaemia, or trauma. Non-specific symptoms include vomiting, diarrhoea, blood per rectum, severe abdominal pain, and an acute abdomen. Crepitus in muscles can sometimes be felt. Mortality is high, and survivors are more likely not to have abdominal involvement, to receive early parenteral antibiotics, have no underlying medical risk factors, and undergo surgical debridement. Hyperbaric oxygen may be useful.
- *Tropical ulcers* in children are most commonly caused by *Fusobacterium* spp.

Osteomyelitis and septic arthritis

- *OM* may be anaerobic in facial or cranial bones following local spread from soft tissue, or in long bones following trauma, haematogenous spread, or bone hypoxia 2° to sickle-cell disease or vascular ischaemia. Infection is likely to be polymicrobial and associated with anaerobic infection elsewhere in the body.
- *SA* due to anaerobes is rare but is more likely to be monomicrobial than OM. It is usually due to haematogenous spread from an anaerobic infection elsewhere in the body.
- *Diagnosis* requires tissue samples of bone or synovial pus. *Peptostreptococcus* and *Bacteroides* are the commonest anaerobic organisms at all sites. *Fusobacterium* may complicate sickle-cell disease, and *Clostridium* may be found with contamination after trauma.
- *Treatment* requires adequate surgical debridement or pus drainage, orthopaedic involvement, and antibiotic treatment with good bone or joint penetration.

Bacteraemia

- *Anaerobic bacteraemia* in children is rare, carries a high mortality, and is usually associated with a localized infection and risk factors such as indwelling catheters or recent GI or pelvic surgery. Children who have malignant disease, particularly leukaemia, chronic renal failure, decubitus ulcers, or a known immunodeficiency, are at increased risk of anaerobic bacteraemia. Infectious mononucleosis has also been reported to predispose to anaerobic bacteraemia. Neonates are at increased risk—anaerobic Gram-positive cocci sensitive to penicillin appear more commonly in the first few days of life and are associated with chorioamnionitis; anaerobic Gram-negative organisms appear later,

are less sensitive to penicillins, and may be associated with necrotizing enterocolitis. Routine culture for anaerobes in previously healthy children who do not present with a possible anaerobic site of infection is not recommended, as the yield is so low. The most commonly recovered organism from anaerobic blood cultures overall is *B. fragilis*.

- *Diagnosis*—blood cultures from children are often taken into single aerobic blood culture bottles. These require smaller quantities of blood than adult bottles. Some anaerobes will be isolated from these, but, if there is a strong clinical suspicion of an anaerobic infection, a separate anaerobic bottle should also be inoculated. This requires larger volumes of blood and may prove difficult in small patients or neonates.

General management

Management of anaerobic infections includes toxin neutralization, surgical debridement or drainage, if appropriate, and antimicrobial therapy (Table 44.1). Surgical involvement in cases of abscess formation, severe skin or bone/joint infection, or GI infection is crucial. Other therapies, such as hyperbaric oxygen in order to improve tissue oxygenation, may be useful but lack evidence.

Antimicrobials

Antimicrobial sensitivities of anaerobes are rarely routinely tested, and little is known about geographical and temporal variation. The *Bacteroides* group are best studied, as these are known to be virulent bacteria with mechanisms to evade antimicrobials. It is important to liaise with the local microbiology laboratory or regional/national anaerobic reference laboratory.

B. fragilis is largely resistant to penicillins but generally sensitive to penicillins with β-lactamase inhibitors. *B. fragilis* is sensitive to carbapenems and metronidazole, but resistant to many cephalosporins. Resistance to clindamycin is rapidly rising. The newer fluoroquinolones, such as moxifloxacin, have been approved by the US Food and Drug Administration (FDA) for use against skin infections that may contain anaerobes. Moxifloxacin has good *in vitro* activity against *Bacteroides*, although resistance is rising in the US. Tigecycline is another recently approved antibiotic with good *in vitro* activity against *Bacteroides* and most other anaerobes, and little resistance known. *Fusobacterium* are largely sensitive to penicillins, penicillins with β-lactamase inhibitors, and cephalosporins. *Prevotella* and *Porphyromonas* spp. have high resistance to penicillins, which may be overcome by the addition of a β-lactamase inhibitor. They are uniformly sensitive to carbapenems and metronidazole. The non-spore-forming Gram-positive bacilli, such as *Propionibacterium* and *Actinomyces*, are usually sensitive to penicillins, β-lactamase inhibitors, cephalosporins, and carbapenems. Most are resistant to metronidazole.

Gram-positive cocci *Peptostreptococcus* have variable resistance to penicillin, metronidazole, and clindamycin, while retaining susceptibility to β-lactamase inhibitors and carbapenems. There is increasing resistance recognized to the newer fluoroquinolones.

Table 44.1 Treatment suggestion for anaerobic infection by clinical presentation

Clinical	Likely organism	Suggested antibiotic	Comments
CNS			
Brain abscess	Mixed	Dependent on organism—if unknown, metronidazole + cephalosporin or carbapenem	
Shunt infection	*B. fragilis* *P. acnes*	Carbapenem + metronidazole, tigecycline Penicillin ± β-lactamase inhibitor, cephalosporin, carbapenem	Largely resistant to penicillin
Anaerobic meningitis	*B. fragilis* *C. perfringens*	Carbapenem + metronidazole, or tigecycline Penicillin or carbapenem or cephalosporin	
Head and neck			
Tooth abscess	Mixed	Co-amoxiclav or macrolide or metronidazole	Surgical drainage first-line
Chronic tonsillitis	*Fusobacterium*, Gram-negative anaerobic bacilli, and *Peptostreptococcus*	Co-amoxiclav in chronic cases	May require β-lactamase inhibitor after repeated use of penicillin
Lemmiere's disease	*F. necrophorum*	Co-amoxiclav or metronidazole or clindamycin	Usually need to cover aerobic organisms as well
Chronic otitis media	Mixed	Co-amoxiclav, macrolide, metronidazole, clindamycin	May also need to cover *Pseudomonas* spp. if present. Surgical debridement may be necessary
Chronic sinusitis	Mixed	Co-amoxiclav, macrolide, metronidazole, clindamycin	

(*Continued*)

Table 44.1 (*Contd.*)

Clinical	Likely organism	Suggested antibiotic	Comments
Pleuropulmonary			
Aspiration pneumonia	*Peptostreptococcus, Fusobacterium*, pigmented *Prevotella, Porphyromonas* spp. and *B. fragilis*	Co-amoxiclav or carbapenem or metronidazole	
Intra-abdominal			
Peritonitis and abscess	*E coli, B. fragilis, Peptostreptococcus, Clostridium*	Cefotaxime and metronidazole, or ampicillin and metronidazole and aminoglycoside	Surgical input essential
♀ genital tract	*Prevotella* spp., *Peptostreptococcus, Porphyromonas, Clostridium* spp., *Actinomyces* spp.	Doxycycline or macrolide and cephalosporin or clindamycin or metronidazole	Covers aerobes, anaerobes, and sexually transmitted pathogens
Skin and soft tissue			
Neonatal omphalitis	*Bacteroides* or *Prevotella*	Co-amoxiclav or metronidazole	
Acne	*Propionibacterium*	Tetracycline	
Bites	*Eikenella*—human *P. multocida*—animal	Co-amoxiclav or clindamycin	
Necrotizing fasciitis	Anaerobic cocci and *B. fragilis* + aerobes	Penicillin and aminoglycoside and metronidazole	
Gas gangrene	*C. perfringens*	Penicillin or macrolide or clindamycin	
Bones and joints			
Septic arthritis	*Peptostreptococcus* or *Bacteroides*	Clindamycin	Surgical drainage important
Osteomyelitis	*Peptostreptococcus, Bacteroides* *Fusobacterium* (sickle-cell) *Clostridium* (trauma)	Clindamycin	Surgical debridement important
	B. fragilis most commonly	Co-amoxiclav, or carbapenem or metronidazole	Rising resistance to penicillin, local resistance patterns important

NB: Antibiotic choices may also need to cover aerobic organisms.

Further reading

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Chapter 45

Arboviruses

See also Chapters 13, 41, 42.

Introduction

Arboviruses are arthropod-borne viruses. They cause disease in domestic and wild animals, and, in humans, they pose a threat to public health because of their epidemic and zoonotic potential. The vectors are species-restricted and determine the geographical distribution and seasonality of each virus. Disease outbreaks caused by arboviruses are sporadic and unpredictable.

Arbovirus infection in humans may cause:

- Acute haemorrhagic fever
- CNS infection (encephalitis, aseptic meningitis, or myelitis)
- Acute polyarthropathy
- Non-specific febrile illness often with rash
- Perinatal illness.

Name and nature of organism

Arboviruses that cause human disease are members of three main virus families: the *Togaviridae* (genus *Alphavirus*), *Flaviviridae*, and *Bunyaviridae*. Most arboviruses have an RNA genome. Arboviral infections are mostly zoonotic, involving a non-human 1° vertebrate host and a 1° arthropod vector. Viral replication in the arthropod vector (mosquitoes, ticks, or sandflies) is a prerequisite step before transmission to the next host.

Epidemiology, transmission, and incubation period

Humans and domestic animals become infected with arboviruses when they encroach on a natural focus of zoonotic infection or the virus escapes this focus via a 2° vector or vertebrate host. Humans are usually 'dead-end' hosts, because they do not produce significant viraemia. Important exceptions are dengue, yellow fever, and chikungunya where vectors spread disease from person to person.

Arboviral infections are vector-dependent and usually seasonal; mosquito-borne infections occur during the wet seasons/summer. In TBE in central Europe, two peaks of activity of *Ixodes ricinus* have been observed: in May/June and in September/October. In colder regions of northern Europe and in mountain regions, a single summer peak is detected. Cases of clinical illness occur more often at the extremes of age. Incubation periods of disease range from 1 to 18 days (Table 45.1).

Table 45.1 Common arboviruses

Name	Human disease	Vector	Geographical distribution	Reservoir	Incubation (days)
Flaviviridae					
St Louis encephalitis	Encephalitis	Mosquito	Americas and Caribbean	Birds	4–14
West Nile fever	Encephalitis	Mosquito	Asia, Africa, Europe, Americas	Birds	5–15
Powassan	Encephalitis	Tick	North America and Asia		4–18
Japanese encephalitis	Encephalitis	Mosquito	Asia	Water birds, pigs	5–14
Tick-borne encephalitis complex	Encephalitis	Tick. Occasional cases by ingestion of 'infected' cow or goat milk	Europe and Asia	Deer, rodents	7–14
Murray Valley encephalitis	Encephalitis	Mosquito	Australia and New Guinea		
Dengue fever	Febrile illness—may be biphasic with rash, haemorrhagic fever, and shock	Mosquito	Tropical areas worldwide	N/A	4–7
Yellow fever	Febrile illness, hepatitis, haemorrhagic fever	Mosquito	Tropical areas of South America and Africa	N/A	3–6
Bunyaviridae					
Rift Valley fever	Febrile illness, ocular disease, meningo-encephalitis, haemorrhagic fever	Mosquito, infected blood and tissues. Ingestion of 'infected' milk	Africa, Saudi Arabia, Yemen, and Indian Ocean	Domestic and wild animals	2–6

Crimean–Congo haemorrhagic fever	Febrile illness, haemorrhagic fever	Tick, infected blood and tissues. Ingestion of 'infected' milk	Africa, Europe, and Asia	Domestic and wild animals, birds	1–13
California serogroup viruses	Encephalitis	Mosquito	Americas, Europe, and Asia	Small mammals	5–15
Oropouche virus fever	Febrile illness	Midge	Central and South America	N/A	2–6
Hantavirus fevers	Haemorrhagic fever with renal syndrome or with cardiopulmonary syndrome	Aerosolized rodent excreta or rodent bites	Asia, Europe, and Americas		
Toscana and Sicilian virus	Febrile illness. Aseptic meningitis	Sandfly	Europe and Asia		
Togaviridae					
Chikungunya virus	Febrile illness, arthropathy, occasional meningo-encephalitis	Mosquito	Africa, Asia, and Europe	N/A	1–12
Eastern equine encephalitis virus	Encephalitis	Mosquito	Americas	Birds	3–10
Western equine encephalitis	Encephalitis	Mosquito	Americas	Birds	2–10
Venezuelan equine encephalitis	Encephalitis	Mosquito	Americas	Small mammals and horses	1–4

(*Continued*)

Table 45.1 (*Contd.*)

Name	Human disease	Vector	Geographical distribution	Reservoir	Incubation (days)
Mayaro virus	Febrile illness and arthropathy		Americas		1–12
Ross River virus	Febrile illness and arthropathy		Australia and Oceania		
O'nyong nyong virus	Febrile illness and arthropathy		Africa		
Sindbis virus	Febrile illness and arthropathy	Mosquito	Africa, Scandinavia, Northern Europe, Asia, and Australia		
Reoviridae					
Colorado tick fever	Febrile illness—may be biphasic	Tick	North America and Asia		1–14
Rhabdoviridae					
Vesicular stomatitis virus		Sandfly and blackfly	Americas and Africa		

In recent decades, the geographical distribution of disease caused by arboviruses has expanded. Outbreaks of West Nile fever have occurred in Europe, especially in the Mediterranean basin. Moreover, Crimean–Congo haemorrhagic fever (CCHF) is endemic in many European countries, and serious outbreaks have occurred, particularly in the Balkans, Turkey, and Southern Federal Districts of Russia. In 2000, Rift Valley fever was reported for the first time outside the African continent, with cases being confirmed in Yemen and Saudi Arabia, and there have been recent reports of chikungunya in the Americas.

Dengue ranks as the most important mosquito-borne viral disease in the world. In the past 50 years, the incidence has increased 30-fold. An estimated 2.5 billion people live in over 100 endemic countries and areas where dengue viruses can be transmitted. Up to 390 million infections occur annually with 500 000 cases of dengue haemorrhagic fever (DHF) and 22 000 deaths mainly among children. Prior to 1970, only nine countries had experienced cases of DHF; since then, the number has increased more than 4-fold and continues to rise.

Japanese encephalitis is the most important cause of arboviral encephalitis, with over 67 000 cases reported annually. Arboviruses are the commonest causes of episodic encephalitis in the US, with a reported incidence of 0.2 per 100 000. However, these statistics may be misleading, because most people bitten by arbovirus-infected insects do not develop clinical disease.

Clinical features and sequelae

The majority of arbovirus infections are asymptomatic or may result in a non-specific flu-like syndrome. Infections are characterized by viral replication in endothelial and macrophage/monocyte lineage cells, inducing type 1 IFN production.

Onset may be insidious or sudden, with fever, headache, myalgias, arthralgias, malaise, and occasionally prostration. Infection may, however, lead to 2° viraemia and subsequent infection of target organs. Which organs are targeted depends on the tropism of the virus. Access to the brain may be via infection of endothelial cells in the cerebral vasculature or invasion of the choroid plexus. 2° viraemia can lead to haemorrhagic fever or encephalitis, with a fatal outcome or permanent neurological sequelae.

Only a very small proportion of infected children progress to overwhelming disease. Antibody-mediated immunity is important in controlling 2° viraemia and progression of disease. Recovery from disease relies on cell-mediated immunity.

Acute haemorrhagic fevers

Dengue has a wide spectrum of clinical presentations. Dengue fever and DHF are caused by four closely related virus serotypes (DEN 1–4). Each serotype is sufficiently different that there is no cross-protection, and epidemics caused by multiple serotypes (hyperendemicity) can occur.

Infection produces sudden-onset fever, headache, retro-orbital pain, extremely painful myalgia (break bone fever), arthralgia, facial flushing/erythema/rash, nausea, and vomiting. The classic dengue fever lasts 2–7 days, with a biphasic fever pattern. It tends to be milder in children than adults.

The white cell and platelet count may drop until the end of the febrile phase. The acute phase may last up to 1 week, with a prolonged convalescence characterized by weakness, malaise, and anorexia.

DHF is an immunopathological consequence of infection in a patient with serotype-specific immunity from a previous infection with a virus of another serotype. Immune enhancement leads to increased uptake of 'new' virus coated with a pre-existing non-neutralizing antibody into macrophages via the Fc receptor. The virus replicates in macrophages, leading to an increased virus load; in turn, macrophages become activated and release inflammatory cytokines.

Disease is more severe in children, and the presence of maternal antibody in infants may result in DHF, even from a first infection with dengue virus. Criteria for DHF include a haemorrhagic tendency (positive tourniquet test, spontaneous bruising, mucosal bleeding, injection site bleeding, epistaxis, haematemesis, bloody diarrhoea), thrombocytopenia (<100 000 platelets/microlitre), and organ involvement (massive GI bleeding, acute liver failure, acute renal failure, encephalopathy or encephalitis, cardiomyopathy). Evidence of plasma leakage (haematocrit >20% higher than expected, pleural effusion, ascites, hypoproteinaemia) is an indication of progression to severe dengue/dengue shock syndrome.

Dengue shock syndrome is defined as DHF plus a weak rapid pulse, a narrow pulse pressure (<20mmHg), poor peripheral perfusion, and reduced level of consciousness. DHF is fatal in up to 30% of untreated cases. The key to survival is early diagnosis and active supportive care.

Yellow fever cases have increased over the past two decades due to declining population immunity to infection, deforestation, urbanization, population movements, and climate change. There are an estimated 200 000 cases of yellow fever, causing 30 000 deaths, worldwide each year. Once contracted, the virus incubates for 3–6 days, followed by infection that can occur in one or two phases.

The first, acute phase usually causes fever, myalgia, prominent backache, headache, rigors, anorexia, nausea, and vomiting. Most patients improve, and symptoms disappear after 3–4 days.

Around 15% of patients enter a second, more toxic phase within 24 hours of the initial remission. High fever returns, and a multi-organ illness follows. The patient rapidly develops jaundice, renal impairment, abdominal pain, vomiting, and a bleeding diathesis. Half of the patients who enter the toxic phase die within 10–14 days; the rest recover without significant organ damage. Up to 50% of severely affected persons without treatment will die from yellow fever.

CCHF has the most extensive geographical distribution of the medically important tick-borne viral diseases. Onset of symptoms is sudden, with fever, myalgia (aching muscles), dizziness, neck pain and stiffness, backache, headache, photophobia, and acute confusion. Other clinical signs include tachycardia, lymphadenopathy, a petechial rash, and mucosal bleeding. There is usually evidence of hepatitis. The severely ill may develop hepatorenal and pulmonary failure after the fifth day of illness. The mortality rate from CCHF is ~30%, with death occurring in the second week of illness. In those patients who recover, improvement generally begins on the ninth or tenth day after the onset of illness.

Acute polyarthropathy

Chikungunya virus has been responsible for an ongoing outbreak in the past 6 years in the Indian Ocean, Europe, Asia, Oceania, Africa, and a small number of cases in the Americas. After infection with chikungunya virus, there is a silent incubation period, lasting 2–4 days on average (range 1–12 days). Clinical onset is abrupt, with high fever, headache, back pain, myalgia, and arthralgia; the latter can be intense, affecting mainly the extremities (ankles, wrists, phalanges), but also the large joints. Skin involvement is present in about 40–50% of cases and consists of a pruriginous maculopapular rash predominating on the thorax, facial oedema, or, in children, a bullous rash with pronounced sloughing, and localized petechiae and bleeding gums. Erratic, relapsing, and incapacitating arthralgia is the hallmark of chikungunya, although it rarely affects children. It may persist for several months.

Neurological complications, such as meningo-encephalitis, have been reported. Chikungunya virus has been isolated from children with clinical signs of encephalitis and meningitis. Among 35 women who were ill with chikungunya at delivery in a recent outbreak, 30 delivered an infected newborn baby, of which 27 were severely affected. The possible risks of embryopathy, fetopathy, and late sequelae are unknown.

Central nervous system infection

TBE includes three subtypes: Western subtype, Far Eastern subtype, and Siberian subtype. The number of human cases of TBE in all endemic regions of Europe has increased by almost 400% in the past 30 years; the risk areas have spread, and new foci have been discovered. The incubation period of TBE is 7 days on average, but incubation of up to 28 days has been described. Approximately two-thirds of human TBE virus infections are asymptomatic.

TBE often has a biphasic clinical course. The first viraemic phase lasts 5 (range 2–10) days and is associated with non-specific symptoms (fever, fatigue, headache, myalgia, nausea). This phase is followed by an asymptomatic interval lasting 7 (range 1–21) days, which precedes the second phase when the CNS is involved (meningo-encephalitis, myelitis, paralysis). The Western European subtype is associated with milder disease, with 20–30% of patients experiencing the second phase, mortality rates of 0.5–2%, and severe neurological sequelae in up to 10% of patients. In children, the second phase of illness is usually limited to meningitis, whereas adults >40 years are at increased risk of developing encephalitis. The Far Eastern subtype is associated with a monophasic illness, with no asymptomatic interval preceding the onset of neurological disease, mortality rates of up to 20%, and higher rates of severe neurological sequelae.

Japanese encephalitis virus epidemics occur in late summer in temperate regions, but the infection is enzootic and occurs throughout the year in many tropical areas of Asia. The incubation period is 5–14 days. Onset of symptoms is usually sudden, with fever, headache, and vomiting. The illness resolves in 5–7 days if there is no CNS involvement. The mortality in most outbreaks is <10% but is higher in children and can exceed 30%. Neurological sequelae in patients who recover are reported in up to 30% of cases.

West Nile virus encephalitis has been the cause of recent outbreaks in North America and Europe. In humans, it usually produces either asymptomatic infection or mild febrile disease with rash, arthritis, myalgias, weakness (a transient poliomyelitis-like 'acute flaccid paralysis' with acute respiratory involvement), lymphadenopathy, and meningo-encephalitis. It can cause severe and fatal infection in <1% of infected patients due to neuroinvasive disease. There is some limited evidence of persistence.

Diagnosis

Arbovirus infection diagnosis is difficult, because many other agents cause similar symptoms.

Laboratory diagnosis of human arboviral disease relies on rapid serologic assays, such as IgM-capture ELISA (MAC-ELISA) and IgG ELISA, soon after infection. Early in infection, IgM antibody is more specific, whereas, later in infection, IgG antibody is more reactive.

Virus isolation and identification from serum, throat swab, CSF, and mosquito vectors is also possible. While PCR has been developed to identify a number of viral agents, such tests are not yet validated for routine rapid identification in the clinical setting.

Management and treatment

Early diagnosis in severe disease directly affects outcome. Treatment is supportive, including antibiotics for any 2° bacterial infections, aggressive management of haemorrhagic manifestations, multi-organ involvement, and neurological complications.

There are no effective antiviral drugs against arboviruses, although ribavirin has been used, with demonstrable benefit in a limited number of observational studies in CCHF. Chloroquine has been used in arbovirus polyarthritis, with anecdotal benefits.

Prevention

Prevention methods include surveillance, vector control (aerial and house-to-house spraying), public education about reducing vector numbers and reducing vector exposure (insect repellents, bed nets, suitable clothing, low-risk outdoor activities, restricted travel to endemic areas), reservoir host control, and the use of vaccines where available.

Human vaccines currently available include yellow fever, TBE, and Japanese encephalitis. Active research in dengue vaccine and chikungunya vaccine is promising.

Future research

- Emergence of arboviruses will continue to occur due to changes in ecological patterns, the natural evolution of invertebrate vectors, vertebrate hosts, and the viruses themselves, combined with rapid movement of people and animals on a global scale.
- Global warming will increase the geographical spread of arboviral infection and will need improved surveillance mechanisms.
- New data on viral replication offer substantial potential for the development of new drugs.

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Chapter 46

Ascariasis

Name and nature of organism

- Ascariasis (also known as common roundworm or large roundworm infection) is caused by the intestinal nematode *A. lumbricoide*s (member of the soil-transmitted helminths).
- Adult worms inhabit the lumen of the small intestine, mainly the jejunum and ileum. Their lifespan is 10–24 months, and then eggs pass into the stool.
- They are white or yellow, and their length ranges from 10 to 40cm (♀ are bigger than ♂)
- *A. lumbricoide*s almost exclusively inhabits humans.

Epidemiology

- Ascariasis is the commonest infection caused by worms in humans and is endemic throughout the world.
- It is present in at least 150 countries worldwide, and >1.2 billion people (approximately one-sixth of the population) are hosts to *A. lumbricoide*s. Infections occur most frequently in the *Americas, China* and *East Asia*, and *Sub-Saharan Africa* (tropical and subtropical areas, and particularly in developing countries with wet climates).
- Children are particularly prone to ascariasis, because of poorer hygiene habits than adults and their tendency to put things in their mouths.
- The global prevalence in children is estimated to be up to 400 million. The commonest age group infected is between 3 and 8 years old. The highest intensity of infection occurs in children harbouring other helminth infections (e.g. *Trichuris trichuria*, hookworm).
- Around 50 million children are believed to have more severe nutritional morbidity due to high infection load. Young children are the most likely to have intestinal obstruction (85% of cases are reported in those aged 1–5 years).

Transmission and incubation period

- Children playing in parks or on ground with contaminated soil can acquire infection from their hands. For this reason, children between 2 and 10 years old are the commonest infected group.
- Transplacental infection has been described (neonatal ascariasis).
- The majority of the patients are asymptomatic but still transmit infection.

Life cycle

- Parasitic infection with *A. lumbricoides* occurs via ingestion of embryonated eggs. These are found in soil and human faeces, and on contaminated food. Eggs can be spread by earthworms, insects, and burrowing animals and can also become airborne in wind-spread contaminated dust, which can be inhaled or swallowed by humans.
- There is little direct information on the interaction of *A. lumbricoides* larvae with humans; life cycle data come from experiments with mice.
- When *A. lumbricoides* eggs are swallowed, they pass into the intestine and hatch in the jejunum, releasing larvae measuring 50–70 microns in length. The larvae enter the portal venous circulation via penetration of the small intestine wall, and migrate to the liver. They also circulate in the lymphatic system.
- The larvae travel via the venous circulation to the pulmonary circulation to the lungs where they enter the bronchial tubes and penetrate the pulmonary capillaries to enter the alveolar spaces. They then ascend into the trachea and are swallowed, thus returning to the small intestine. They mature into adult worms over 14–20 days, mate, and lay eggs.
- The cycle from ingestion to maturation takes 18–42 days in humans. The adult parasite lives in the gut for 6–24 months.
- A ♀ worm may contain up to 27 million eggs and can produce ~200 000 eggs per day. In the presence of ♂ worms, the eggs are fertilized and therefore become infective. Eggs are discharged into faeces (~9 weeks after the initial ingestion of eggs) and incubate in the soil. Any fertilized eggs will then become infectious, once they embryonate. *A. lumbricoides* eggs are resistant to environmental stresses.

Clinical features and sequelae

Asymptomatic infection is the commonest, and the first sign of ascariasis is often excretion of a worm in the faeces, particularly in children in endemic areas. Symptoms occur during migration and mainly in patients with a high burden of worms and depend on direct damage, the immunological response, and the nutritional status.

Intestinal symptoms

- Ascariasis is often *asymptomatic*.
- Sometimes cause *non-specific abdominal symptoms* (nausea, vomiting, abdominal pain, diarrhoea, loss of appetite, anal itching).
- Severe intestinal symptoms could include *malnutrition*, loose protein, steatorrhoea, and lactose intolerance in a high burden of infection.
- Growth retardation and even *cognitive delay* have been described in these children.
- *Intestinal obstruction*: mature worms may form a bolus, causing intestinal obstruction (most often in the terminal ileum).
  - It is commoner in children between 1 and 5 years (85% of cases in children).
  - The worm bolus may also cause *intussusception* or volvulus.

- Symptoms are: tachycardia, fever, vomiting, constipation, and colicky abdominal pain; sometimes emesis contains the worm, and a palpable mass can be observed.
- The patient may develop *sepsis* and septic shock.
- Increasing severity of symptoms is an indicator of progression of the obstruction, gangrene, or *perforation*. Fatal cases 1%.

Pulmonary ascariasis

- During the migration of larvae into the lungs, symptoms, like pneumonitis, with associated asthma or wheeze or rales, cough 1–2 weeks after infection, can be observed (Loeffler´s syndrome: respiratory symptoms, eosinophilia, and lung infiltrates), and chest pain, blood tinge (or even a worm) in sputum, and shortness of breath. These signs may persist for several days.
- Sometimes a worm can migrate and obstruct the airway, causing respiratory distress and even respiratory arrest.

Hepatobiliary and pancreatic ascariasis

Larvae can also migrate into the biliary tree, and then into the liver or pancreas; biliary tract, liver, and gall bladder blockage may result. Eggs or worm fragments deposited in the liver or biliary tract precipitate local reactions.

- Acalculous cholecystitis (pain plus tenderness in upper right quadrant).
- Ascending cholangitis (often with fever, tachycardia, tachypnoea, jaundice, enlarged liver with severe pain, plus tenderness in upper right quadrant or diffuse).
- Appendicitis.
- Biliary colic (associated with worms in ampullary orifice; occurs without fever or jaundice).
- Pancreatitis (vomiting likely, with pain plus tenderness of the epigastrium, upper left quadrant).
- Hepatic abscess (associated with intrahepatic duct blockage; tender, enlarged liver, pain plus tenderness in upper right quadrant).
- Gastric haemorrhage.
- Peritonitis and/or peritoneal granulomatosis.
- Meckel diverticulum inflammation.
- Obstructive jaundice.

Other localizations

- Worms may migrate to the upper respiratory tract (throat, nose, lachrymal ducts, inner ear), eyes, vagina, kidneys, ureter, and bladder. Larval migration may cause fever, convulsions, skin rash, and conjunctivitis. A key feature is often *eosinophilia*. Death of worms in tissue leads to inflammation, necrosis, and abscess formation. Migrated larvae may enter the brain, spinal cord, and kidney tissue but cannot survive, resulting in granuloma formation in these areas. (Table 46.1)
- About the sequelae, the mortality rate with severe complications of infection may be up to 5%. Mortality is estimated at 10 000–100 000 deaths per year, of which the majority are children.
- The rate of complications ranges from 11% to 67%. Only a small percentage of infections causes serious pathology.

Table 46.1 Symptoms associated with infection

	Symptoms	Comments
Gastrointestinal	Non-specific abdominal symptoms, obstruction, sepsis, malnutrition	Mortality 1%
Airway	Asthma, cough, Loeffler's syndrome (respiratory symptoms, eosinophilia, and lung infiltrates)	Respiratory arrest
Hepatic and biliary tract	Cholecystitis, cholangitis, jaundice, appendicitis, pancreatitis, hepatic abscess, gastric haemorrhage, peritonitis	
Others	Rash, fever, convulsion	Brain, spinal cord, kidney granuloma

- Chronic ascariasis is linked to malnutrition due to *malabsorption*. Children are particularly susceptible to protein, caloric, or vitamin A deficiency, resulting in physical and mental retardation syndromes, cognitive impairment, poor academic performance, and increased likelihood to catch other infectious diseases.

Diagnosis

- A stool sample is advised if the patient has non-specific GI symptoms and lives/has travelled within the last 1–2 years to an area where ascariasis is widespread.
- Presence of *A. lumbricoides* is usually diagnosed by microscopic examination confirming the presence of eggs in a stool sample. Re-examination 3 weeks after treatment to check eggs and worms are eradicated is advised.
- Microscopy is performed, using either a direct method (mixing stool with saline) or after concentrating the sample. Fertilized eggs are easier to identify than unfertilized eggs. It should be borne in mind that ♂ only infections are possible, and then eggs are not present.
- Rarely, the diagnosis may be made by the study of adult worms that have been passed into the stool, coughed, or vomited out or even passed out of the nose.
- Microscopic examination of gastric contents may reveal larvae and/or eggs, and examination of the sputum may reveal larvae.
- An FBC may show eosinophilia or anaemia, particularly during the phase of migration into the lungs.
- Signs of malnutrition are apparent in patients with a heavy burden of infection.
- Imaging investigations for the diagnostic imaging of complications of ascariasis include abdominal ultrasound, CT scanning, abdominal or chest radiography, or magnetic resonance cholangiopancreatography (MRCP).

- Serology: only for wide screening. PCR: is developing but commonly is not available.
- Exploratory surgery may rarely be required, depending on the infection site.

Differential diagnosis

Infection with *Trichuris*, appendicitis, malabsorption syndromes, asthma (for pulmonary ascariasis), pancreatitis, cholecystitis, cholelithiasis, and hypersensitivity pneumonitis.

Management

In resource-limited settings with high burden, WHO advocates for preventive chemotherapy—the regular administration of antihelminthic drugs to at-risk populations—to control the morbidity due to soil-transmitted helminthiasis. However, reinfection occurs rapidly, especially in the absence of targeted hygiene education and measures to improve sanitation and water supply. Some studies have found that well nutrition could decrease infection and reinfection rates.

In areas where helminths are common, de-worming activities can be done once or twice a year, including de-worming pregnant women after the first trimester to reduce maternal anaemia and increase birthweight. In children, regular treatment against helminth infections contributes significantly to improving growth and cognitive development.

Antihelminthic chemotherapy

- Oral antihelminthics are the first line of therapy to eradicate intestinal roundworms (Table 46.2). They act against the adults, not the larvae. Symptoms usually disappear within 1 week of starting treatment. These drugs are not generally recommended if patients have a large worm burden, e.g. with acute abdominal pain, because of the risk of precipitating complete bowel obstruction. Also must be avoided in case of pulmonary symptoms.
- In general, these drugs are extremely well tolerated .The commonest side effects (Table 46.3) of these drugs are GI intolerance: nausea, vomiting, abdominal pain, and diarrhoea. Rarely, CNS symptoms (headache and dizziness), and extremely rare adverse effects are rash (especially Stevens–Johnson syndrome, toxic epidermal necrolysis), agranulocytosis, angio-oedema.

First-line drugs

- Mebendazole, albenzadole, and pyrantel pamoate (pregnant women).

Care

In the case of acute abdominal symptoms, conservative treatment is first advised, with the antihelminthic to be administered after symptoms have subsided. Also, in the case of partial intestinal obstruction, before resorting to surgery and in the absence of toxic signs (fever, tachycardia, vomiting, abdomen pain, or an immobile, palpable mass), the following supporting care methods, administered using a nasogastric tube, may be effective:

Table 46.2 Chemotherapeutic agents for treatment of ascariasis

Chemotherapeutic agent	Formulation	Dosage guidelines	Paediatric use
Mebendazole (efficacy 95%)	100mg, chewable tablet	100mg, twice daily, for 3 days or 500mg single dose	>2 years*
Albendazole (efficacy 100%)	400mg tablet	15mg/kg or 400mg in a single dose, age >2 15mg/kg or 200mg in a single dose, ages 1–2 years	>1–2 years**
Pyrantel pamoate (efficacy 90%)	Oral suspension (250mg/5mL)	11mg/kg (up to max of 1g per day) single dose Repeat at 2 weeks Treat all family members	>6 months
Piperazine	Syrup (750mg/5mL) >1 year	50–75mg/kg/qd, max 3.5g) 2 days More toxic Less used Paralyses the worm (useful in intestinal obstruction) Repeat at 1 week	1–2 years
Nitazoxanide (efficacy 50–80% if heavy burden)		>12 years: 500mg/12 hours 4–11 years: 200mg/12 hours 1–3 years: 100mg/12 hours 3 days	>1 year
Levamisole	50mg tablet	>10kg to 18 years, at 2.5–3mg/kg (max 150mg) in a single dose	No (named-patient basis only)
Ivermectin (efficacy 70%)	2mg tablet	200 micrograms/kg One dose	>5 years and 15kg

* There is a placebo-controlled randomized trial where there was no increase in the incidence of any side effects in children (aged 6–59 months).

** Albendazole: 2–6 years, off-label.

Table 46.3 Adverse events and contraindications

Drugs	Adverse events	Precautions*
Mebendazole	*GIs*, rash, hepatitis, seizures, Stevens–Johnson syndrome, toxic epidermal necrolysis, agranulocytosis, angio-oedema, alopecia	Cimetidine Insulin Metronidazole Phenytoin CI in pregnant and lactating women
Albendazole	GIs, hepatitis, headache, neurological symptoms, leucopenia, Stevens–Johnson	Cimetidine Ritonavir Dexamethasone Praziquantel Phenytoin
Pyrantel pamoate	GIs Headache, rash, hepatitis, sleep disturbance	Theophylline Piperazine antagonist Myasthenia gravis Caution if hepatitis CI in neonatal period (contains benzoate)
Piperazine**	*GIs* Headache, rash, neurological symptoms (ataxia, convulsions), hypersensibility, bronchospasm, angio-oedema	Fenotiazins CI in patient with seizures or neurological disease or renal disease due to accumulation
Nitazoxanide	GIs Headache, hypotension, yellow sclerotic, hepatitis	Caution in diabetes patients CI in allergic to salicylates CI in neonatal period (contains benzoate)
Ivermectin	Tachycardia, cough, Stevens–Johnson, conjunctivitis, headache, leucopenia, hepatitis	Typhoid vaccine Mazzoti reaction if *Onchocerca* co-infection
Levamisole	GIs, headache, dizziness *Demyelinating encephalitis*	Allergy to the drug, hepatitis, epilepsy, juvenile arthritis, Sjögren's syndrome Ivermectin/albendazole (possible interactions)

* More adverse events or interactions can be observed if both drugs are combined. To check all the interactions, see the drug profile before use.

** Piperazine: only used in case of intestinal obstruction or biliary infestation. Piperazine and pyrantel pamoate are antagonistic. Never use under 3 months of life.

CI, contraindicated; GIs, gastrointestinal symptoms—nausea, vomiting, abdominal pain, and diarrhoea.

- IV fluids, plus antibiotics, possibly with an antihelminthic
- Racine ± mineral oil plus an antihelminthic or Gastrografin®
- IV fluids, possibly with an antispasmodic (alternatively may be given with a saline enema).

Surgical procedures

In cases of intestinal or liver obstruction, or abdominal infection, surgical removal of the *Ascaris* may be needed (although very rarely in Europe). In endemic regions, ascariasis is a major cause of several pathologies requiring surgery, including intestinal obstruction, appendicitis, volvulus, intussusception, ischaemic bowel, and hepatobiliary obstruction.

Management of complications

Pulmonary disease

Most cases do not require therapy. Bronchospasm can be managed with conventional therapy. Severe cases can be managed with systemic steroids and oxygen supplementation.

Hepatobiliary ascariasis

Aggressive antibiotic therapy for a suspected infection and early direct removal of worms from hepatobiliary ducts by endoscopic therapy effectively combats hepatobiliary ascariasis (HPA). Antihelminthics are then given, once abdominal symptoms improve.

Prevention

- Prevention relies on improved sanitation, education of communities, and early chemotherapeutic intervention.
- Sanitary disposal of human waste, which can contain eggs, is important in preventing spread, but not affordable in many regions.
- In areas where human faeces are used as fertilizer, fruit and vegetables must be cooked, where possible, or cleaned with iodine solution.
- Ascariasis is not spread directly from person to person.
- Children should be taught to avoid putting things in their mouths and to wash hands thoroughly.
- The emerging resistance to benzimidazoles that has been reported may compromise universal prophylactic strategies—new classes of antihelminthics are required.

Future research

- Antihelminthic resistance is not yet a public health problem in humans; nevertheless, drug efficacy should be monitored where large-scale de-worming programmes are in place.
- A number of open research questions and operational challenges still need to be addressed such as monitoring the safety of tablet administration in children 1–3 years old and the advocacy for new paediatric formulations, further assessment of the cost-effectiveness of de-worming activities, and the interactions with vaccines and with co-infection with TB, malaria, and HIV.

Further reading

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Chapter 47

Aspergillosis

See also Chapters 2, 20, 23, 24, 27.

Introduction

Aspergillosis encompasses a broad spectrum of diseases, from colonization and allergic hypersensitivity to invasive, necrotizing, and life-threatening infections.

Name and nature of organism

- Group of moulds: aerobic, spore-forming, catalase-positive, and thermophilic.
- Second to *Candida* organisms as the cause of opportunistic fungal infections.
- Over 185 species (30–40 cause human disease).
- Commonest human pathogens:
  - *A. fumigatus*—causes over 70% of human infections, can grow at >40°C
  - *A. flavus*—common in sinusitis, produces aflatoxin (toxin/carcinogen) which contaminates nuts
  - *A. niger*—main pathogen in otomycosis
  - *A. terreus*—resistant to amphotericin, important commercial uses, disseminates readily
  - *A. nidulans*—specific to patients with CGD.
- Contaminate starchy foods, organic matter, and farms/building sites.
- Used commercially in food and pharmaceutical production, and as research organisms.
- Grow in fluffy white colonies on most mycological media.
- Produce septate hyphae with dichotomous 45° branching and tiny conidia spores (easily airborne, penetrate the lower respiratory tract)—beware hospital building work and immunocompromised children—a bad mix.
- Exhibit angiotropism and produce toxic metabolites that inhibit phagocytosis.

Epidemiology

- Ubiquitous worldwide, daily inhalation of hundreds of spores.
- Causes large fatal avian outbreaks (especially parrots/ducks).
- More prevalent in autumn/winter in Northern hemisphere.
- Affects all races, equal sex distribution, at any age.
- Most people are naturally immune.

Invasive disease

- Usually seen only if immunosuppressed (e.g. post-transplant, on chemotherapy or steroids, functional neutrophil defects such as CGD, IV drug users, GVHD, or graft rejection).
- Neutropenia for over 10 days is a major risk factor.
- Incidence varies by the underlying condition.

Allergic disease

- High rates of positive *Aspergillus* skin tests in children with cystic fibrosis (50%) and asthma (25%), but only 1–2% develop allergic bronchopulmonary aspergillosis (ABPA).

Transmission and incubation period

- Spore transmission by inhalation or inoculation.
- Normal immune system usually eliminates spores.
- Respiratory tract is the usual portal of entry and infection site.
- Increased disease risk if immunosuppressed, with possible auto-inoculation from previous colonization.
- Incubation depends on host factors and the degree of exposure.

Clinical features and sequelae

See Tables 47.1 and 47.2.

- Persistent fever—high index of suspicion in continued febrile neutropenia—basis of empiric antifungals at around 5 days in most guidelines.
- May have features of underlying disease (e.g. clubbing in cystic fibrosis).
- Severity depends on the immune status and site involved.
- Four main pulmonary diseases: aspergilloma, ABPA (including severe asthma with fungal sensitization, SAFS), invasive aspergillosis (IA), and chronic necrotizing pulmonary aspergillosis (CNPA). Rarer hypersensitivity reactions include malt worker's lung (extrinsic allergic alveolitis) and bronchocentric granulomatosis.
- Can affect any organ (disseminated disease when two or more involved), e.g. lung, sinuses, brain, skin (around CVC), bone.
- Multi-organ infection occurs via haematogenous spread, with tissue infarction and necrosis.
- Forty-five to 95% mortality.

Complications include:

- Major haemorrhage from erosion into the pulmonary artery
- Pseudomembranous tracheobronchitis (airway occlusion from fungal and necrotic debris)
- DIC.

Table 47.1 Clinical manifestations of invasive disease

Diagnosis	Frequency and associated conditions/risk factors	Symptoms and signs	Complications, morbidity, and mortality
Localized IA (pulmonary)	In up to 25% of immunocompromised patients, e.g. long-term steroid use, neutropenia, post-haematological or solid organ transplant, CGD, advanced-stage AIDS, diabetes mellitus, severe sepsis	May be asymptomatic if severely immunocompromised Fever, cough, dyspnoea, tachypnoea, progressive hypoxaemia, pleural rub Occasionally haemoptysis or pneumothorax	Multifocal cavitating infiltrates Local extension into chest wall, brachial plexus, vertebral column, or widespread dissemination Death from progressive respiratory failure or occlusive tracheobronchitis Often rapid progression, mortality 40–95% 90% of invasive cases are localized to lungs If responds to treatment, still 50% chance of relapse with future immunosuppression
Multi-organ involvement (disseminated disease)	Occurs in 25% of initially localized cases Higher risk if more immunocompromised	Affects end-organs (including kidneys, GI tract, thyroid), soft tissue, and bone Fever, chills, abscesses, thrombi, delirium, hepatic and renal failure, jaundice, abdominal pathology (pain, obstruction, haemorrhage)	DIC and shock Mortality rate high, depends on affected organs
CNPA	Rare, although underdiagnosed Seen in moderate immunosuppression (alcoholism, chronic steroid use), collagen vascular disease, underlying lung pathology (e.g. chronic obstructive pulmonary disease), previous thoracic surgery	Subacute pneumonia unresponsive to antibiotics Low-grade fever, malaise, weight loss, night sweats, dyspnoea, cough, signs of consolidation, may have haemoptysis	Cavitation of lung infiltrates, pneumothorax, progressive respiratory failure 40% mortality, even in treated cases Often treated empirically for TB before diagnosis May only be detected post-mortem

(*Continued*)

Table 47.1 (*Contd.*)

Diagnosis	Frequency and associated conditions/risk factors	Symptoms and signs	Complications, morbidity, and mortality
Endocarditis	After cardiac surgery (especially open heart) or on foreign material (e.g. prosthetic valve)	Murmur, fever, peripheral embolic events	Poor prognosis, 100% mortality without surgery Consider lifelong oral prophylaxis (infection can recur on replaced prosthetic valve) *Aspergillus* also causes pericarditis and myocarditis Second commonest fungal cause
Invasive sinusitis	Rare Commoner in tropics/subtropics Immunocompromise not essential	Nasal discharge/epistaxis, fever, headaches/sinus tenderness Dark nasal lesions, mucosal ulceration, necrotic nasal septum or turbinates May have facial swelling	Often delayed diagnosis Can be acute and fulminant or chronic and indolent
Cerebral	Seen in 5–40% of invasive cases Frequency highly dependent on underlying condition—BMT recipients at highest risk	Depend on severity of immunosuppression Raised ICP, hemiparesis, focal seizures, cranial nerve palsies (moderate immunocompromise) Generalized features with altered mental state and seizures (severe immunocompromise)	Commonly 100% mortality Beware of drug interactions between antifungals and anticonvulsants Meningeal signs, papilloedema, and fever uncommon
Endophthalmitis	Part of invasive disease in immunocompromised patients IV drug abusers may have ocular involvement alone	Pain, photophobia, visual loss Retinitis with infiltrates and haemorrhages, iridocyclitis, progressive vitreous involvement obscuring fundus	Retinal detachment, necrosis, and blindness Often presents with coexisting endocarditis *Aspergillus* also causes keratitis Always do an echocardiogram

Eumycetoma (maduromycosis)	70% affect the foot Risk factors: agricultural work, trauma, poor nutrition, walking barefoot, tropics/subtropics	Triad of tumefaction, sinus formation with purulent exudate and granulomata in subcutaneous tissues Usually painless, slowly progressive	Spread to muscle and bone, causing deformity and loss of function, with significant morbidity Occasionally spreads via blood or lymphatic system No definitive treatment (combination of medical and surgical)
Cutaneous aspergillosis	1° (surgical wounds, burns, vascular catheters) or 2° (disseminated from haematogenous spread) Seen in 5–10% of invasive disease	Red papules/nodules or haemorrhagic bullae, may be tender. Widespread lesions in disseminated disease Most commonly on head and limbs	

Table 47.2 Clinical manifestations of non-invasive disease

Diagnosis	Frequency and associated conditions/risk factors	Symptoms and signs	Complications, morbidity, and mortality
ABPA	2–10% of patients with asthma and cystic fibrosis (excess mucus traps spores) Also in chronic eosinophilic pneumonia and bronchiolitis obliterans organizing pneumonia Highly suspicious if central bronchiectasis in asthma Genetic predisposition if HLA-DR2 positive (HLA-DQ2 may be protective) Commonly occurs with allergic fungal sinusitis SAFS describes patients with severe asthma who do not quite meet ABPA criteria	Cough and wheeze with worsening of previous respiratory symptoms Fever, general malaise, haemoptysis, sputum production, dyspnoea, respiratory distress Can mimic asthma exacerbation or pneumonia Fleeting infiltrates on chest radiograph unresponsive to antibiotics	Hypersensitivity from fungal colonization, causing persistent irritation Relapsing and remitting course Worsens asthma control, increasing steroid dependence 35% of exacerbations are asymptomatic but still result in lung damage (e.g. bronchiectasis) Five stages (I to V). Stage V is most severe with progressive fibrosis and irreversible lung function decline
Aspergilloma	10–20% of those with pre-existing cavitary disease (e.g. TB, cystic fibrosis, emphysema, sarcoidosis, pneumocystis pneumonia) Can develop 2° to invasive disease	Often asymptomatic. Haemoptysis in 50%. Also cough, fever, weight loss, general malaise. Usually have symptoms for over 3 months before presentation Can occur in other cavities (e.g. sinuses) May be seen incidentally on CXR	10% spontaneously resolve; 85% improve after surgery; 5% have lifelong illness Risk of chronic cavitary pulmonary aspergillosis if immunocompromised Mortality depends on haemoptysis severity Chronic infection from non-allergic colonization in pre-existing cavity

Allergic rhinosinusitis	Rare cause (<5% of those with chronic symptoms) Commoner if atopic disease, nasal polyps, previous nasal surgery Commonly in adolescents/young adults	Chronic symptoms: post-nasal discharge or purulent rhinorrhoea, nasal congestion, sinus tenderness, headaches Frequent relapses of symptoms	Type I hypersensitivity reaction Risk of 2° bacterial infection (suspect if increasing pain) Rarely extends to adjacent areas (e.g. sudden vision loss 2° to nerve compression)
Otomycosis (Singapore ear)	Accounts for 10% of all otitis externa After ear injury or instrumentation, bacterial infection, in humid climates Do not need to be immunocompromised	Otalgia, pruritus, ear discharge (grey–white, thick debris containing hyphae), tinnitus Complain of ear feeling 'blocked'	Otitis media, tympanic membrane perforation, external auditory canal osteitis Can result in deafness Treat with topical antifungals

Worst prognosis if:
- Invasive aspergillosis in AIDS
- Severe invasive sinus disease post-bone marrow transplantation (BMT)—usually *A. fumigatus* or *A. flavus*
- Cerebral invasive disease—non-specific focal areas, may ring-enhance
- Bilateral diffuse lung disease
- Continued immunosuppression, persistent neutropenia, relapsed leukaemia
- Delayed/suboptimal therapy.

Diagnosis

High index of suspicion is required if fever in an immunocompromised host does not respond to broad-spectrum antibiotics.

Remember:
- Serological tests unlikely to be positive if immunosuppressed
- Positive cultures from non-sterile sites (e.g. lung/sinus) may represent colonization, so correlate with the clinical picture
- Only cultured from the sputum in 8–34% of those with invasive disease—a negative culture does not exclude disease
- Appropriate specimens: blood, urine, sputum, endotracheal secretions, CSF, sinus washout, BAL, synovial/pleural/peritoneal fluid, bone marrow, nails, hair, needle biopsy
- Microscopy for fungi using Grocott's or Gomori methamine silver stain
- Positive culture for definitive diagnosis:
  - Takes up to 4 weeks
  - Blood cultures rarely positive
  - Fungal media increases isolation chances
- Galactomannan assay:
  - Galactomannan is a circulating antigen (*Aspergillus* cell wall component)
  - Detectable 5–8 days before clinical signs
  - Weekly levels used as screening tool or to assess treatment response—but poor sensitivity
  - Combine with PCR of BAL fluid to increase detection sensitivity/specificity (positive galactomannan in BAL fluid more significant than in blood)
  - Especially accurate in patients with haematological malignancies or transplants
  - False positives commoner in children (with autoantibodies, other invasive mycoses, airway colonization, caspofungin/piperacillin/tazobactam use)
  - False negatives seen in non-neutropenic patients or those already on antifungal treatment/prophylaxis.
- Other assays include 1,3-β-glucan (another circulating antigen) and Limulus (endotoxin detection)
- Allergy investigations:
  - Skin prick tests (ABPA excluded if negative) and positive radioallergosorbent test (RAST)
  - Anti-*Aspergillus* antibodies (elevated precipitin levels)
  - IgE (often >1000 in ABPA, falls on steroid treatment, serial levels indicate progress)

- Imaging:
  - Chest radiograph useful in allergic and infective disease; note: chest CT findings often much more abnormal than X-ray—frequently surprising!
  - CT/MRI of the involved area in invasive disease.

Specific findings

Aspergilloma
- Usually in upper lobes.
- CT: mass shifts within the cavity when the patient moves.

Allergic bronchopulmonary aspergillosis
- Mucus: degenerating eosinophils and fungal hyphae.
- Imaging: mucoid impaction with (perihilar) pulmonary infiltrates.

Allergic rhinosinusitis
- Nasal discharge: fungal elements.
- CT: central hyperattenuated areas within the sinus cavity.

Invasive aspergillosis
- Histology: acute inflammatory infiltrate, angioinvasion, tissue necrosis.
- Lung imaging: solitary or multiple nodules, cavitations, wedge-shaped pleural-based infarcts, diffuse alveolar infiltrates. Early CT shows 'halo' sign (haemorrhage around central necrotic nodule), with later 'air crescent' sign (as nodule cavitates)—much less common in children who usually show just dense focal consolidation.
- Sinus disease: fluid opacification on MRI, unilateral involvement of multiple sinuses, absent air–fluid levels and smooth thickened sinus lining on CT.
- If cerebral involvement, imaging may show infarction or abscess with ring enhancement.

Management and treatment

Invasive disease:
- Improve host defence systems by reducing/discontinuing immunosuppressants; if possible, consider G-CSF if neutropenic
- Better survival with earlier treatment, so start empirical therapy as soon as clinically suspicious (e.g. no response to broad-spectrum antibiotics within 5 days).

Allergic disease:
- Complete fungal eradication is difficult, so aim for symptom control
- Consider:
  - Surgical resection if localized non-responding disease
  - Bronchial artery embolization for massive haemoptysis.

Beware:
- Side effects when altering medicines (e.g. adrenal suppression after steroid use)
- Increased risk of surgical procedures in patients with already limited pulmonary function.

Antifungals

- Very limited pharmacokinetics data for most drugs in children.
- Limited direct comparison studies—almost no data on combination/salvage therapy.
- Systemic antifungals are not indicated in non-allergic colonization.
- Only use combination therapy if treatment failure or continued progression on monotherapy.

Choices

See Table 47.3.

Table 47.3 Summary of treatment options in aspergillosis by clinical disease

Diagnosis	Medical treatment	Surgical management
Aspergilloma	Only treat if symptomatic. Multiple cavities may need lifelong treatment Prolonged course of oral itraconazole produces some resolution in 60% (voriconazole as alternative)	Partial lung resection if massive haemoptysis (difficult if scarring or pleural adhesions)
ABPA	Aim to reduce IgE levels to normal range for non-ABPA-affected asthmatic patient. Restart treatment if levels rise to above twice that limit Oral corticosteroids (inhaled less effective), e.g. prolonged course of oral prednisolone If chronic or recurrent, use itraconazole for faster clinical and radiological resolution. Also facilitates steroid tapering, reducing total dose (alternatives: voriconazole, posaconazole) Case reports of new anti-IgE monoclonal antibody (omalizumab) to reduce inflammation	
Allergic sinusitis	Steroids and antifungals (topical nasal or systemic) reduce recurrence Immunotherapy If possible mucormycosis, then start amphotericin or posaconazole as first line (voriconazole ineffective)	Endoscopic sinus surgery improves drainage if obstructive symptoms Resect nasal polyps Debridement of sinuses removes inciting fungal allergic mucin

(*Continued*)

Table 47.3 (*Contd.*)

Diagnosis	Medical treatment	Surgical management
Eye disease	Endophthalmitis: systemic and intravitreal antifungals Keratitis: topical and systemic (± intracameral) antifungals	May be needed in refractory disease—partial vitrectomy in endophthalmitis or keratoplasty in keratitis
IA	IV voriconazole or liposomal amphotericin as first-line (better tolerated and increased efficacy than amphotericin deoxycholate) Add caspofungin in severe infections (other salvage therapies: amphotericin, posaconazole) Therapy usually for minimum of 4–12 weeks May benefit from adjuvant IFN-γ if not neutropenic (especially in CGD) Consider treating neutropenia or reducing any immunosuppression	Resection of: • Localized disease with failed medical therapy • Infected cardiac valves or vegetations • Cerebral lesions • Necrotic sinus tissue • Cutaneous lesions • Areas of OM or soft tissue infection • Lesions contiguous with heart or great vessels, involving chest wall or risk of pulmonary artery perforation • Any mass before starting intensive chemotherapy or immunosuppression
CNPA	Same first-line treatment as IA (most evidence supports itraconazole use only, because the other triazoles are newer) Oral treatments preferred, as prolonged course of several months needed for clinical and radiographic resolution	Resect localized disease if failed medical treatment, especially if bleeding from necrotic area

Macrolides

- Amphotericin:
  - AmBisome® is widely used as first-line therapy
  - Broad-spectrum, effectiveness reduced by concomitant use of triazoles
  - Poor penetration into cavities
  - Nephrotoxic (especially in haematology and diabetic patients)—lipid preparations reduce the risk of systematic reactions, hypokalaemia, and renal impairment, but are more expensive.

Antifungal triazoles

- Affect CYP450 enzyme system, so beware of drug interactions.
- Most are broad-spectrum (fluconazole not active against *Aspergillus*).

- Voriconazole:
  - First line for IA, and salvage therapy for other fungal infections
  - Not effective against mucormycosis
  - Try to avoid in pregnancy (fetal risk)
  - Monitor levels in non-responders: may have low levels, as pharmacokinetics very complex
  - Transient visual loss may be seen in children.
- Itraconazole:
  - Poor absorption in severely ill patients (altered gastric pH)
  - Useful if not tolerating standard antifungals.
- Posaconazole:
  - Doses not established in children <12 years
  - Better activity against zygomycosis/mucormycosis infections than other azoles
  - Available in oral and IV formulations.

Echinocandins

- Micafungin.
- Caspofungin—use in refractory IA or if intolerant to other therapies.
- Narrow spectrum of activity; only use if confirmed diagnosis.
- May worsen hepatic/renal dysfunction and myelosuppression.
- Levels ↑ by ciclosporin, ↓ by carbamazepine, phenytoin, rifampicin, dexamethasone.

Prevention

General precautions

- Careful use of immunosuppressants (including steroids).
- Education of patients at risk.
- Examine for chronic sinus colonization before transplant conditioning.
- Close attention to ventilation systems and during construction/renovation work—conduct formal risk assessment before the builders start!

If immunocompromised or known hypersensitivity/allergy

- Care with invasive procedures; avoid skin trauma.
- Use laminar airflow, particulate air filtration and positive air pressure cubicles.
- Avoid high-risk environments (dusty areas, marshes/forests, compost heaps/rotting vegetation) and activities (gardening).

Prophylactic antifungals

- Posaconazole is sometimes recommended as first-line prophylaxis, especially in high-risk haematology patients with GVHD or neutropenia. Others include itraconazole (good in CGD) and micafungin.
- Voriconazole is used as 2° prophylaxis in previously treated patients needing further immunosuppression.
- Inhaled amphotericin is useful post-lung transplantation with positive sputum colonization or intranasally to control nasal colonization.

Future research

As medical advances lead to increased transplantation and longer stays on intensive care, more evidence is needed to support the best combination treatment regimens and how to treat refractory infections. Azole resistance is reported with associated management implications.

Further population studies, including who benefits most from prophylaxis, susceptibility factors (e.g. defective mannose-binding lectin production), and resistance mechanisms, will allow better targeted approaches to infection. Research into a vaccine is ongoing.

Further reading

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Chapter 48

Botulism

See also Chapter 30.

Name and nature of organism

- *C. botulinum, C. butyricum*, and *C. baratii* are anaerobic, spore-forming, Gram-positive bacilli.
- Ubiquitous organisms, with spores widely distributed in soil, dust, vegetables, silage, manure (*C. butyricum* associated with marine environments).
- Produce neurotoxins (types A–G); most cases due to types A or B (*C. botulinum*), occasionally E (*C. butyricum*), and rarely F (*C. baratii*).
- Toxin binds irreversibly to peripheral nerves and prevents acetylcholine release at the neuromuscular junction, leading to flaccid paralysis.

Epidemiology

- *Food-borne botulism* arises from contaminated foods that have been preserved under anaerobic conditions. Most cases are associated with home-preserved meats, fish, and vegetables, and canned products. There were 37 cases reported in England and Wales between 1980 and 2013, of which 27 occurred as an outbreak in 1989 due to hazelnut yoghurt contaminated with toxin-containing canned hazelnut flavouring. Sporadic cases have been associated with imported foods from southern and eastern Europe.
- *Wound botulism* occurs following contamination of wounds due to penetrating injuries and is most frequently seen in the context of injection drug use. There were 147 cases reported in England and Wales between 2000 and 2013.
- *Intestinal colonization botulism* occurs mostly in infants, especially <6 months of age (median age of onset: 10 weeks), and is more common in breastfed infants. A few cases have occurred in adults. Ingestion of spores from contaminated honey, dried formula milk, or the environment leads to germination, gut colonization, and toxin production. Infant botulism due to *C. butyricum* (type E toxin) has been associated with contact with terrapins. There were 16 cases reported in England and Wales between 1980 and 2013 (11 of these since 2007).

Transmission and incubation period

- *Food-borne botulism* is due to absorption of preformed toxin from the GI tract. Timing of symptoms is dependent on the dose of toxin absorbed; typically, onset is 12–36 hours (median 24 hours) post-ingestion but can occur from 6 hours to 8 days after eating contaminated food.
- *Wound botulism* occurs after environmental contamination of a wound with *C. botulinum* spores, followed by germination and production of toxin in the anaerobic conditions of a wound abscess.
- *Intestinal colonization botulism* is due to intestinal colonization and production of toxin. It appears to occur particularly around the time of infant weaning when the flora of the GI tract is changing.
- Rare iatrogenic cases of botulism have occurred following the use of botulinum toxin in the US.
- Aerosolized toxin is a potential route of infection following bioterrorism.

Clinical features and sequelae

- Neurological features are similar, irrespective of the route of toxin entry.
- Botulism is characterized by an acute descending, symmetrical, flaccid paralysis, in the absence of fever and with no loss of sensory awareness.
- Cranial nerve palsies often predominate initially: double vision, extraocular weakness, ptosis, facial palsy, dysphagia, dysarthria.
- Weakness of the neck, arms, and respiratory muscles usually follows; respiratory arrest can occur.
- The child is afebrile and does not appear septic. Autonomic nervous system involvement leads to a dry mouth, dilated pupils, cardiovascular changes, and bladder involvement.
- Botulinum toxin does not cross the blood–brain barrier, so mental status is unaffected.
- *Food-borne botulism* can be associated with GI symptoms, such as nausea, vomiting, diarrhoea, and abdominal cramps, followed by constipation.
- *Intestinal colonization botulism* in infants may present with early constipation, followed by non-specific manifestations of intoxication such as lethargy, failure to feed, hypotonia, drooling, and decreased crying.
- *Differential diagnoses* include myasthenia gravis, Guillain–Barré syndrome (this is an ascending paralysis, whereas botulism is a descending paralysis; also Guillain–Barré syndrome is very rare in infants and has elevated CSF protein), tick paralysis, toxic exposure (carbon monoxide, ethanol, organophosphates, paralytic shellfish poisoning), poliomyelitis, CNS brainstem infections, stroke, and CNS mass lesions.

Diagnosis

- Diagnosis is by detection of botulinum toxin or isolation of the organism.
- Samples should be collected and sent to a national reference laboratory (in the UK, discuss with PHE: call 0208 200 6868/4400; 24-hour service), including faeces (minimum 10g in a sterile container), vomitus or gastric washings (minimum 10g in a sterile container), serum (minimum 10mL, prior to the administration of antitoxin).
- In infants, a rectal washout may be required to obtain a stool sample if constipated.
- Potentially contaminated food samples should be obtained as a matter of urgency and discussed with the PHE reference laboratory.
- LP, edrophonium challenge, and brain imaging may be required to clarify the diagnosis (the CSF and neuroimaging are normal in botulism).
- Electromyography can be helpful (findings consistent with neuromuscular junction blockage, normal axonal conduction, and potentiation with rapid repetitive stimulation are indicative of botulism).

Management and treatment

Food-borne botulism

- Specific equine-derived antitoxin must be given as soon as possible—do not await diagnostic tests; in the UK, this is available from PHE.
- Repeat doses may be given within 24 hours if deterioration continues.
- No role for antibiotics.
- Supportive care, including ventilation, hydration, and nutrition.

Wound botulism

- Surgical debridement is essential.
- IV penicillin and metronidazole.
- Specific equine-derived antitoxin (as for food-borne botulism).

Intestinal colonization (infant) botulism

- Human-derived botulinum immunoglobulin (BabyBIG®) should be obtained from Infant Botulism Treatment and Prevention Programme (California, USA) (🖰 <http://www.infantbotulism.org>; discuss with the on-call physician +1 510 231 7600). BabyBIG® is licensed for use in cases caused by botulinum toxin A or B but has been successfully used to treat cases caused by toxin E. It does not have activity against toxin F.
- Antibiotics should be avoided, as they may further disturb the gut flora and increase toxin production. Aminoglycosides, in particular, should be avoided due to neuromuscular-blocking activity.
- Supportive care may be required for several weeks, with attention to airway protection, ventilation, treatment of 2° infection, management of constipation, and adequate nutrition. Mortality is very low with a prompt diagnosis and supportive care.

- Cases of infant botulism have been complicated by *C. difficile* infection, leading to toxic megacolon and necrotizing enterocolitis.
- Full recovery is possible due to the growth of new nerve endings.

Prevention

- Proper handling and preservation of foods.
- Infants should not consume honey.
- In the UK, inform PHE of suspected cases immediately, so that other exposed individuals can be traced.
- Standard precautions should be employed for hospitalized cases.
- Person-to-person spread of botulism does not occur.

Further reading

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Chapter 49

Brucellosis

See also Chapters 33, 45.

Introduction

Brucellosis is the commonest bacterial zoonosis globally, with over half a million new cases annually. Human disease is transmitted via the consumption of unpasteurized dairy products or direct contact with infected animals, particularly aborted fetuses. ~10–30% of all cases are seen in children.

Name and nature of organism

- *Brucella* spp. are small Gram-negative, facultative, intracellular, uncapsulated coccobacilli that localize within cells of the reticuloendothelial system. The outer cell membrane has a dominant lipopolysaccharide component, which is the principal factor in determining virulence.
- There are six species within the genus *Brucella: B. abortus, B. melitensis, B. suis, B. ovis, B. canis*, and *B. neotomae*. Human infection is mainly caused by *B. melitensis, B. abortus*, and *B. suis*.

Epidemiology

- *Brucella* infection is widespread throughout the world. Endemic areas include the Middle East and Central Asia, the Mediterranean rim, Eastern Europe, Africa, and Central and South America.
- Misdiagnosis of brucellosis in malaria-endemic areas means cases are under-reported.

Transmission and incubation period

- Brucellosis is a zoonosis. The main reservoirs are cattle, sheep, goats, and swine. Additionally, it is found in a number of wild animals.
- The incubation period varies, depending on the species, the route of transmission, and the infective dose. In approximately half the cases, the incubation period is short, typically 5–30 days, but other cases can be up to 24 months.

Modes of transmission

- Ingestion of unpasteurized dairy products (e.g. milk and cheese) and raw or undercooked meat.
- Inoculation through cuts, abrasions, and mucosal membranes from infected animals and their secretions.

- Accidental self-inoculation by veterinarians performing vaccinations.
- *Brucella* spp. are highly infectious, spread via the aerosol route. There is a risk of inhalation in laboratories and abattoirs, and this makes *Brucella* spp. a potential bioterrorism agent.
- Person-to-person transmission via blood transfusion, BMT, transplacentally, or via breastfeeding is rare.

Clinical features and sequelae

Acute brucellosis

In children, brucellosis is often a mild, self-limiting illness when caused by *B. abortus*. A more severe illness occurs with *B. melitensis*. A key element in the history is exposure to an infected animal or consumption of contaminated food.

Symptoms are diverse and non-specific and include:

- Fever (78%)—undulant; rises and falls like a wave; very variable
- Weakness and lethargy
- Excessive sweating
- Anorexia
- Weight loss/failure to thrive
- Arthralgia and myalgia
- Abdominal pain
- Headache.

Clinical findings are often minimal but may include hepatosplenomegaly and lymphadenopathy.

Complications

- Osteoarticular involvement (common, 25–70% of patients): monoarthritis of the hip or knee is the commonest presentation, or it may mimic JIA with systemic features. Spondylitis, OM, and sacroiliitis are also reported.
- Genitourinary (rare in children): epididymo-orchitis, glomerulonephritis, and renal abscesses.
- Neurological (4–13% of patients): demyelination, optic neuritis, peripheral neuropathies, chorea, radiculopathy, meningoencephalitis, depression, brain abscesses, stroke, and intracranial haemorrhage.
- Cardiovascular (rare): endocarditis, aortic and cerebral aneurysms, arterial and venous thromboses.
- Pulmonary (rare): pneumonitis and pleural empyema.
- Ocular (often missed): uveitis.
- Mucocutaneous (rare): erythematous papular lesions, purpura, petechiae, urticarial, cutaneous vasculitis, dermal cysts, and Stevens–Johnson syndrome.
- Haematological (<60% of patients, but usually mild): anaemia, leucopenia, thrombocytopenia, pancytopenia, immune thrombocytopenic purpura.

In pregnancy, brucellosis carries an increased risk of abortion and intrauterine transmission. Congenital brucellosis is very rare.

Chronic brucellosis

Brucellosis can also cause chronic symptoms that include recurrent fevers, myalgia, fatigue, depression, and arthralgias. This form is primarily caused by *B. melitensis* and is rare in children. Chronic localizing infection occurs when there is a persistence of infection in an abscess or other specific area.

Brucellosis should be suspected as a cause of fever in the returning traveller.

Natural history and prognosis

- With adequate treatment, the majority of children make a full recovery. There is a risk of relapse, despite appropriate treatment, due to the presence of sequestered organisms within macrophages or treatment failure.
- Brucellosis is rarely fatal, with a case fatality rate of under 2%. Cardiac involvement, mainly as endocarditis, is the main cause of mortality.

Diagnosis

- The gold standard diagnostic test is isolation of the organism from blood, bone marrow, pus, CSF, or joint fluid, although negative isolation does not exclude infection. Culture is difficult, as the organism is slow-growing. Compared to blood cultures, bone marrow cultures have a higher sensitivity and a shorter culture time, and are useful in patients with previous antibiotic use.
- Serological tests are the main tools of diagnosis in endemic areas. Sensitivity ranges from 65% to 95%, but the specificity is low due to the high prevalence of antibodies in the healthy population of endemic areas. Serological tests that are commonly used include the standard agglutination test (SAT), the microscopic agglutination test (MAT), and the Rose Bengal test (RBT). Commercial ELISAs have a high sensitivity, but a lower specificity than that of the agglutination tests, and are useful in the diagnosis of neurobrucellosis.
- PCR has been used and is undergoing validation.
- Point-of-care testing kits are available and are currently under evaluation for use in the field.
- Screening of family members should be considered to increase early diagnosis and prevention of complications.

Management and treatment

- *Brucella* is an intracellular organism and requires prolonged treatment with antibiotics that can penetrate macrophages to reduce the risk of relapse.
- A combination of two agents is recommended.
- The most effective treatment for adults and children over 8 years is 6 weeks of doxycycline with a parental aminoglycoside for the first 1–2 weeks. Doxycycline with an aminoglycoside appears to be superior to doxycycline with rifampicin and has lower rates of adverse events

than doxycycline–rifampicin regimens. Rifampicin with a fluoroquinolone is less efficacious but remains a third-line regimen.
- Treatment failure or relapse is 5–7% for doxycycline–streptomycin regimens, and 11–17% for doxycycline–rifampicin regimens.
- In young children and pregnant women, 6 weeks of co-trimoxazole and rifampicin is the treatment of choice. Gentamicin for 5 days plus co-trimoxazole for 6 weeks is an alternative.
- Prolonged triple therapy (for up to 1 year) is recommended for neurobrucellosis, using doxycycline/rifampicin/co-trimoxazole or ceftriaxone/rifampicin/co-trimoxazole or ceftriazone/doxycycline/rifampicin, depending upon the age of the child.
- Children should be monitored clinically (resolution of fever and symptoms) and serologically for up to 2 years after completing treatment.
- Brucellosis is a notifiable disease in most countries.

Prevention

- Elimination of brucellosis in animals through vaccination, testing, and slaughter of infected herds and testing of milk.
- Education of farmers, butchers, abattoir workers, and clinical and laboratory staff as to the risks of brucellosis and appropriate measures.
- Food hygiene, educating people to pasteurize or boil milk and dairy products, and ensuring adequate preparation of meat.
- Screening of organ and blood donors to reduce the risk of person-to-person transmission.
- No human vaccines are yet available.

What's next?

- The validation of rapid diagnostic technologies to improve the identification of brucellosis as a cause for fever in malaria-endemic areas.
- RCTs to optimize treatment regimens.
- Research into human genotypes that may affect individual susceptibility to brucellosis.

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Chapter 50

Campylobacter

Name and nature of organism

- Gram-negative, spiral, flagellated, microaerophilic motile rods.
- One of the commonest infective bacterial causes of gastroenteritis in the world.
- Over 20 species and subspecies currently listed, several of which are pathogenic in humans.
- The *Campylobacter* spp. most frequently associated with human infection are: *C. jejuni, C. coli*, and less commonly *C. upsaliensis* and *C. fetus; C. lari* and *C. hyointestinalis* rarely cause disease—predominantly affecting the immunocompromised host.
- *C. fetus* is a rare cause of invasive disease in the neonate.

Epidemiology

In Europe

- Campylobacteriosis has been the most commonly reported zoonosis in the EU, followed by salmonellosis and yersiniosis.
- Most cases are sporadic; however, outbreaks do occur, associated with an infected source of food, milk, or water.
- Peak incidence in children <5 years (especially infants) and young adults.
- Risk factors for infection include spending time on a farm, contact with raw meat, household pets (especially kittens and puppies), and travel to areas of high incidence.
- In temperate climates, seasonal variations in incidence have been demonstrated, with infection being commoner in late spring and summer. Strain variation is important, as some are more pathogenic than others.

In the resource-poor setting

- Children <2 years old are most frequently affected.
- Rates of up to 45% in children with diarrhoea have been reported when culture and PCR have been used.
- Bacterial–viral (norovirus, rotavirus) co-infection is common (up to 40%), especially for *C. jejuni*.
- There is no seasonal variation.
- Infection in later life is rare, thought to be a result of immunity developed through frequent exposure in childhood.

Transmission and incubation period

- *Campylobacter* is a zoonotic infection. Animal hosts include domestic, wild, and farm animals (especially poultry).
- The incubation period ranges from 1 to 7 days but can be up to 11 days.
- Minimum infective dose is low: 500–800 organisms.
- Transmission is thought to be most commonly via the oral route from contaminated food (especially chicken), unpasteurized milk, or water.
- Direct transmission from person to person is rare but has been reported. *C. fetus* infection of the newborn may occur, the source of the infection being the mother.

Pathophysiology and immunity

Infection is established in the jejunum, ileum, and often the colon and rectum, causing inflammation and oedema via:

- Production of enterotoxin
- Direct invasion of intestinal epithelial cells
- Induction of local inflammatory responses.

Humoral immunity plays a key role in protection against disease. This theory is supported by the severe and prolonged infection experienced by individuals with hypogammaglobulinaemia. The role of cellular immunity is unclear; however, HIV-infected individuals have a more severe and prolonged course. *Campylobacter*-specific IgG can be demonstrated following infection and has been shown to be protective against disease. *Campylobacter*-specific secretory and serum IgA are associated with protection against disease.

Clinical features

- *Campylobacter* infection can be asymptomatic. Disease is mostly intestinal but can also be extraintestinal. Common clinical features of GI infection include:
  - Diarrhoea—can be profuse and watery, with blood streaking, pus, and mucus
  - Abdominal cramps and pain—can be mistaken for appendicitis or intussusception
  - Vomiting—less common
  - Fever, malaise, headache.
- In most children, this is a mild illness of 1–2 weeks, but a few children develop a severe picture mimicking inflammatory bowel disease. The infection can persist with chronic symptoms or rarely bacteraemia—especially in the immunocompromised host.
- Extraintestinal infection, such as meningitis, OM, and endocarditis, is rare. Severe invasive disease is more likely in the immunocompromised.
- *C. jejuni* infection of the newborn usually presents as intestinal infection, whereas *C. fetus* more frequently presents as premature labour, sepsis, or meningitis. Neonatal infection usually acquired at the time of birth from maternal infected stool. Mortality is a rare, but possible, outcome, especially at the extremes of age or with immunocompromise.

Complications

Potential complications are mostly immunologically based and include:

- Pseudoappendicitis: severe abdominal pain prior to onset of diarrhoea caused by acute ileocecitis. Typically rebound tenderness and guarding are absent
- Guillain–Barré syndrome: *Campylobacter* infection is a common antecedent to Guillain–Barré syndrome and is thought to be related to lipo-oligosaccharides that mimic gangliosides, leading to autoimmune damage to peripheral nerves
- Miller–Fisher syndrome: variant of Guillain–Barré syndrome (ophthalmoplegia, ataxia, areflexia)
- In China, outbreaks of severe acute motor axonal neuropathy occur—Chinese paralytic syndrome—with rapid onset of severe paralysis
- Reactive arthritis— in young men, around 2 weeks later, especially in the knees
- Reiter's syndrome (asymmetrical arthritis, urethritis, ophthalmitis)—HLA-B27 association
- HUS
- Erythema nodosum.

Investigation and diagnosis

- Dark field microscopy, phase contrast, and Gram stain of stool—by recognition of characteristic morphology (spiral morphology and darting/spinning motion). Assay sensitivity is estimated at 50–90%, and it is lower for Gram stain.
- More commonly isolated from stool by culture, using selective media for *Campylobacter*, which suppresses the growth of normal flora. Species other than *C. jejuni* may be missed using this technique.
- Serologic testing can be used to detect a recent infection, especially in patients with Guillain–Barré syndrome and reactive arthritis.
- Organisms can be isolated from blood cultures and other extraintestinal sites of infection.

Management and treatment

- Mainstay of treatment is supportive, ensuring adequate hydration, electrolyte replacement, and analgesia, if necessary.
- Antimotility agents should not be used.
- *Antibiotics can be used for more severe or prolonged infection (>1 week) and infection in immunocompromised children.*
- Antibiotics have been shown to shorten the duration of symptoms and excretion of *Campylobacter* when used early in infection.
- Macrolides (clarithromycin) are suitable first-line oral agents. *Campylobacter* is inherently resistant to penicillins and increasingly

ciprofloxacin-resistant globally. Macrolide resistance is <5% in most parts of the world.
- Other than macrolides, fluoroquinolones, aminoglycosides, and carbapenems are suitable alternative agents.
- Antibiotic treatment should be for 5–7 days for GI infection.
- *Antibiotic resistance is a global concern, and treatment of mild disease should be avoided to help limit the emergence of resistance*.
- For invasive infections, a longer course of antibiotics may be necessary.
- Once an isolated organism's specific antibiotic sensitivity is known, antibiotic treatment should be adjusted accordingly.

Outcome

- Most infection is self-limiting, with full resolution of symptoms.
- Relapse, chronic infection, and carriage state can occur and are more likely if immunocompromised.
- Excretion of organisms has a mean duration of 16 days when not treated with antibiotics.
- Severe invasive infection is rare but most commonly occurs in the neonate or immunocompromised and has a high associated mortality.
- Reactive arthritis is usually self-limiting.

Prevention of further cases

Preventive measures include:
- Storing cooked and raw food separately
- Thorough cooking of potentially contaminated food
- Washing work surfaces and utensils following the preparation of raw foods, especially poultry, but also red meat
- Taking care when visiting farms, ensuring handwashing after contact with farm animals. Careful handwashing when handling domestic animals, especially young animals with diarrhoea.

Normal enteric precautions are usually sufficient to control person-to-person spread.

Future research

There is currently no vaccine for *Campylobacter* infection. Vaccine research is limited by the theoretical risk of Guillain–Barré syndrome.

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Chapter 51

Candidiasis

See also Chapters 2, 17, 23, 35, 47, 96.

Name and nature of organism

- Infection due to *Candida* spp.
- Over 200 species identified, but only 12 are of medical importance.
- Single-cell eukaryotic yeast that reproduces by asexual budding.
- *Candida* surface proteins mediate adhesion to epithelium, followed by invasion.

Epidemiology

- Superficial candidiasis is common and occurs worldwide.
- Invasive disease (candidaemia, single- or multiple-organ acute or chronic infection) is associated with significant morbidity and mortality in special patient populations (ICU, oncology, transplant, or immunocompromised patients).
- The majority of cases are caused by *C. albicans*.
- Non-*albicans* species, such as *C. parapsilosis, C. glabrata, C. krusei, C. lusitaneae*, and *C. tropicalis*, increasingly identified, especially in invasive disease or immunocompromised patients.
- *C. glabrata* is frequently resistant, and *C. krusei* invariably resistant, to fluconazole.

Transmission and incubation period

- *Candida* is part of the normal commensal flora of the mouth, GI tract, vagina, and skin in ~20% of individuals.
- Colonization increases with age and during pregnancy. Infants acquire their mothers' *Candida* spp.
- Alteration of host flora (e.g. following broad-spectrum antibiotics), immunosuppression, and severe illness predispose to yeast overgrowth and infection. Risk factors for invasion are colonization (skin and gut), prolonged neutropenia, and loss of mucosal (e.g. intestinal) integrity, while reduced T-cell numbers or function lead to severe mucosal and/or invasive disease.
- It can be acquired by person-to-person contact or from contaminated material. In hospitalized patients, such as neonates in the NICU, the presence of indwelling catheters (intravascular, ureteral, etc.) predisposes to colonization.
- Sexual transmission can occur.
- Incubation period is variable and not well described, but probably 2–5 days.

Clinical features and sequelae

Oropharyngeal candidiasis

- White plaques on buccal and gingival mucosa, tongue, and palate—difficult to scrape off.
- May also present with erythematous mucosa or angular stomatitis.
- Oral pain may lead to reduced oral intake.
- Dysphagia or pain on swallowing should prompt consideration of oesophageal candidiasis.

Oesophageal candidiasis

- Oropharyngeal candidiasis, in combination with dysphagia or retrosternal pain on swallowing (highly predictive).
- Associated with underlying advanced HIV infection, chemotherapy, or other cause of immunosuppression.
- Differential diagnosis includes CMV and HSV oesophagitis, which may co-occur with *Candida*.

Skin infection

- Occurs in moist, occluded sites such as axillae and groins.
- Common in napkin area of infants where it presents as a confluent erythematous rash with satellite lesions—can lead to skin breakdown.

Nail infection

- Chronic *Candida* paronychia is usually 2° to repeated, prolonged immersion of hands in water.
- Can cause onychomycosis with thickened, friable nails.
- Differential diagnosis is dermatophyte infection, which is commoner.

Vulvovaginitis/cystitis

- Uncommon in prepubertal girls, in whom a non-infectious cause of vulvovaginitis is more likely.
- Commoner beyond puberty.
- Risk factors include underlying diabetes, pregnancy, HIV, use of antibiotics or oral contraceptive pill.
- Presents with vulvovaginal erythema, irritation, pruritus, pain on micturition, and discharge (usually thick, white, and curd-like, but can be thin).
- Cystitis is associated with immunodeficiency, prematurity, prolonged catheterization, and prolonged antibiotic courses—always check for upper renal tract invasion.

Chronic mucocutaneous candidiasis

- Rare immunodeficiency due to specific T-cell defect.
- Chronic, severe onychomycosis and mucocutaneous candidiasis.
- Associated with autoimmune polyendocrinopathy type I, ectodermal dysplasia, and thymomas.
- Often requires chronic suppressive therapy with fluconazole or itraconazole.

Invasive candidiasis

- Severe, life-threatening condition, mainly affects critically ill and immunocompromised patients. Intravascular catheters are an important source of infection in immunocompetent hosts.
- Risk factors: prematurity, multiple-site colonization, neutropenia, presence of CVC, immunosuppression (malignancy, transplantation, other), prolonged broad-spectrum antibiotic administration, TPN, preceding septicaemia, recent abdominal complicated surgery/necrotizing enterocolitis, intensive care therapy.

Clinical presentation

- Candidaemia: sometimes presents as septic shock but frequently has insidious onset. In premature neonates, clinical signs may be subtle (thrombocytopenia, hyperglycaemia, rash). High associated mortality (up to 40%). CNS spread common in preterm neonates—CME.
- Single- or multiple-organ infection (CNS, cardiovascular, osteoarticular, eye infection). Usually is preceded by protracted candidaemia. Difficult to eradicate.
- UTI: ranges from asymptomatic cystitis 2° to urethral catheterization to pyelonephritis. Therapy can be withheld in uncomplicated asymptomatic cystitis if catheter can be withdrawn.
- Chronic disseminated candidiasis or hepatosplenic candidiasis: special clinical entity encountered in oncology patients under chemotherapy after resolution of neutropenia, often in the absence of candidaemia. Inflammatory reaction of the host contributes to the pathogenesis, and corticosteroid treatment, in combination with antifungal agents, may occasionally be beneficial.

Diagnosis

- Skin, oropharyngeal, and vaginal swabs can be cultured on Sabouraud agar plates, with growth of characteristic yeast colonies in 1–2 days.
- Nail clippings should be examined by direct microscopy of wet mounts in potassium hydroxide, and cultured on Sabouraud agar plates.
- Isolation of *Candida* from a non-sterile site may represent colonization, rather than infection.
- *C. albicans* produces a classical 'germ tube' form when incubated in human serum—used as a rapid, but not certain, test to confirm *C. albicans* spp.—and therefore usually fluconazole-sensitive.
- Diagnosis of invasive disease is often late or elusive. Isolation of *Candida* spp. in blood, other sterile fluids, or tissue samples confirms infection, but blood culture sensitivity is up to 60%. Implementation of newer biologic markers, such as 1,3-β-D-glucan, mannan, and anti-mannan antibodies, or molecular methods (PCR) for earlier diagnosis are under evaluation.

Management and treatment

Oropharyngeal candidiasis

- Oral nystatin solution or miconazole gel.
- Treat for 48 hours beyond clinical resolution.
- Ensure sterilization of dummies and feeding bottles, especially in recurrent candidiasis.
- Severe, persistent, or recurrent cases may require oral fluconazole and should prompt consideration of underlying immunodeficiency.

Oesophageal candidiasis

- Oral fluconazole for 7 days (or until symptoms resolved).
- Itraconazole should be used in fluconazole-refractory cases. In cases due to fluconazole-resistant *Candida* spp., amphotericin should be used.

Napkin candidiasis

- Topical nystatin cream plus oral nystatin to prevent reinfection from GI tract.
- Treat for 48 hours beyond clinical resolution.

Nail infection

- Ensure samples taken for culture to distinguish from dermatophyte infection.
- Infection associated with paronychia may respond to topical treatment with imidazole lotion, alternating with an antibacterial lotion.
- For nail plate infection, oral itraconazole appears most effective and may be used for 1 week per month for 2 months.

Vulvovaginal candidiasis

- Topical clotrimazole pessary or 10% vaginal cream.
- Use of a steroid-containing preparation may reduce irritation.
- Single-dose oral fluconazole is an alternative.
- For severe disease, repeat oral fluconazole dose after 72 hours.
- Topical vaginal preparations may damage latex condoms—check and advise.

Invasive candidiasis

Empiric therapy

- As prompt treatment is essential for outcome and the diagnosis may be elusive, a high index of suspicion is required in high-risk patients (oncology, NICU/PICU), and empiric antifungal therapy is justified in the context of fever/critical illness and neutropenia. Colonization data may help guide treatment. Amphotericin and echinocandins are the most commonly used antifungal agents in neutropenic or critically ill patients. Fluconazole can be safely used in immunocompetent, less seriously ill patients.

Treatment of documented infections

- Candidaemia: early appropriate treatment and removal/replacement of indwelling catheters, particular in non-neutropenic patients, is essential

for outcome. Amphotericin preparations (AMB deoxycholate in neonates, lipid preparations in older children) and echinocandins (mainly micafungin in neonates, and caspofungin or micafungin in infants and older children) are recommended as first-line agents. Always consider CNS involvement in neonates with candidaemia (LP). Treat for 14 days after sterilization of blood cultures and symptom resolution; 21 days minimum for meningo-encephalitis. Anticipation of complications/dissemination, especially in immunocompromised patients; further investigations (fundoscopy—always after treatment with echinocandin; ultrasound/CT imaging) may be required.

- Single- or multiple-organ infection (CNS, cardiovascular, osteoarticular, eye infection): usually is preceded by protracted candidaemia. Prolonged (weeks to months) therapy necessary. Removal of prosthetic material and possible surgical debridement may be required. Lipid formulations of amphotericin or echinocandins are most commonly used as first-line agents. Fluconazole can be used in clinically stable patients, as well as an adjuvant or consolidation therapy. Combination therapy can be used in complicated cases.
- UTIs: isolated cystitis can possibly be managed by removal of urinary catheter in non-critically ill patients. In neutropenic and/or critically ill patients and neonates, UTI should be treated as candidaemia, as well as symptomatic UTIs. Fluconazole and amphotericin preparations are preferred as first-line agents.
- Chronic disseminated candidiasis (hepatosplenic candidiasis): prolonged (weeks to months) therapy with antifungals in combination with corticosteroids, as host inflammatory reaction is involved in the pathogenesis.

Prevention

- *Oropharyngeal candidiasis*: sterilization of dummies and teats; if breastfeeding, check for maternal nipple infection.
- *Napkin candidiasis*: attention to hygiene and regular changing of nappies.
- *Vulvovaginal candidiasis*: if recurrent, may benefit from decolonization of gut, which may be source of infection; if sexually active, screen and treat partner for penile candidiasis.
- *Invasive disease*: preventive strategies include infection control measures and administration of antifungal prophylaxis in special high-risk patient groups.

Infection control measures

- Avoidance of horizontal transmission (hand hygiene, aseptic procedures, etc.).
- Avoidance of vertical transmission (neonates) by treating maternal vaginal candidiasis prior to delivery (preterms).
- Judicious use of broad-spectrum antibiotics.

Antifungal prophylaxis

- Identification of patient groups that would most benefit by prophylactic administration of antifungal agents is a subject of clinical research. Prophylaxis is currently recommended for preterm neonates, children under treatment for leukaemia at high risk for fungal infections, and children undergoing HSCT.
- More specifically, for preterm neonates with a birthweight <1500g, oral nystatin and lactoferrin/+ *Lactobacillus rhamnosus* GG is proposed, while fluconazole administration is recommended for neonates with a birthweight <1000g, taking into account the local frequency of invasive candidiasis and other individual risk factors. Highest risk is ELBW, surgical condition, and prolonged antibiotics.
- Patients with acute myeloid leukaemia, recurrent leukaemia, and following allogeneic HSCT have a high risk of developing invasive candidiasis and/or other IFIs; fluconazole, voriconazole, or micafungin are the most commonly used agents for prophylaxis. Patients with acute lymphoblastic leukaemia and solid tumours who are receiving dose-intense chemotherapy, with or without autologous HSCT, have a lower risk of developing invasive candidiasis; however, during profound and prolonged neutropenia (ANC <500/mm^3 for >10 days), posaconazole (>12 years of age) or voriconazole (>2 years of age) are used for prophylaxis. Finally, antifungal prophylaxis may be of benefit in solid organ transplant recipients, as well as children in PICU, but indications are ill-defined.

Up-to-date and new information

- New guidelines for management of candidiasis have been developed in Europe.
- Prophylaxis of extremely premature neonates with fluconazole has been proven efficacious in reducing neonatal candidiasis and possibly mortality.
- New systemic antifungal agents have been utilized in the management of candidiasis in children.

What's new?

- The increasing burden of disease due to non-*C. albicans Candida* spp. and resistance.
- Fluconazole prophylaxis in extremely premature neonates.
- Newer antifungal agents in paediatrics.

What's next?

- Risk–benefit analysis of prophylactic prevention strategies.
- Better studies of non-culture diagnostic methods in children.
- More studies of pharmacokinetics and efficacy of antifungal agents in neonates and children.

Further reading

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Chapter 52

Cat scratch disease

See also Chapters 15, 45.

Name and nature of organism

- The causative organism is *B. henselae*.
- *B. henselae* is a Gram-negative coccobacillus that can also cause bacillary angiomatosis and bacillary peliosis hepatitis, reported mainly in patients with HIV.

Epidemiology

- Cat scratch disease is rare and occurs mainly during the autumn and winter. In the UK, there are around 100 confirmed cases/year in all ages.
- It is most commonly seen in children and adolescents.
- Cats are the common reservoir for *B. henselae*, and, in 90% of the cases, there is a history of close contact with cats, most frequently kittens. Up to half of all cats are infected at some time.

Transmission and incubation period

- Cat fleas (*Ctenocephalides felis*) transmit the microorganism between cats, but their role in transmission of *B. henselae* to humans has not been defined.
- Bacteraemia in cats associated with human disease is common.
- Cat scratch inoculates the microorganism in the human skin.
- No evidence of person-to-person transmission exists.
- It usually takes 7–12 days from the scratch to the appearance of the 1° skin lesion.
- Lymphadenopathy occurs 5–50 days (median 12 days) from the appearance of the skin lesion.

Clinical features and sequelae

- In otherwise healthy people, the most important clinical manifestation is lymphadenopathy, involving the nodes that drain the site of inoculation (usually axillary, cervical, epitrochlear, or inguinal nodes), following scratches on the hands and arm.
- The appearance of lymphadenopathy is usually preceded by a red skin papule at the presumed site of inoculation.
- The skin that covers the involved nodes is tender, warm, and red.

- Fever and mild systemic symptoms occur in about a third of children.
- In normal children, most cases just get better with no treatment, and usually no diagnosis is made either.
- Very rarely, systemic spread occurs, leading to PUO, with widespread lymphadenopathy and granulomatous lesions causing hepatosplenomegaly.
- Other very rare complications include a remarkably benign encephalopathy, aseptic meningitis, neuroretinitis, osteolytic lesions, pneumonia, erythema nodosum, thrombocytopenic purpura, relapsing bacteraemia, and endocarditis.
- Classically, but rarely, infection can cause Parinaud's oculoglandular syndrome, in which direct infection into the eye gives unilateral conjunctivitis and preauricular lymphadenopathy.
- Bacillary angiomatosis are multiple vascular skin lesions that are often papular. Bacillary peliosis are similar vascular granulomatous lesions in the liver and spleen. These are both seen only in people with significant immunocompromise—classically AIDS.

Diagnosis

- Immunofluorescence assay (IFA) or EIAs are commercial tests for serum IgM and IgG antibodies to the pathogen. The IgM is not very useful, and a rise in IgG titres is best.
- PCR testing of clinical specimens appears promising but is still mainly a research tool.
- A lymph node biopsy classically shows granuloma, and cat scratch disease is one of the main diagnoses to consider. There are other diseases that produce a similar picture, including brucellosis and mycobacterial infections. The classic stain is the Warthin–Starry stain, which may show the organism.
- Inflammatory markers, CRP, and ESR are generally raised.

Management and treatment

- Most children just get better by themselves, and reassurance is all that is usually required. In a normal child, spread and complications are very rare. Even when the rarer complications do occur, a very good outcome is usually seen in previously normal children.
- As you would expect, response to antibiotics is limited. Azithromycin has been used, with only a moderate benefit. There are no good clinical trials.
- Antibiotic treatment is recommended for patients with systemic disease and is mandatory for immunocompromised individuals.
- Macrolides, co-trimoxazole, rifampicin, ciprofloxacin, and parenteral gentamicin are all effective. The optimal duration of their administration is not known.

- In patients with severe or systemic disease (such as endocarditis), therapy should include the addition of IV gentamicin for a minimum of 2 weeks.
- In immunocompromised patients, longer durations of antimicrobial therapy may be appropriate (up to 3 months) to prevent relapse. This depends on the severity of the immunocompromised, and specialist advice should be sought.
- Doxycycline or macrolides are effective for the treatment of bacillary angiomatosis and bacillary peliosis hepatitis. Treatment duration should be at least 2 weeks (cutaneous manifestations only) or at least 4 weeks for patients with visceral lesions.
- In cases with suppurative lymph nodes, surgical drainage may be indicated.

Prevention

- Immunocompromised subjects should avoid close contact with cats completely or, at a minimum, stay away from cats that scratch or bite and are <1 year. For example, do not buy a kitten for a child with newly diagnosed leukaemia.
- Sites of cat scratches should be immediately washed.
- Treating cat flea infestations may reduce cat-to-cat transmission of *B. henselae*.
- Testing of cats for *B. henselae* infection is not recommended.

Future research

- More information on the prevalence of the different clinical manifestations and sequelae is required.
- Standardization of diagnostic PCR assays is needed for use in routine clinical practice.
- The risk–benefit balance of antibiotic therapy, the optimal drug, and duration are all still unclear.

Further reading

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Chapter 53

Chickenpox—varicella-zoster

See also Chapters 10, 34, 38.

Name and nature of organism

- VZV is one of the eight herpesviruses known to infect humans.
- VZV is known by many names, including chickenpox virus, varicella virus, zoster virus, human herpesvirus 3 (HHV-3).
- VZV virions are spherical and 150–200nm in diameter.
- VZV DNA is a single, linear, double-stranded molecule.
- The capsid is surrounded by a number of proteins that play a critical role in initiating the process of viral replication in infected cells.
- It is very susceptible to disinfectants.

Epidemiology

- Chickenpox virus, also known as varicella-zoster, is a highly contagious viral illness that occurs mainly during childhood.
- Chickenpox virus is a member of the herpes family of viruses and, like other neurotropic herpes viruses, develops latency in the dorsal root ganglion.
- Following 1° infection, reactivation can occur throughout life. This reactivation takes the form of 'shingles' or dermatomal zoster where the virus reactivates along a nerve root, causing a painful vesicular rash.
- In the UK, 1° infection has a peak incidence in the winter and early spring.
- In England and Wales, the incidence of chickenpox is 1290 per 100 000 person-years.
- Most pregnant women exposed to chickenpox are immune, and only 3 per 1000 pregnancies are complicated by 1° chickenpox infection.
- It is possible to contract 1° chickenpox from a person with shingles.
- Varicella can develop between 1 and 16 days of life in infants born to mothers with active varicella around the time of delivery.
- Chickenpox is a notifiable disease in Northern Ireland and Scotland, but not in England and Wales.

Transmission and incubation period

- Chickenpox is one of the most contagious childhood infections, and the household attack rate for non-immune individuals who come into close contact is around 90%. School contact tends to be lower at 12–33%.

- The virus is spread by direct contact or airborne droplets, followed by mucosal invasion of the upper respiratory tract and conjunctiva or direct contact with infected vesicles.
- 1° infection causes chickenpox. Asymptomatic infection is unusual, but some cases are so mild that they go unrecognized.
- There is a 1° viraemic phase, followed by a 2° viraemia to the skin and mucosal surfaces.
- Children are contagious from 1 to 2 days before the onset of the rash, due to respiratory excretion, and then via the skin until all the lesions have crusted over.
- The incubation period is 10–21 days, but most children usually become ill around 14–16 days after contact.
- The incubation period can be much shorter in immunosuppressed patients or longer if the child has received varicella zoster immunoglobulin (VZIG).
- Each child in a family who develops varicella tends to develop sequentially worse disease, with the final child being the most unwell.
- Young infants, adolescents, adults, and pregnant women tend to have more severe disease with a higher rate of complications.
- The current two-dose vaccine schedule provides 98% immunity for children and 75% immunity for adolescents and adults, and breakthrough infection in both groups is milder, with fewer lesions and systemic symptoms than unvaccinated individuals. Shingles is rare after vaccination.
- Reinfection with chickenpox is rare, and other vesicular rashes in childhood are often difficult to differentiate in the early stages of the disease.

Clinical features

- The classical sign of chickenpox infection is the generalized, cropping vesicular rash and intense pruritus. The rash is seen mostly on the head and trunk but can occur in any area of the skin and conjunctiva. The rash appears in crops, with new lesions occurring for 3–6 days following the 1° lesion. The majority of lesions will heal without scarring, and the disease resolves within about 1 week following symptom onset.
- A detailed medical history is crucial in cases where the diagnosis is uncertain, and establishing recent exposure to varicella can be helpful.
- Diagnosis is important, so that parents are counselled about contact avoidance and symptom relief. Hospital admission should be avoided, wherever possible, to avoid unnecessary nosocomial outbreaks.
- Adolescents may complain of a prodrome of nausea, myalgia, headache, and loss of appetite, but symptoms in younger children are usually non-specific, although fever is practically universal.
- In immunocompromised children, including those with HIV or on long-term steroids, progressive, severe varicella can develop. This is characterized by high fever of long duration, continuing eruption of cropping lesions, and the appearance of complications. In some cases, despite adequate treatment, the disease can be fatal. Haemorrhagic varicella, with bleeding into and around lesions, is also seen, but is rare.

- Patients most at risk of developing recurrent varicella or shingles infection:
  - HIV infection
  - High-dose corticosteroids (over 2mg/kg daily for longer than a week)
  - Congenital T-lymphocyte deficiencies or combined immunodeficiency
  - Children with chronic cutaneous or pulmonary disorders.
- Differential diagnosis: chickenpox is usually distinctive, but other causes of vesicular rash include:
  - Herpes simplex (not usually disseminated)
  - Herpes zoster (usually dermatomal)
  - Hand, foot, and mouth disease (Coxsackie virus)
  - Enterovirus
  - Impetigo
  - Syphilis
  - Smallpox.

Complications

Severe complications are rare and are seen in around 1/100 000 children. Any child with fever beyond 5 days of rash onset should have a medical review to rule out bacterial infection.

Pneumonitis

- Varicella pneumonia primarily occurs in older children and adults.
- Respiratory symptoms usually appear 3–4 days after the rash.
- The pneumonia may be unresponsive to antiviral therapy and may lead to death.

2° skin infection

- Skin lesion infections are common and occur in 5–10% of children. These lesions provide a portal of entry for virulent organisms; rapidly spreading cellulitis, septicaemia, and other serious infections may occur.
- The commonest infectious organisms are Group A Streptococcus (GAS) and *S. aureus*. Varicella places the patient at high risk for acquiring invasive GAS disease. In addition to toxic shock syndrome (TSS), GAS may cause necrotizing fasciitis, bacteraemia, osteomyelitis (OM), pyomyositis, gangrene, subgaleal abscess, arthritis, and meningitis.
- Staphylococci may cause cellulitis, impetiginous pox infections, staphylococcal scalded skin syndrome, TSS, pericarditis, and OM.

Neurological complications

- Acute post-infectious cerebellar ataxia is the commonest neurological complication, with an incidence of one case per 4000 patients with varicella. Ataxia has a sudden onset that usually occurs 2–3 weeks after the onset of varicella. Manifestations may range from mild unsteadiness to complete inability to stand and walk, with accompanying incoordination and dysarthria. Manifestations are maximal at onset; a waxing and waning course suggests another diagnosis. The sensorium

is clear, even when the ataxia is profound. The condition may persist for 2 months. The prognosis for patients with ataxia is good, but a few children may have residual ataxia, incoordination, or dysarthria. Brain imaging should be considered to rule out a concurrent space-occupying lesion.

- Encephalitis occurs in 1.7 patients per 100 000 cases of varicella among otherwise healthy children aged 1–14 years. The disease manifests during acute varicella a few days after rash onset. Lethargy, drowsiness, and confusion are the usual presenting symptoms. Some children may have seizures, and encephalitis can rapidly progress to deep coma. This serious complication of varicella has a 5–20% mortality rate.
- Reye's syndrome was associated with varicella when aspirin use was common. Identification of this association now has made paracetamol/acetaminophen the preferred drug, and Reye's syndrome has become very rare.
- Other neurological complications include aseptic meningitis, myelitis (including Guillain–Barré syndrome), polyradiculitis, stroke, and meningo-encephalitis.

Herpes zoster—shingles

- Herpes zoster recurrence is a delayed complication of varicella-zoster infection, occurring months to years after the 1° infection in about 15% of patients. The complication is caused by virus that persists in the sensory ganglions. Herpes zoster consists of a unilateral vesicular rash, limited to 1–3 dermatomes. The rash is often painful in older children and adults. Among the health benefits of routine varicella immunization in childhood may be a lifelong decreased risk for reactivation of the virus as shingles.
- There are few systemic symptoms and no systemic dissemination in immunocompetent individuals, but post-herpetic neuralgia can persist for weeks to months after resolution of the rash.

Other complications

- Otitis media in 5% of children.
- Hepatitis is a self-limited accompaniment of varicella. Severe hepatitis with clinical manifestations is infrequent in otherwise healthy children with varicella. Liver involvement is independent of the severity of skin and systemic manifestations. Identify right upper quadrant pain with or without associated jaundice.
- Retinitis and optic neuritis have been reported as rare complications of varicella in children who are immunocompetent.
- Other reported complications include glomerulonephritis, haemorrhagic varicella, thrombocytopenia, myocarditis, appendicitis, pancreatitis, Henoch–Schönlein purpura, orchitis, iritis, and keratitis. Extracutaneous complications increase proportionately to the age of the patient.

Varicella in pregnancy

- Non-immune pregnant women coming into contact with varicella are at risk of developing *in utero* infection leading to congenital varicella syndrome or contracting severe disease themselves.

- Infection of the fetus during the first 20 weeks of gestation can cause fetal death or the very rare congenital varicella syndrome, mainly characterized by limb atrophy and scarring of the skin of the extremities. In some cases, CNS and eye diseases can occur.
- Infection of the fetus during the second 20 weeks of pregnancy can cause unapparent fetal varicella, with subsequent herpes zoster in early life, without having had extrauterine varicella.
- In newborn infants, varicella can be fatal if the mother develops the disease from 5 days before to 2 days after delivery. If varicella develops in the mother >5 days before delivery and the gestational age is ≥28 weeks, the neonate is likely to be protected by maternal specific IgG antibodies.

Diagnosis

- No investigations are usually necessary in an otherwise well child. In children where the diagnosis is unclear or where the diagnosis has implications for other family members or in pregnant women, detection of viral DNA from vesicular fluid by PCR has the highest sensitivity.
- VZV can be detected by PCR or isolated by culture from scrapings of a vesicle base during the first 3–4 days of eruption. Isolation from other sites is less sensitive.
- Determination of specific IgG antibody in serum can be useful to retrospectively confirm the diagnosis. These antibody tests may be false-negative and are not as reliable in the immunocompromised.
- Determination of specific IgM is not reliable for routine confirmation of acute infection, but positive results indicate current or recent VZV infection.

Management and treatment

The mainstay of treatment is supportive care. This includes adequate oral fluid, antipyretics, and observation of possible complications. There is some evidence that overwrapping can lead to worse disease eruptions, so parents should be counselled to keep the child cool. There is controversy about whether the use of NSAIDs increases the risk of necrotizing soft tissue infection and invasive GAS infections associated with chickenpox infection. So ibuprofen as an antipyretic in chickenpox is also not advised. Additionally, an increased risk of Reye's syndrome has been suggested where children with varicella are treated with aspirin.

- *Itching*: calamine lotion can alleviate itching. Chlorphenamine (INN) can also alleviate itching caused by chickenpox in children aged over 1 year. Advice should be given to keep the child's nails short in order to prevent further skin trauma and 2° bacterial infections.
- *Aciclovir*: several drugs are available with activity against varicella, but these are only routinely used in the immunocompromised population. Aciclovir is currently the only drug licensed for the use of varicella in children. Studies have shown that, in otherwise healthy children, aciclovir treatment shortens the disease course by only ~1 day of fever

and rash. Some experts recommend oral aciclovir for non-immune household contacts, as they are likely to have more severe disease. If considering aciclovir treatment, bear in mind that the drug is only effective if given within the first 48 hours of the rash eruption, as viral replication ceases 72 hours after the first crop of vesicles appear. Valaciclovir has been licensed for use in adults, and recent data suggest that this has good oral bioavailability in children, but there is no current plan to license for chickenpox. Aciclovir should only be given to adolescents and adults and should not be routinely prescribed in otherwise healthy children over 1 month of age in whom the disease is likely to be mild. However, children of any age with severe disease should be treated with IV aciclovir.

- *Immunoglobulin therapy*: immunoglobulin therapy is not effective once the disease is established but should be considered in neonates and the immunocompromised. This takes the form of IM VZIG or IVIG. Immunoglobulin should ideally be given within 96 hours of significant exposure and not delayed past 7 days.
- *Varicella vaccine*: in susceptible individuals, additional prevention is available in the form of the vaccine, given 3–5 days after exposure, where indicated. The varicella vaccine is currently not part of the routine vaccination schedule in the UK, but it is in a number of other European countries and the US. Where routinely administered, vaccination has significantly modified varicella epidemiology, both reducing clinical disease and shifting the incidence to higher age groups, especially where vaccination is not universally taken up. In surveillance areas with high vaccine coverage, the rate of varicella disease decreased by ~85%

Prevention

- In addition to standard cleanliness, airborne and contact precautions are recommended in medical facilities for children with varicella or herpes zoster until crusting of the skin lesions. This period can last up to 1 week (until all lesions have crusted over) for otherwise healthy subjects with mild disease or several weeks for immunocompromised children with severe disease.
- For exposed susceptible patients, airborne and contact precautions from 10 days until 21 days after exposure to the index patient are indicated; these precautions should be maintained until 28 days after exposure for those who received VZIG or the usual IVIG.
- Respiratory precautions are recommended for neonates born to mothers with varicella and should be continued until 21 or 28 days of age if they received VZIG or IVIG. Infants with varicella embryopathy do not require isolation.
- For children managed in the community, the following advice should be given:
  - Stay away from school or nursery, and do not go on air travel until 6 days after the last spot has appeared
  - Avoid contact with people who are immunocompromised, pregnant women, and infants aged ≤4 weeks.

- For immunocompetent patients with localized zoster, contact precautions are indicated until all lesions are crusted. Immunocompromised patients who have zoster (localized or disseminated) and immunocompetent patients with disseminated zoster require airborne and contact precautions for the duration of illness.
- In case of exposure to VZV, chemoprophylaxis is not routinely indicated. Potential interventions for susceptible people exposed to a person with varicella include varicella vaccine, administered 3–5 days after exposure, and, when indicated, VZIG (one dose up to 96 hours after exposure) or, if VZIG is not available, IVIG (one dose up to 96 hours after exposure). Advice on contact prevention is given in Table 53.1.

Table 53.1 Advice for contact avoidance in varicella infection

Chickenpox	Shingles
Stay away from school or nursery until 6 days after last vesicle has appeared	Stay away from school or nursery until all lesions are crusted
No air travel until 6 days following last vesicle appearance	
Avoid contact with pregnant women, immunocompromised patients, and infants under 4 weeks of age	

Definition of significant exposure

- The Department of Health in the UK considers the presence of the following factors as indicative of significant exposure to VZV:
  - Type of VZV infection in index case: contact with chickenpox, disseminated zoster, immunocompetent individuals with exposed lesions, and immunosuppressed patients with localized zoster (because of greater viral shedding)
  - Timing of exposure: exposure to index case from 48 hours before onset of rash until crusting of lesions; or day of onset of rash until crusting (for localized zoster)
  - Closeness and duration of contact: residing in the same household, maternal/neonatal contact, contact in the same room for a significant period of time (15 minutes or more), face-to-face contact, hospitalized in the same paediatric ward or hospital room as a patient with varicella; close contact (i.e. touching or hugging) with a person with active herpes zoster lesions.
- Establishing a history of chickenpox or demonstrating IgG antibodies to VZV determines susceptibility in healthy people.
- In immunocompromised persons testing for VZV, IgG antibodies is recommended, regardless of their history of chickenpox.

Varicella-zoster vaccine

- Varicella vaccine is the best option for the prevention of VZV infection in immunocompetent people. It is a live-attenuated preparation of

the serially propagated and attenuated wild Oka strain. Subcutaneous administration is recommended, although IM administration has been demonstrated to result in similar rates of seroconversion.

- The following patients should not receive varicella vaccine:
  - People who are receiving high doses of systemic corticosteroids (2mg/kg per day or more of prednisone or its equivalent) for at least 14 days. The recommended interval between discontinuation of corticosteroid therapy and immunization with varicella vaccine is at least 1 month.
  - Children with impaired humoral immunity may be immunized, but VZV vaccine should not be administered to children with cellular immunodeficiency. Exceptions include children with acute lymphocytic leukaemia in continuous remission for at least 1 year, with a lymphocyte count >700/microlitre and a platelet count >100 × 10^3/microlitre, and children with HIV infection in CDC class 1 or 2 with a stable $CD4^+$ T-lymphocyte percentage of ≥25%.
  - Pregnant women, because the possible effects on fetal development are unknown. On the contrary, varicella vaccine should be administered to nursing mothers who lack evidence of immunity. There is no evidence of excretion of the vaccine strain in human milk or of transmission to infants who are breastfeeding.
  - Varicella vaccine should not be administered to people who have had anaphylactic-type reaction to any component of the vaccine, including gelatin and neomycin.
  - Otherwise healthy children with moderate or severe acute disease, with or without fever.
- An immunocompromised person or a pregnant mother in the same household is not a contraindication for immunization of a child.
- Varicella vaccine is safe and well tolerated. Adverse events, usually mild, occur in 5–35% of the cases in the first 42 days after vaccination (mainly between days 5 and 26). High fever is rare, and it occurs with the same frequency as in children receiving placebo; 3–5% of vaccinated children develop a generalized varicella-like rash, which includes only 2–5 skin lesions, usually maculopapular, rather than vesicular. Severe adverse events, such as anaphylaxis, encephalitis, ataxia, erythema multiforme, Stevens–Johnson syndrome, pneumonia, thrombocytopenia, seizures, Guillain–Barré syndrome, and death, have been reported, but, in most of the cases, a causal association cannot be determined and/or the patient was immunocompromised.
- VZV vaccine has been associated with the development of herpes zoster, mainly in immunocompromised, but also in immunocompetent children. However, herpes zoster in immunized people may also result from natural varicella infection that occurred before or after immunization.
- Vaccine-associated virus transmission to contacts is rare, and only in the case of a rash developing in the immunized person.
- The administration of varicella vaccine during the presymptomatic or prodromal stage of illness does not increase the risk of vaccine-associated adverse events or more severe natural disease.

- Varicella vaccine can be administered simultaneously with other recommended vaccines. If not administered at the same visit, the interval between administration of varicella vaccine and other live-attenuated vaccines (including MMR) should be at least 28 days.
- When the vaccine was approved, a single dose for individuals <13 years, and two doses for older people, were recommended. There are now data that indicate that a single dose may be ineffective in preventing outbreaks, so a routine two-dose vaccination programme is recommended in some countries (first dose at age 12–15 months and the second at least 3 months later).
- Children aged ≥13 years and adults should receive two doses 4–8 weeks apart.

Varicella-zoster immunoglobulin

- VZIG should be given to susceptible people at high risk of developing severe disease with significant exposure to VZV:
  - Immunocompromised children
  - Susceptible pregnant women
  - Newborn infants whose mother had onset of varicella within 5 days before delivery or within 48 hours after delivery
  - Hospitalized premature infants (>28 weeks' gestation) whose mothers lack a reliable history of varicella or serological evidence of protection, hospitalized premature infants (<28 weeks' gestation or ≤1000g birthweight), regardless of maternal history of varicella or VZV serostatus.
- VZIG prophylaxis may be ineffective in preventing varicella in immunocompromised patients; careful monitoring and drug treatment at first sign of illness are recommended.
- Any patient to whom VZIG is administered to prevent varicella should subsequently receive varicella vaccine, according to recommendations appropriate for their age; the first dose of vaccine should be given 3 months after VZIG administration. If VZIG has been given within 3 weeks of administering a live vaccine, the vaccine should be repeated 3 months later.
- The currently available vaccine is >95% effective in preventing moderate or severe disease. Mild infections are prevented in 70–85% of the cases.
- Children who develop varicella, despite vaccination, usually have a very mild disease with <30 vesicles, low fever, and rapid recovery.
- Whether Reye's syndrome results from administration of salicylates after immunization for varicella in children is unknown. However, salicylates should be avoided for 6 weeks after administration of varicella vaccine.
- Duration of immunity is not established. Available data suggest that protection can last for at least 20 years. However, these data have been collected in a period with a significant circulation of wild-type VZV, and consequently with a high probability of natural boosting in immunized people.
- Varicella vaccination is recommended for susceptible health-care workers.

Future research

- Further studies on the changing epidemiology of varicella and herpes zoster in relation to the extended use of varicella vaccine in different countries are required.
- Efficacy and safety of varicella vaccination, especially when administered in the tetravalent form combined with measles, mumps, and rubella, should be evaluated with more data in children with chronic underlying disease.
- Post-marketing surveillance safety studies on the use of combined measles, mumps, rubella, and varicella vaccines, as well as long-term evaluation of the duration of immunity, in the general population are required.

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Chapter 54

Chlamydia pneumoniae infection

Name and nature of organism

- Obligate intracellular Gram-negative bacteria with a unique life cycle involving two forms—the extracellular, infectious elementary body (EB) and the intracellular, metabolically active reticulate body (RB).

Epidemiology

- All isolates of *C. pneumoniae* appear to be closely related serologically.
- The proportion of community-acquired pneumonias associated with *C. pneumoniae* ranges from 2% to 19%, varying with geography, age group examined, and diagnostic methods used.
- First infections are especially common between the ages of 5 and 15 years.
- Infection and reinfections are common, because the period of immunity after a single infection is short.
- There is no evidence of seasonality.

Transmission and incubation period

- *C. pneumoniae* is transmitted from person to person through respiratory secretions.
- Spread of infection is enhanced by close proximity.
- The mean incubation period is 21 days.
- Nasopharyngeal shedding can occur for up to 6 months after acute disease.

Clinical features and sequelae

- There are no characteristic clinical features that distinguish *C. pneumoniae* from other common respiratory pathogens.
- Patients may be asymptomatic or mildly to moderately ill with upper and/or lower respiratory tract involvement.
- Pneumonia is the most important disease, and it usually presents with mild constitutional symptoms, including low-grade fever, malaise, headache, cough, pulmonary rales, and non-exudative pharyngitis.

- Illness can be prolonged, and cough can persist 2–6 weeks with a biphasic course.
- Wheezing is a common clinical manifestation in children; *C. pneumoniae* has also been associated with exacerbations of chronic asthma.
- Co-infection of *C. pneumoniae* with other respiratory pathogens is common.
- The reported association of *C. pneumoniae* infection with the development of atherosclerosis and cardiovascular disease has not been confirmed.

Diagnosis

- Specific diagnosis is based on isolation of the organism by culture or positive NAAT; specimen types include posterior nasopharynx swabs, sputum, and BAL fluid.
- The microimmunofluorescence (MIF) antibody test is currently considered the best serological test. A 4-fold increase in IgG titre or an IgM titre ≥1:16 is considered indicative of acute infection.
- Specific IgM antibodies appear 2–3 weeks following 1° infection, and specific IgG antibodies peak after 6–8 weeks.
- Many children with culture- or NAAT-documented infection do not have detectable antibodies by MIF tests.
- Immunohistochemistry can be used to detect *C. pneumoniae* in tissue specimens, but it requires skill and control antibodies in order to avoid false positive results.

Management and treatment

- Macrolides are the drugs of choice in paediatrics.
- Tetracycline, doxycycline, or quinolones are also effective but can only be administered in older patients.
- A 5-day course of azithromycin was shown to be effective in eradicating *C. pneumoniae* from the nasopharynx in 80% of children with pneumonia.
- Treatment may need to be continued for several weeks in some patients to reduce the risk of failure or recurrences.

Prevention

- Standard precautions are recommended.

Future research

- The association between *C. pneumoniae* and exacerbations of chronic asthma needs to be further clarified.
- The role of *C. pneumoniae* in respiratory viral and bacterial co-infections requires more research.
- The optimal duration of antimicrobial treatment should be determined by well-designed clinical trials.

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Chlamydia psittaci infection

Name and nature of organism

- Obligate intracellular Gram-negative bacteria with a unique life cycle involving two forms—the extracellular, infectious EB, and the intracellular, metabolically active RB.

Epidemiology

- The major reservoir of *C. psittaci* are birds, especially pigeons, parrots, and turkeys.
- The term psittacosis commonly is used for the human disease, although the term ornithosis more accurately describes the potential for all birds, not just psittacine birds, to spread this infection.
- Disease due to *C. psittaci* is worldwide distributed and tends to occur sporadically in any season.
- The main risk factor is exposure to birds, but up to 20% of infected patients have no history of exposure.
- Infection is rare in children.

Transmission and incubation period

- Healthy and sick birds may harbour and transmit the organism, usually via aerosols from faecal dust or nasal secretions. Excretion of *C. psittaci* can be intermittent or persistent for weeks or months.
- Those exposed to infected animals (e.g. workers at poultry farms, pet shops, pet owners) are at high risk of infection.
- The incubation period is between 5 and 21 days.

Clinical features and sequelae

- Psittacosis is an acute febrile respiratory infection, with high fever, non-productive cough, headache, and malaise. Severe interstitial pneumonia can occur, particularly in the immunocompromised. This is a difficult diagnosis to think of, unless one asks specifically about pets!
- Rare complications are pericarditis, myocarditis, endocarditis, hepatitis, and encephalitis.

Diagnosis

- Traditionally, diagnosis has been confirmed by demonstrating a 4-fold increase in IgG antibody titre, determined by complement fixation testing, between acute and convalescent specimens obtained 2–3 weeks apart.
- In addition to the 4-fold increase in IgG titre, a single MIF IgM titre of 1:32 or greater confirms a suspected case.
- MIF IgM tests may be false-negative early during the acute illness.
- Isolation of the agent from the respiratory tract can only be performed in a reference laboratory due to the potential biohazard.

Management and treatment

- Standard isolation precautions are recommended.
- Tetracyclines are the drugs of choice, except for children younger than 9 years.
- Macrolides (erythromycin, azithromycin, clarithromycin) are the alternatives for children younger than 9 years of age (<12 years in the UK).
- In severely ill patients, use IV doxycycline.
- Treatment should be administered for at least 10–14 days after defervescence.

Future research

- There is an urgent need for information and for awareness campaigns directed at professional health-care workers and the general public.
- Implementation of new diagnostic methods in medical laboratories is an important area of research.

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Chapter 56

Chlamydia trachomatis infection

Name and nature of organism

- Obligate intracellular Gram-negative bacteria with a unique life cycle involving two forms—the extracellular, infectious EB, and the intracellular, metabolically active RB.

Epidemiology

- There are two biovars LGV and trachoma which cause oculogenital diseases other than LGV. There are many serovars with specific clinical and epidemiological features:
  - Serovars A through C are the cause of trachoma
  - Serovars B and D to K cause genital and perinatal infections
  - Serovars L (1, 2, 3) cause LGV.
- Oculogenital serovars of *C. trachomatis* are the cause of the most prevalent STI in industrialized countries, causing urethritis in men, cervicitis and salpingitis in women, and inclusion conjunctivitis and pneumonia in infants.
- The highest rates of infection are found in sexually active young people; in the UK, a national *C. trachomatis* screening programme found positive screens in 9.5% of women and 8.4% of men.
- Co-infection rates with other STIs are high.
- *C. trachomatis* is the commonest cause now of ophthalmia neonatorum.
- Asymptomatic infection of the nasopharynx, conjunctivae, vagina, and rectum can be acquired at birth.
- Sexual abuse should be considered when *C. trachomatis* infection is diagnosed in children beyond infancy who have vaginal, urethral, or rectal chlamydial infection.
- LGV serovars are worldwide in distribution and are especially prevalent in tropical and subtropical areas. Recently, outbreaks of LGV have been reported among MSM.
- Trachoma, which is a scarring conjunctivitis, is the commonest preventable cause of blindness in the world; poverty and lack of sanitation are risk factors.
- Pelvic inflammatory disease (PID) and tubal factor infertility are important long-term outcomes.

Transmission and incubation period

- Genital infection is sexually transmitted; reinfections are common.
- Up to 10% of infants born to mothers with active, untreated chlamydial infection develop clinical conjunctivitis; symptoms develop 5–14 days after delivery.
- Around 5% of infants born to mothers with active, untreated chlamydial infection may develop pneumonia; onset is usually 1–3 months after delivery.
- Perinatally acquired infections can persist for as long as 3 years.
- Infection is not known to be communicable in infants and children.
- The incubation period of *C. trachomatis* illness can significantly vary. One week is the mean period.
- LGV is infectious during active disease, and perinatal transmission is rare.
- Trachoma can be spread from eye to eye; flies are a vector between humans.

Clinical features and sequelae

- Neonatal conjunctivitis:
  - Conjunctival injection, swollen eyelids
  - Eye discharge can vary from scanty mucoid to a copious purulent discharge
  - In contrast to trachoma, scars and pannus formation are rare.
- Pneumonia in infancy:
  - It is an afebrile disease with a slow onset and benign course
  - Usually characterized by repetitive cough, tachypnoea, and rales
  - Hyperinflation often accompanies the interstitial infiltrates seen on chest radiographs, although wheezing is uncommon
  - Peripheral eosinophilia is a characteristic laboratory finding.
- Infection of the genital tract:
  - Wide spectrum of disease, with 75% of women and many men being asymptomatic
  - Symptoms, consisting of mucoid discharge and dysuria, are usually less acute than with gonorrhoea
  - Main clinical presentations are: urethritis, cervicitis, endometritis, salpingitis, proctitis
  - Epididymitis occurs in ♂, as well as Reiter's syndrome (arthritis, urethritis, and bilateral conjunctivitis)
  - Children who have been sexually abused may acquire vaginitis and rectal infections which are usually asymptomatic
  - In post-pubertal ♀, *C. trachomatis* can cause PID, which can present with perihepatitis and ascites (Fitz–Hugh–Curtis syndrome)
  - Recurrent or chronic salpingitis can lead to ectopic pregnancy or (tubal factor) infertility.

- LGV is a chronic disease characterized by:
  - Initial ulcerative lesion of the genitalia
  - The second stage is characterized by unilateral tender and suppurative inguinal or femoral lymphadenitis with enlarging, painful buboes
  - In the tertiary stage, rectovaginal fistulae and strictures can be seen.
- Trachoma is the consequence of repeated and chronic infections:
  - The initial infection is a follicular conjunctivitis, which may result in scarring and entropion (eyelid turning inward)
  - Chronic trauma to the cornea (abrasions by eyelashes) causes neovascularization and scarring of the cornea.

Diagnosis

Laboratory diagnosis

- Specimens—adequate samples for direct detection should contain columnar epithelial cells, which need to be transported in special media if cell culture is to be performed.
- Direct fluorescent antibody (DFA) test—high sensitivity for good-quality (i.e. large number of epithelial cells present) conjunctival and ♂ urethral specimens.
- Cell culture—gold standard, labour-intensive, and not widely available.
- NAATs are highly sensitive for the detection of genital infections; non-invasive testing is possible (urine and self-collected vaginal swabs).
- In cases with medico-legal implications (i.e. sexual abuse of children or rape), only direct detection by isolation of *C. trachomatis* in cell culture or detection by NAAT (with confirmation by a second NAAT using a different target) is acceptable.

Disease-specific management

- Ocular trachoma is usually diagnosed clinically in countries with endemic infection:
  - Two out of four criteria should be present: (1) lymphoid follicles on upper tarsal conjunctivae; (2) typical conjunctival scarring; (3) vascular pannus; (4) limbal follicles
  - Confirmation by culture, staining, or NAAT during active stage of disease
  - Serological tests are not helpful due to high seroprevalence in endemic populations.
- Neonatal pneumonia due to *C. trachomatis* can be suspected when the chest radiograph shows interstitial infiltrates and hyperinflation, and blood cell count demonstrates eosinophilia (≥0.3–0.4 × 10^9/L); culture of nasopharyngeal swab specimens confirms the diagnosis; an acute MIF serum titre of *C. trachomatis*-specific IgM may be elevated (≥1:32).
- LGV can be diagnosed by culture or a positive NAAT from a specimen aspirated from a bubo or by serological testing.

- Diagnosis of genitourinary chlamydial disease should prompt investigation for other STIs, including syphilis, gonorrhoea, and HIV infection.
- When an infant has been infected, it is recommended to evaluate the mother for chlamydial infection, as well as other STIs.

Management and treatment

- Neonatal conjunctivitis and pneumonia:
  - Topical treatment of chlamydial conjunctivitis is ineffective and unnecessary
  - Oral macrolides are the drug of choice for conjunctivitis and/or pneumonia—erythromycin or clarithromycin for 14 days or azithromycin for 3–5 days
  - Because efficacy is only 80%, follow-up is recommended, and a second course can be necessary
  - If erythromycin is used, the risk of development of hypertrophic pyloric stenosis has to be taken into account in infants <6 weeks. The risk of hypertrophic pyloric stenosis may be lower with azithromycin.
- Uncomplicated genital infections are treated as follows:
  - Children: macrolide (erythromycin or clarithromycin 7–14 days; may use azithromycin as a single dose in children >8 years or in those who weigh at least 45kg)
  - Adolescents: macrolide, doxycycline, or a quinolone for 7 days
  - Doxycycline and quinolones are contraindicated during pregnancy.
- Trachoma can be treated by either the topical or oral route:
  - Mild cases are usually treated with topical tetracycline or erythromycin ointment, given twice a day for 2 months or twice a day for the first 5 days of the month for 6 consecutive months
  - Oral erythromycin or doxycycline (for children aged ≥8 years) for 40 days are administered in the most severe cases
  - A simple and effective alternative is represented by mass treatment to all residents of a village with a single dose of azithromycin
  - Treatment is aimed at treating individuals with active infection and reducing infection load in endemic communities, but will not reverse scarring. High rates of macrolide resistance are a problem after mass treatment.
- LGV is treated with:
  - Doxycycline (patients ≥8 years) for 21 days
  - Erythromycin base (patients <9 years) for 21 days.
- A diagnosis of *C. trachomatis* infection in an infant should prompt treatment of the mother and her sexual partner(s).
- Repeat testing (preferably by culture) is recommended 3 weeks after treatment in pregnant women.

Prevention

- Pregnant women at high risk of *C. trachomatis* infection (i.e. women aged <25 years and those with multiple sexual partners) should be targeted for testing the presence of *C. trachomatis*.
- Prophylaxis of infants born to infected mothers (who are at high risk of infection) is not usually recommended, because its efficacy is not known. They should be treated if infection develops.
- Sexually active adolescents and young adult women aged <25 years should be tested at least annually for *C. trachomatis* infection during gynaecological visits, even if no symptoms are present or barrier contraception is reported; education on reducing transmission (e.g. condom use) is an essential part of prevention programmes.
- In areas that are endemic for trachoma, WHO implements the SAFE approach: surgery, antibiotics, face washing, and environmental improvement. Azithromycin once or twice a year or topical tetracycline twice daily for 6 weeks has been effective in treating large populations.
- Non-specific preventive measures for LGV include education, condom use, and case reporting.

Future research

- The role of maternal chlamydial infection in prematurity and in perinatal death.
- Standardized diagnostic tests for different infections caused by *C. trachomatis* have to be identified.
- More data are required on tolerability and efficacy of newer oral macrolide antibiotics, such as azithromycin, roxithromycin, or clarithromycin, for chlamydial infections in neonates.
- Efforts to find a vaccine for *C. trachomatis* are ongoing.

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Chapter 57

Cholera

Name and nature of organism

Cholera is a bacterial infection of humans caused by *V. cholerae,* a Gram-negative bacillus divided into >100 serogroups. *V. cholerae* serogroup O1, biotype El Tor, serotype Ogawa or Inaba, is the principal pathogen. In 1993, a new serogroup *V. cholerae* O139 was reported in southern India and has been responsible for outbreaks in Bangladesh and Thailand. Other serogroups may cause diarrhoea, but not the clinical or epidemiological pattern of cholera.

The principal pathogenic factor is the polypeptide cholera endotoxin, comprising two subunits A and B. The B subunit attaches to the epithelial cells and 'allows' entry of the A subunit into the cells. The A subunit 'switches on' cyclic adenosine monophosphate (AMP), resulting in the efflux of water, bicarbonate, and electrolytes, and the clinical dehydration and electrolyte imbalance that characterizes cholera. In 2000, the full genome of *V. cholerae* was sequenced, and the location of the genes coding for the A (Ctx A) and B (Ctx B) toxin subunits determined.

Cholera is a faecal–oral disease and occurs where sanitation and water supplies are inadequate, particularly in the poorer areas of the world. *Vibrio* can survive for long periods in aquatic environments and so provide a reservoir of infection when public health infrastructure is compromised. The infective dose of cholera is relatively high (10^2–10^{10} organisms), and infectivity is increased in achlorhydria and chronic gastritis.

Epidemiology

Cholera remains badly controlled in multiple epidemic and endemic areas across the globe. Cholera occurs endemically in south and South East Asia and in sub-Saharan Africa, and has recently returned to the Americas with ongoing transmission in Haiti. The estimated annual incidence of cholera is of 1.4 million to 4.3 million cases, resulting in 28 000 to 142 000 deaths worldwide. A total of 1.4 billion people are still exposed to the risk of cholera in endemic countries. Those are essentially people with limited access to safe drinking water and sewage disposal such as residents of overcrowded periurban slums, remote rural areas, refugees and internally displaced persons (IDPs) during humanitarian emergencies, and marginalized populations. In recent years, large cholera epidemics proved difficult to control and resulted in thousands of cases and deaths in Angola, Zimbabwe, and Haiti.

While cholera is not of immediate public health importance in Europe, movements of population from endemic countries or from countries facing

a cholera epidemic make the importation of cholera a possibility. In 2013, imported cholera cases were reported by Australia, Canada, Chile, Israel, Italy, Japan, South Korea, the UK, the US, and Venezuela. Of those countries, only Mexico reported a significant indigenous cholera transmission following the importation of a case, resulting in 187 cases reported in 2013.

Transmission and incubation period

Infection occurs following ingestion of food or water contaminated by faeces containing high concentrations of *V. cholerae*. The common sources of infection, apart from water contaminated at its source or during storage, include seafood, fruits, and vegetables.

Cholera transmission may occur through a faecal–oral route ('person to faeces to person') or through direct infection from the environment (environmentally acquired infection). During an outbreak, most cases are a result of faecal–oral, often called fast, transmission.

The incubation for symptomatic disease ranges from a few hours to 5 days. The incubation period may be shorter with a high ingested dose.

Clinical features and sequelae

Only 20% of people infected with *V. cholerae* will develop symptoms (i.e. 80% remain asymptomatic, although they still excrete *V. cholerae* during 1–2 weeks, on average, and are therefore also sources for transmission during this period).

Most symptomatic cases will present as a mild acute watery diarrhoea. Severe cholera (10% of symptomatic cases) is characterized by the abrupt onset of profuse watery diarrhoea and vomiting, resulting in dehydration, along with hypokalaemia and hypoglycaemia. Signs of dehydration include: lethargy or unconsciousness, dry mouth, sunken eyes, increased thirst, decreased urine, and the skin going back slowly when pinched.

In severe cases, without rapid and appropriate rehydration and correction of electrolyte imbalance, death can result very quickly from hypovolaemic shock and associated metabolic complications.

Diagnosis

In endemic areas of developing countries or during epidemics, most cholera cases are diagnosed clinically. Laboratory confirmation is only used to confirm the aetiology of the outbreak at its inception and to guide public health measures.

Routine laboratory techniques are able to isolate *V. cholerae* from stool specimens or rectal swabs. Stools are cultured on selective media, and suspect colonies tested for agglutination with O1 and O139 antisera.

RDTs for cholera detect cholera antigens in stools or rectal swabs by immunochromatography. In contrast to culture, they can be performed at the patient's bed and give immediate results. However, RDTs currently

available lack specificity, resulting in an important proportion of false positive results, which restrict their use to a public health, rather than an individual, diagnostic tool.

Management and treatment

Early detection and timely and effective case management of cholera cases with oral or IV rehydration reduce the case fatality rate to <1%, even in difficult contexts like complex humanitarian emergencies and crisis situations.

Dehydrated patients who can drink should be given low-concentration ORS immediately and at frequent intervals in small quantities to compensate for fluid losses. The approximate amount (in mL) of ORS solution to be given in the first 4 hours can be calculated by multiplying the patient's weight in kg by 75. For example, a child of 20kg should be given 1500mL of ORS in 4 hours. ORS solutions should be prepared with safe water.

Patients with severe dehydration and conditions that prevent drinking should be rehydrated IV. Ringer's lactate solution is the best option (or normal saline if Ringer's lactate is not available) to be given at 30mL/kg in the first 30 minutes, and at 70mL/kg in the following 2.5 hours (1 hour and 5 hours, respectively, for infants).

Appropriate antibiotics can reduce the volume and duration of cholera diarrhoea and the excretion of cholera *Vibrio*. They may be given to moderate and severe cases, or to severe cases only. Adults should be given a single dose of 300mg of doxycycline. A single dose of azithromycin should be given to pregnant and lactating women (1g) and to children under 12 years of age (20mg/kg).

Zinc supplementation significantly reduces the severity and duration of diarrhoea in children and should be given at a dosage of 20mg per day for children older than 6 months, or 10mg per day in those younger than 6 months, for 10–14 days.

Isolation and barrier nursing precautions should be established to reduce the risk of transmission within health-care settings treating cholera patients.

Cholera control

The long-term solution for cholera control (which benefits all diseases spread by the faecal–oral route) undeniably lies in economic development and universal access to potable water and adequate sanitation, which remain the mainstay of preventing both epidemic and endemic cholera. Interventions targeting environmental conditions include the development of piped water systems with water treatment facilities, as well as the construction of systems for sewage disposal and latrines.

Most of those interventions, however, require substantial long-term investments and high maintenance costs, difficult to access and sustain by the least developed countries where they are also most needed and where rapid urbanization exceeds the capacities of the municipalities to construct and maintain water and sewage networks in many places.

Surveillance of cholera cases and deaths is critical to guide interventions and lead to timely response activities. In endemic areas, surveillance helps anticipate the seasonal occurrence of cholera and enhance activities such as preparedness plans, training of health-care staff, and pre-positioning of supplies. The monitoring of outbreaks is key to organizing the response and the allocation of resources.

Oral cholera vaccines (OCVs) are a safe and effective tool that could complement and improve cholera prevention and control strategies. Although marketed for 20 years, OCVs have essentially been used for travellers, and rarely for populations exposed to endemic or epidemic cholera. There are two WHO pre-qualified OCVs available on the market, both administered in two doses given at least 7 days apart.

Pre-emptive vaccination with OCVs could be performed in cholera-endemic areas, including during humanitarian crises, as an additional means for cholera prevention and control. In such settings, vaccination should be targeted at high-risk areas and high-risk population groups such as displaced populations in camps with precarious living conditions, underserved populations in resource-poor settings, etc. Mass vaccination campaigns with OCVs may also be organized on a reactive basis, as part of the response to a cholera outbreak.

Health education campaigns, adapted to local culture and beliefs, should promote the adoption of appropriate hygiene practices such as handwashing with soap, safe preparation and storage of food, and breastfeeding. Awareness campaigns during outbreaks also encourage people with symptoms to seek immediate health care.

Future research

Renewed attention to cholera in recent years is creating a new dynamic for research and innovation in all domains of cholera control, notably for:

- The development of a renewed strategy to ensure access to oral rehydration therapy, including community-based delivery strategies
- The development of single-dose, safe, effective, and affordable cholera vaccines
- The surveillance of the emergence of altered variants and drug-resistant strains of *V. cholerae*
- The development of improved cholera RDTs
- The development of innovative health promotion strategies and tools.

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Chapter 58

Clostridium difficile

Nature and name of organism

- *C. difficile* is a spore-forming, obligate anaerobic, Gram-positive bacillus.
- It is a commensal bacterium of the human intestine.
- *C. difficile* is the commonest cause of antimicrobial-associated diarrhoea and is a common health care-associated pathogen.
- The ability of *C. difficile* to form spores that resist many common disinfectants and can survive for months on environmental surfaces makes it particularly prone to nosocomial transmission.
- The extracolonic spore form is heat-resistant, acid-resistant (permitting safe passage through the stomach), and antibiotic-resistant.
- Colonic injury and inflammation results from the production of two protein toxins: toxin A ('enterotoxin') and toxin B ('cytotoxin'); a third toxin has also been identified (binary toxin) associated with a hypervirulent strain (see Epidemiology, p. 490–1).

Transmission, incubation, and pathogenesis

- Reservoirs of *C. difficile* may be endogenous (chronic infection/carrier) or environmental.
- Transmission of *C. difficile* occurs by the faecal–oral route through contact with *C. difficile* spores.
- The ability of *C. difficile* to form spores enables the bacteria to remain in the physical environment for prolonged periods, facilitating transmission.
- *C. difficile* is highly transmissible via fomites (including items in patient rooms, as well as the hands, clothing, and stethoscopes of health-care workers).
- The incubation period is not known with certainty.
- People who remain asymptomatically colonized with *C. difficile* over longer periods of time appear to be at decreased risk for the development of *C. difficile* infection (CDI), in contrast to the situation with other MDR pathogens.
- The period between exposure to *C. difficile* and the occurrence of CDI has been estimated to be a median of 2–3 days after initiation of antibiotic therapy, although it may occur up to 10 weeks after antibiotic discontinuation, as a result of the prolonged perturbation of the lower intestinal microbiota.
- The main virulence factors of the enteropathogenic *C. difficile* are two toxins toxin A and toxin B, although it is likely that multiple factors determine whether a strain is virulent and/or epidemic.

- Non-toxigenic strains of *C. difficile* do not cause CDI.
- Toxins A and B are glycosyltransferases that disrupt the cytoskeleton and tight junctions of the cells, resulting in apoptosis and inflammation of the intestinal epithelial cell layer.
- Both toxins cause extensive epithelial tissue damage, resulting in fluid loss and diarrhoea, although it is thought that toxin B only becomes effective once the intestinal epithelium has been damaged.
- Both toxins A and B also promote neutrophil chemotaxis to localize in pseudomembranes and the underlying intestinal mucosal layer.
- A binary toxin (*C. difficile* toxin, CDT) has been associated with increased disease severity and poor outcome; it induces the formation of microtubule-based protrusions, increasing the adherence of bacteria.
- CDT has been associated with hypervirulent strains *C. difficile* NAP1/B1/027 and NAP7,8/BK/078.
- A novel virulence factor Srl (sensitivity regulation of *C. difficile* toxins) has recently been identified; it may modulate the toxin sensitivity of intestinal epithelial cells, enhancing the cytopathic effect of *C. difficile* toxins.

Pathological changes

- Extensive multifocal yellow–white adherent and raised plaques are seen on the intestinal inflamed mucosa when endoscopy is performed; with progression of disease, these plaques enlarge and coalesce, forming the characteristic 'pseudomembranes' (Fig. 58.1).
- Microscopically, there are 'volcano' or 'mushroom' lesions, composed of neutrophils, mucin, and fibrin, that appear to erupt out of colonic glands; the underlying mucosa often shows ischaemic-like damage (crypt withering, mucosal necrosis) and inflammation.

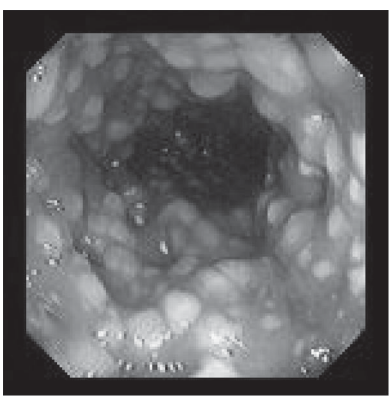

Fig. 58.1 Characteristic endoscopic findings of pseudomembranous colitis. Raised pale plaques are seen on an inflamed mucosa.
(Reproduced with the permission of D. M. Martin, from JR <http://www.endoatlas.com/>).

Epidemiology

- Over the past decade, the incidence of CDI has approximately doubled in adults and children, with a particular rise in incidence among patients presenting from the community.
- Its incidence has grown among populations previously believed to be at low risk, namely previously healthy patients in the community.
- The changing epidemiology of CDI has occurred largely in parallel with the emergence of a hypervirulent strain of *C. difficile*, referred to as the *North American pulsed-field gel electrophoresis type 1 (NAP1) strain*.

C. difficile infection in children

- Because CDI is not a reportable disease, surveillance data in children are limited.
- There are many challenges to understanding the role of *C. difficile* in children, largely because of the high numbers of children who carry the bacteria without developing symptomatic CDI.
- As well as among adults, several studies have shown a rise in CDI among children, particularly in young children aged 1–5 years.
- It is thought that the gradual increase could also be attributed to greater disease awareness, increased testing, and new, more sensitive diagnostic techniques, rather than an increase in the disease itself.
- Rates of normal colonization in infants aged <1 year range from 14% to 71%, with ~4.2–50% of colonized infants carrying toxigenic strains of the bacterium.
- *C. difficile* colonization in infants is affected by premature birth, feeding mode (breast or formula), composition of the intestinal microbiota, and age.
- Pathogenic strains circulating in asymptomatic infants from the community may represent a potential reservoir for transmission to others.
- By 2 years of age, *C. difficile* is evicted as a commensal, with resulting decrease in the colonization rate, reaching levels similar to those observed in healthy adults (<5%).

Hypervirulent strain: NAP1/B1/027

- This epidemic strain (NAP1/PCR ribotype 027) was first described in the 1980s following outbreaks in a number of North American states.
- To date, many factors, such as antibiotic resistance, sporulation ability, and toxin production, have been proposed to contribute to the potential difference in virulence of historical ribotypes and *C. difficile* NAP1, even if the relevance of these factors is still greatly debated.
- This strain is characterized by higher than usual toxin A and B production, the presence of a third toxin, binary toxin, and high-level resistance to fluoroquinolone antibiotics.

Risk factors for *C. difficile* infection

Antibiotics

- Exposure to antibiotics remains the pre-eminent risk factor for CDI, and their effect can persist for weeks to months after they are stopped.
- The effect of antibiotics is presumed to be a disruption of the normal gut microbiota, thus allowing proliferation of *C. difficile*.

- Any antibiotic can cause CDI, commonly clindamycin, cephalosporins, quinolones, metronidazole, vancomycin, co-amoxiclav, and especially multiple antibiotics.

Exposure to toxigenic C. difficile

- Risk for CDI has been shown to correlate with length of hospital stay, but recently discharged patients and patients who live in long-term care facilities or other health-care settings are also at increased risk.
- Infection is caused by a hypervirulent strain.

Gastric acid suppression

- Many studies showed an increased risk of CDI associated with the use of proton pump inhibitors (PPIs).

Severe illness and complex chronic conditions

- Chronic underlying medical conditions, as well as major GI surgery, have been shown to be a risk factor for *C. difficile* infection in children, and this association is most likely related to increased exposure to both *C. difficile* and prolonged antibiotic therapy:
  - Inflammatory bowel disease
  - Cystic fibrosis
  - Solid organ transplant
  - Abdominal surgery.

Clinical features and sequelae

The clinical spectrum of CDI varies widely, ranging from asymptomatic carriage to severe and fulminant pseudomembranous colitis that can be fatal.

Spectrum of clinical disease

Asymptomatic carrier

- Neonates and infants are usually asymptomatically colonized, and clinical illness is rarely reported before 24 months of age.
- It has been speculated that neonates and/or infants may lack the cellular machinery to bind and process the toxins of *Clostridium* spp.
- The typical rate of colonization with *C. difficile* in asymptomatic and otherwise healthy adults is <5%. In contrast, high colonization rate is reported among adult hospitalized patients (up to 20%) and in chronic care wards and long-term care facility residents (up to 50%).
- High colonization rates are reported during epidemic settings or for high-risk populations.

C. difficile diarrhoea

- Most symptomatic children experience mild to moderate watery diarrhoea that is typically profuse and frequent (up to 15 times per day), associated with fever, anorexia, abdominal pain, and leucocytosis.
- Diarrhoea of CDI is rarely bloody, although it can be in severe cases.
- Some patients may lose significant amounts of serum proteins in the stool, causing hypoalbuminaemia, oedema, and ascites.

Pseudomembranous colitis

- Patients with CDI frequently have pathognomonic findings on lower endoscopy.
- *C. difficile* colitis can be non-specific, or there may be release of proteins and inflammatory cells, which coalesce to form yellowish pseudomembranes.

Fulminant colitis

- Patients with severe CDI frequently have abdominal pain caused by ileus, colonic dilation, toxic megacolon, bowel perforation, and peritonitis.
- In some children, there may be marked abdominal distension, but minimal diarrhoea.
- Marked leucocytosis and lactic acidosis are worrying signs and should prompt surgical consultation.
- Although severe CDI is reported among children, complications related to CDI are uncommon, ranging from 0% to 12%.

Extraintestinal manifestations

- Extraintestinal manifestations of CDI are rare but include reports of bacteraemia, peritonitis, perianal abscess, surgical site infections, and musculoskeletal infections.

Clinical disease in children <2 years of age

- Clinical illness is rarely reported before 2 years of age, but severe disease does occasionally occur in infants with co-morbidities such as Hirschsprung's disease and cystic fibrosis.
- Although testing of infants is not recommended, recent data have shown that 26% of children hospitalized with CDI were infants younger than 1 year, and 5% were neonates.

Relapse and reinfection

- Recurrent episodes of CDI can cause significant morbidity, occurring in up to 25% of patients, due either to relapsed infection with the original strain or reinfection with a new strain.

Diagnosis

- The diagnosis of *C. difficile* requires clinical suspicion, based on the presence of specific risk factors, in a patient with clinical manifestations of intestinal disease.
- The diagnosis of CDI rests on:
  - Excluding other causes of intestinal disease, AND
  - Documenting the presence of pseudomembranous colitis in the absence of another cause (as diagnosed during endoscopy), OR
  - Microbiological evidence of toxin-producing *C. difficile* in stool.
- Isolation of *C. difficile* without toxin may just represent normal bowel colonization. Organism and host response determine whether infection with *C. difficile* will result in colonization or infection.

- Evaluation for alternative enteropathogens should be considered as well, particularly in younger children; ~10% of CDI cases may have a concomitant pathogen detected.

Diagnostic difficulties in children

- The microbiological tests used for the detection of toxin-producing *C. difficile* in the stools of adults are the same as those used in children, including infants <2 years of age.
- Because of the wide rate of colonization in children, diagnostic strategies in young children should be different from those in adults and older children.
- *Neonates and children aged <1 year*:
  - Routine testing for *C. difficile* should be not recommended
  - Testing of these infants should be limited to those with Hirschsprung's disease or other severe motility disorders or in an outbreak situation.
- *Children aged 1–2 years*:
  - Routine testing should be discouraged
  - Careful clinical correlation is required
  - Other commoner GI pathogens that cause diarrhoea (e.g. rotavirus) should first be excluded
  - Only unformed stools should be tested.
- *Children aged >2 years*:
  - Can be tested in the same manner as older children and adults.
- Stool testing should not be repeated for 'test of cure'. Testing for recurrences <4 weeks after initial testing is only useful when the results of repeat testing are negative.

Choice of diagnostic testing method for *C. difficile*

- When testing for *C. difficile*, it is important to detect the toxin, and not just the organism. Importantly, the presence of the toxin in the bowel lumen is associated with clinical disease (Table 58.1).

Available tests

- Available tests are divided into:
  - Tests for detection of the toxin (cytotoxicity assay, EIA, NAAT)
  - Tests for detection of the organism (culture, common antigen testing).
- Toxin detection tests are preferred, because tests that detect the presence of the organism have the potential to yield false positive results (up to 25%) because isolates may be non-toxigenic strains.
- Various algorithms, involving a combination of available methods, for CDI testing are commonly used, but none is satisfactory.
- The gold standards are cell cytotoxicity and toxigenic cell culture, but both are too slow for clinical testing or for use in clinical trials.
- The performance of algorithms has not been formerly evaluated in children.

Table 58.1 Comparison of diagnostic tests for *C. difficile*

Method	Methodology	Sensitivity (%)	Specificity (%)	Turnaround time (hours)	Comments
Direct faecal cytotoxicity test	Faeces are added to a cell culture system, and the laboratory analyses whether a demonstrated cytotoxic effect is neutralized by a specific antitoxin	77–86	97–99	24–48	Of the two gold standards: less sensitive versus toxigenic culture, and slow
EIA for toxins A and B	Direct stool test for toxins A and/or B	60–92	93–99	1–2	Compared with cell cytotoxicity and toxigenic culture
EIA for glutamate dehydrogenase	The enzyme glutamate dehydrogenase is expressed at high levels by all strains of *C. difficile* and is referred to as the common antigen	71–100	67–99	1–2	This test has been commonly suggested for screening, although does not detect toxigenic strains
Toxigenic culture for *C. difficile*	A stool culture for *C. difficile*, followed by a toxin assay of *C. difficile* colonies	95–100	96–100	48	Also regarded as a reference standard method for the diagnosis of CDI. Not provided by most clinical laboratories
Nucleic acid amplification (PCR and LAMP)	Real-time PCR (RT-PCR) and loop-mediated isothermal amplification (LAMP) are NAATs that can be used to detect the presence of toxin genes directly from stools	88–100	88–97	3	Amenable to both batch and on-demand testing. Most sensitive, rapid single test available, but also most costly

Management and treatment

- Discontinuation of antimicrobial agents is the first step in treating CDI and may suffice in mild CDI without systemic signs.
- Treatment of asymptomatic carriage is not recommended.
- Antimicrobial therapy is indicated in children with mild to severe CDI or an underlying GI tract disease or immune compromise; regimen depends upon the severity of symptoms.
- Both metronidazole and vancomycin are effective against *C. Difficile*.
- Metronidazole is recommended as the first-line therapy in mild to moderate disease because of the cost and the concern over emerging VRE. Dosing in children 2 months to 18 years of age is 7.5mg/kg every 8 hours orally or IV; the oral route is preferred, unless contraindicated (ileus or severe general conditions), and long-term use should be avoided, owing to the risk for neurotoxicity.
- Vancomycin is recommended in severe CDI and non-responders; it is only effective if given orally at 40mg/kg per day in four divided doses.
- Recommended duration of therapy is 10–14 days.
- Patients with a first recurrence will usually respond to a second course of the same treatment; for the second or third recurrence, oral vancomycin, given in tapered or pulsed regimen, is recommended.
- Other antibiotics, such as nitazoxanide, fidaxomicin, and teicoplanin, have also been used.
- Nitazoxanide has a similar cure rate to vancomycin in adults.
- Fidaxomicin is a macrocyclic compound that is poorly absorbed from the GI tract, reaching high intraluminal concentrations. The rate of recurrence is approximately half, compared to vancomycin, presumably due to the mild effect of the drug on the resident colonic microbiota. Approved for treatment of CDI in adults; it is currently undergoing investigation in children.
- Teicoplanin can be used to treat *severe CDI*. No data in children are available to date.
- Antiperistaltic medications should be avoided, because they may obscure symptoms and cause toxic megacolon.
- Consider surgery in the setting of severe disease such as bowel perforation with peritonitis and toxic megacolon.
- Probiotics are not recommended for the treatment of CDI. Data on controlled studies in children are lacking.
- Faecal transplantation (enteric administration of donor stool flora) has been described in only two case reports of children with *C. difficile* recurrent and refractory colitis; its use to date is not recommended.

Prevention and control

- The first step in preventing CDI in the health-care setting is to implement the correct use of the antimicrobial therapy, which can be achieved with ASPs, effective in reducing the rates of CDI and in preventing outbreaks.

- Hand hygiene and use of gloves with symptomatic patients is highly recommended for preventing CDI and the transmission of spores.
- Handwashing with soap and water is preferred, because alcohol-based gels are not sporicidal.
- Contact precautions and environmental decontamination using hypochlorite solutions are key control measures.
- The use of probiotics in the prevention of CDI in children is controversial. Probiotics are not recommended by AAP, while a 2013 meta-analysis on 4213 patients suggests that probiotics are both safe and effective for preventing CDI. Controlled trials on their use in paediatric CDI are needed.

Future research

- Evaluation of the optimal testing and the ideal algorithm to diagnose CDI in paediatrics. An RDT should be validated in order to detect the presence of toxigenic strains and avoid over-treatment in children.
- Performing of clinical trials focused on the evaluation of drug formulations specific for paediatric CDI.
- Identification and characterization of suitable vaccine candidates against *C. difficile* in children. Include children early in the clinical trial development programmes of preventive vaccines currently under clinical evaluation.

Further reading

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Chapter 59

Conjunctivitis

See also Chapters 31, 46, 57, 68, 104, 107.

Introduction

Conjunctivitis is the most frequently presenting disorder of the eye. It is usually self-limiting, and the risk of long-term complications is low. It involves inflammation of the conjunctiva; associated corneal involvement gives rise to keratoconjunctivitis.

Conjunctivitis may be due to bacterial or viral infection or allergic hypersensitivity (not addressed here).

Causative organisms

Bacteria are responsible for 33–78% of cases (especially in infants and toddlers).

- More likely in non-epidemic conjunctivitis.
- Commonest organisms involved are *H. influenzae, S. pneumoniae* (encapsulated and non-encapsulated isolates), and *M. catarrhalis*.
- Conjunctivitis–otitis syndrome occurs in 20–73% of cases of bacterial conjunctivitis (most cultures yield *H. influenzae*).
- Role of staphylococcal spp. in pathogenesis is controversial—they are isolated from the conjunctivae of children with conjunctivitis and asymptomatic children at equal rates.
- *N. meningitidis* rarely causes conjunctivitis.
- Neonatal conjunctivitis (ophthalmia neonatorum) is usually caused by *N. gonorrhoeae* (<1 week of age) or *C. trachomatis* (>1 week of age). Resistance is an increasing problem in both.
- Other bacteria occasionally implicated in neonatal infection include *S. aureus* and *S. epidermidis, P. aeruginosa*, and *viridans* streptococci.

Viral conjunctivitis is commoner in school-aged children and adolescents.

- Adenoviruses are responsible for 20% of all cases of conjunctivitis.
  - Serotype 3 (and occasionally 4 or 7) causes pharyngoconjunctival fever
  - Other serotypes (especially 8, 19, and 37) cause epidemic keratoconjunctivitis.
- HSV type 1 also causes conjunctivitis, usually in preschool children. HSV type 2 is usually responsible for neonatal infections.
- Molluscum contagiosum may be implicated in adolescents.
- Acute haemorrhagic conjunctivitis (AHC), mainly occurring as epidemics in the tropics, is caused by two picornaviruses Coxsackie type A24 and enterovirus type 70 (also rarely adenovirus 11).

Transmission is by direct contamination (fingers, towels, etc.) with respiratory or ocular secretions. Wearing contact lenses increases the risk of getting conjunctivitis. Adenovirus is particularly contagious, with an infection rate in household contacts of around 25%. The virus remains in the conjunctiva for 14 days, and the faeces for 30 days. The incubation period for adenovirus is 3–29 days (mean 11 days), and 1–3 days for most bacterial infections (except for those caused by *C. trachomatis*, for which it is 5–14 days).

UK and European epidemiology

Infective conjunctivitis is common worldwide. Approximately one in eight schoolchildren has an episode of acute infective conjunctivitis each year. This means there are >1 million episodes per year in the UK, accounting for 1% of consultations in 1° care. The prevalence of bacterial conjunctivitis increases in the winter and spring, and viral conjunctivitis is commoner in the summer and autumn.

Enterovirus 70 thrives for longer periods in areas of high humidity, hence AHC is found mainly in the tropics (especially Asia).

The widespread use of the pneumococcal conjugate vaccine may significantly reduce *S. pneumoniae* as a cause of conjunctivitis.

Clinical presentation and differential diagnosis

The symptoms and signs are similar in viral, bacterial, and allergic conjunctivitis. They include itching, burning, mucopurulent or purulent discharge, eyelid oedema, and conjunctival erythema. Itching is commoner in allergic conjunctivitis. Associated pharyngitis and/or preauricular adenopathy suggest a viral aetiology (usually adenovirus). Purulent discharge with gluey or sticky eyelids is highly suggestive of bacterial conjunctivitis (probability of 96% in one study), as is associated otitis media. Papillae on the conjunctiva and bilateral disease are also more likely in bacterial infections. However, one cannot reliably predict the aetiology on clinical examination alone.

Ocular pain and photophobia are uncommon, except in adenovirus keratoconjunctivitis. Other symptoms and signs that should prompt referral include: reduced visual acuity, recent eye surgery, abnormal pupils, restricted or painful eye movements, and history of trauma.

The main differential for acute infective conjunctivitis is allergic conjunctivitis, but other possibilities include the following: presence of a foreign body, blepharitis, orbital cellulitis, subconjunctival haemorrhage, ophthalmic shingles, episcleritis, scleritis, iritis, acute glaucoma, dry eye syndrome, corneal abrasion, arc eye (through exposure to intense ultraviolet light), and chemical irritation. Other diagnoses to consider may include measles and Kawasaki disease.

Adenovirus conjunctivitis

Adenovirus conjunctivitis usually presents as one of three recognized conditions, and the symptomatic phase lasts from 4 to 14 days.

- Follicular conjunctivitis—is the commonest type. Follicles develop from aggregation of lymphocytes and appear as small, pale, avascular areas, surrounded by a network of blood vessels. Typical features include:
  - Preauricular adenopathy
  - Hyperaemia
  - Watery discharge
  - Oedema of eyelids
  - Rhinitis
  - Pharyngitis
  - Itching.
- Pharyngoconjunctival fever—transmission may be linked to poorly chlorinated pools and ponds. Typical features include:
  - Pharyngitis
  - Fever
  - Chemosis
  - Hyperaemia
  - Preauricular adenopathy
  - Occasional small petechial haemorrhages.
- Epidemic keratoconjunctivitis—this usually occurs in older children and adults. There is an early follicular response and a late papillary response. Punctate epithelial defects are seen with fluorescein, and later subepithelial corneal infiltrates develop. In severe cases, conjunctival pseudomembranes and eyelid swelling develop. Typical features include:
  - Severe discomfort
  - Photophobia
  - Conjunctival oedema
  - Blurred vision.

Herpes simplex virus conjunctivitis

HSV conjunctivitis may be associated with a 1° infection or a recurrence. Transmission occurs via direct contact with another person or auto-inoculation, and 80% of cases are unilateral. There is a follicular inflammatory response, and keratoconjunctivitis occurs in 50%. It is difficult to differentiate clinically from adenoviral infection. Typical features include:

- Serous discharge
- Preauricular adenopathy
- Keratitis
- Occasional lid vesicles
- Associated URTI and gingivostomatitis.

Acute haemorrhagic conjunctivitis

AHC is highly contagious. Symptoms develop in <48 hours, last for 3–5 days, and resolve over 10 days. Typical features include:

- Sudden onset of hyperaemic conjunctiva
- Chemosis
- Oedema of eyelids

- Excessive tears
- Photophobia
- Discomfort.

Ophthalmia neonatorum

Gonococcal conjunctivitis tends to occur 3–5 days after birth but can present later. Chlamydial conjunctivitis usually has a later onset than gonococcal conjunctivitis; the incubation period is 5–14 days.

Typical features of gonococcal conjunctivitis include:

- More severe than other causes of ophthalmia neonatorum
- Purulent conjunctivitis, which is usually bilateral
- Corneal involvement has been reported, including diffuse epithelial oedema and ulceration that may progress to perforation of the cornea and endophthalmitis
- May be systemic manifestations.

Typical features of chlamydial conjunctivitis:

- Range from mild hyperaemia with scant mucoid discharge to eyelid swelling, chemosis, and pseudomembrane formation
- May be associated with extraocular involvement, including pneumonitis.

Investigations

Routine bacterial and viral eye swabs for culture are not usually required on the grounds of time delay and cost. Viral culture may be appropriate in epidemic case clusters.

Exceptions

- Suspected HSV—viral culture, PCR, and/or antigen detection tests should be performed. Fluorescein stains required to look for associated dendritic ulcers. Appropriate viral culture medium is needed, and the best samples are vesicle aspirates. Conjunctival scrapings have a lower sensitivity.
- Ophthalmia neonatorum—ensure that eye swabs are sent for microscopy and culture and that the laboratory is aware that *N. gonorrhoeae* is being tested for, so that appropriate culture media is chosen. A special conjunctival swab for *Chlamydia* culture is also required. EIAs, DFA assays, and PCR testing are also suitable for *Chlamydia* detection in conjunctival specimens.

Management and treatment

- Excellent infection control measures are required in the clinical setting and in the community to prevent further spread:
  - Thorough handwashing, glove use, instrument disinfection, and use of eye drops in individual or unit-dose containers should be employed in clinics and hospitals
  - Affected children and their carers should wash their hands regularly with soap, especially after applying eye drops or ointments (use a

different container for each eye). Sharing of towels, cups, etc. should be avoided. Regular disinfection of surfaces (e.g. taps, doorknobs) and changing of pillowcases are recommended.

- Exclusion from day care or nursery is controversial and is not recommended in the UK.
- Supportive care is indicated for all types of conjunctivitis:
  - Cold compresses—improve swelling and discomfort
  - Artificial tears (especially in keratitis)—reduce discomfort and photophobia, and relieve itching and burning
  - Topical vasoconstrictors.
- Acute bacterial conjunctivitis is usually self-limiting. A Cochrane systematic review found that clinical remission occurs within 2–5 days in 65% (99% CI 59% to 70%) of microbiologically confirmed cases treated with placebo. Most children therefore do not require any topical or systemic antibiotics.
- However, topical antibiotic treatment of acute infective conjunctivitis (ointment or drops) can shorten the clinical course, may reduce spread and discomfort, and allows the child to return to normal activities earlier (may be attractive to working parents). Evidence for more rapid clinical and microbiological remission is stronger if patients are treated early (within 2–5 days of presentation), as opposed to late (within 6–10 days). The number needed to treat is six for early clinical remission, and 13 for late clinical remission.
  - Choice of antibiotic depends on cost and local resistance patterns.
  - Active topical antibiotics include fluoroquinolones, chloramphenicol, gentamicin, neomycin, tobramycin, erythromycin, trimethoprim–polymyxin, and fusidic acid. A recent RCT showed that azithromycin 1.5% eye drops provided a more rapid clinical cure than tobramycin 0.3% eye drops in the treatment of purulent bacterial conjunctivitis in children, with a more convenient twice-a-day dosing regimen. Another RCT demonstrated that polymyxin B–trimethoprim had an equivalent clinical response rate to that of moxifloxacin.
  - Chloramphenicol is commonly used in the UK, and the risk of aplastic anaemia appears to be very small.
  - Systemic antibiotics may be required when there is associated otitis media.
- Generally, there is no place for corticosteroids (especially in HSV)—side effects include superinfection, glaucoma, and cataracts. Rarely, topical steroids may be used (with ophthalmological supervision) if there is pseudomembrane formation and signs of severe inflammation or visual loss.
- Most cases of viral conjunctivitis are self-limiting, particularly adenovirus, and 2° bacterial infection is uncommon.
  - There is no specific anti-adenoviral agent for local infection.
  - Cidofovir may be used systemically for immunocompromised patients with disseminated adenoviral infection.
- Children with suspected ocular HSV infection should be seen by an ophthalmologist and are usually treated with a topical antiviral agent such as aciclovir or valaciclovir. Neonates with suspected herpetic

infection should be treated with systemic aciclovir. Infants with neonatal HSV keratitis should also receive a topical antiviral agent such as trifluridine, Idoxuridine, or vidarabine.

- Ophthalmia neonatorum—prompt treatment of gonococcal conjunctivitis is very important, since this organism can penetrate an intact corneal epithelium and rapidly cause corneal ulceration. Because of the rapid progression of gonococcal conjunctivitis, patients with acute neonatal conjunctivitis should be treated for gonococcal conjunctivitis until culture results are available, using ceftriaxone as a single dose. Topical neomycin ointment should be used. Saline eye irrigation should be commenced immediately and at frequent intervals until the discharge is eliminated.
- Chlamydial conjunctivitis—infants with this are at risk of later pneumonitis. Oral erythromycin for 14 days is the current standard treatment.
- Conjunctivitis—sticky eyes, not otherwise thought to be due to gonococcus or *Chlamydia*, should be treated with topical neomycin until results of swabs are known.

Follow-up and outcome

- Acute infective conjunctivitis is usually a self-limiting condition which does not require specific follow-up.
- The risk of serious complications from untreated conjunctivitis is generally low, but this depends on the patient's immune status and the aetiology of the disease.
- The majority of bacterial cases resolve by 5 days without treatment.
- In viral disease, the symptomatic phase usually lasts for a maximum of 2 weeks, but some symptoms may persist for up to 6 weeks. The infection usually starts in one eye but spreads easily to the other eye.
  - Pharyngoconjunctival fever usually lasts for 4 days.
  - AHC typically resolves within 5–7 days.
- Children with keratoconjunctivitis should be seen by an ophthalmologist, as severe cases may lead to conjunctival desiccation, and eventually scarring and adhesion of the palpebral and bulbar conjunctivae. Asymmetrical scarring can result in amblyopia in young children.
- 1° HSV disease is usually self-limiting, but recurrent disease may lead to corneal opacification and visual loss. These patients should be followed up by an ophthalmologist.
  - Infection in newborns tends to be more severe due to their impaired immunity, absence of conjunctival lymphoid tissue, and lack of tears. Serious systemic complications, such as encephalitis, may occur.
- Mothers whose babies are diagnosed as having either gonococcus or chlamydial infection need referral for treatment for themselves and for contact tracing, etc.

Future research

- With the increasing trend toward no antibiotic treatment for acute infective conjunctivitis, more data are needed on the risk of adverse events when no treatment is given and the effect on transmission rates.
- More work is needed to establish whether antibiotic use for suspected bacterial cases may be cost-effective, e.g. by preventing time off work for parents.
- There is scope to try to find rapid and reliable diagnostic tools to differentiate between bacterial and viral conjunctivitis.
- Further research into antiviral therapies is required:
  - Purified concentrated human IgG has been shown to have antiviral properties against adenoviral serotypes *in vitro* and in rabbits
  - Zalcitabine and stavudine (nucleoside reverse transcriptase inhibitors) have demonstrated antiviral activity against adenovirus serotypes 3, 4, 8, 19, and 37 in cell culture studies
  - Povidone–iodine 0.8% may potentially reduce contagiousness in adenoviral infections.

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Chapter 60

Cryptosporidiosis

See also Chapters 19, 20, 21.

Name and nature of organism

- A gastroenteritis-like illness that is self-limiting in immunocompetent individuals.
- Caused by a protozoan parasite that infects epithelial cells.
- Most human infections are due to *C. parvum* or *Cryptosporidium hominis*.
- Infection with unusual species and genotypes can occur.

Epidemiology

- Infection occurs worldwide in adults and children, commonly in young children.
- Prevalence of infection is higher in developing countries.
- Outbreaks have followed failure of domestic water purification.
- Outbreaks can occur in institutions.
- Fewer than ten oocysts are required to cause infection.
- There are around 4000 reported cases/year in the UK.

Transmission

- Infection occurs following the ingestion of oocysts, which are shed in human or animal faeces, or via contaminated water, food, or on fomites.
- Oocysts release sporozoites, which invade epithelial cells and form trophozoites. Trophozoites then sexually or asexually reproduce and produce more oocytes.
- Symptoms occur up to 14 days after the ingestion of oocysts.
- Oocysts may be shed for 1–15 days after the resolution of symptoms.

Clinical features and sequelae

- Infection mainly affects the small intestine but can be spread throughout the GI tract.
- Asymptomatic infection can occur.
- Invasion of the luminal enterocyte border leads to villous atrophy, blunting, crypt cell hyperplasia, and mononuclear cell infiltration of the lamina propria.
- Watery diarrhoea, abdominal pain, nausea, and vomiting are the commonest features.

- Fever, anorexia, and fatigue can occur.
- Infection is usually self-limiting, lasting 10 days to 3 weeks.
- Weight loss and failure to thrive may be severe, particularly in malnourished children.
- Seronegative reactive arthritis has been reported.
- Persistent and severe infection can occur in immunocompromised patients.
- Infection outside the GI tract is rare in immunocompetent individuals.
- Biliary and pancreatic infection can lead to complications, such as sclerosing cholangitis and pancreatitis, in the immunosuppressed. Infection in the biliary tree can act as a reservoir, leading to reinfection.
- Pneumatosis cystoides intestinalis, in which gas-containing cysts develop in the bowel wall, can occur in advanced HIV infection.
- Respiratory involvement and sinusitis have been reported in the immunocompromised, but the mechanism of infection is unclear.

Diagnosis

- Microscopic examination of stool specimens for oocysts, but infection cannot be excluded by analysing one stool sample only.
- EIAs and immunochromatological tests are available to test for the presence of oocyst wall antigens.
- Improved sensitivity is obtained using immunomagnetic staining.
- PCR also gives better sensitivity and the ability to type different species.
- Oocysts can be seen on gut biopsy specimens.

Management and treatment

- Symptomatic treatment with rehydration therapy, as required.
- Drug treatment is of limited benefit. There is no curative treatment.
- Several drugs have been tested in clinical trials, including nitazoxanide, paromomycin, rifabutin, several macrolides (azithromycin, clarithromycin, and spiramycin), and the administration of bovine hyperimmune colostrums, but a Cochrane review of trials found insufficient evidence that any drug is able to reduce or cure the symptoms of *Cryptosporidium* infection or to effectively kill the organism among immunocompromised patients.[1]
- A 3-day course of nitazoxanide has been shown to reduce the duration of diarrhoea and the parasite load in HIV-negative children, but with no effect in HIV-positive children.[2]
- In the immunocompromised patient, the infection responds when the immune system recovers. Low $CD4^+$ lymphocyte counts are associated with fulminant disease.
- Relapses of infection can occur if the infection has not been completely cleared.

Prevention

- Water supplies must be well maintained and protected against environmental contamination.
- Attention to personal hygiene is the key to preventing person-to-person spread.
- Infected people should be excluded from work, school, or other institutions until 48 hours after the diarrhoea has subsided.
- Oocysts are resistant to many commonly used disinfectants, including chlorine.
- Immunocompromised patients may be advised to boil all water for drinking.

Future research

- Use of protease inhibitors in ART for HIV may have a beneficial effect in the treatment of cryptosporidiosis, above the effect on immune reconstitution, by inhibiting parasite development.
- *C. parvum* relies on inosine 5′-monophosphate dehydrogenase (IMPDH) to produce guanine nucleotides and is highly susceptible to IMPDH inhibition. Both ribavirin and mycophenolic acid inhibit IMPDH and have been shown to have dose-dependent effect on *C. parvum* development and therefore may be of potential benefit.

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Chapter 61

Cytomegalovirus

See also Chapters 10, 15, 19, 20, 31.

Name and nature of organism

- CMV is a human herpesvirus (HHV-5) of the *Betaherpesvirinae* subfamily.
- It is a large, enveloped, double-stranded DNA virus.
- 1° infection is followed by latency established primarily in cells of the myeloid lineage.
- In cell culture, infected cells swell up (cyto—cells, megalo—increase size, virus).

Epidemiology

- CMV is ubiquitous. Seropositivity increases with age and varies within and between populations. A higher prevalence is generally described in populations with lower socio-economic status. The majority of children in resource-poor countries are seropositive by 1 year of age, with a slower, more gradual increase in acquisition over time in developed countries (around 25% seropositivity by 1 year of age).
- The prolonged excretion of high levels of virus observed during the early years of childhood (whether congenitally or post-natally acquired) is thought to be a major contributor to the spread of CMV infection in the developed world, particularly in the day-care setting.
- Seropositivity in pregnant women in the UK is around 60%. In Europe, congenital infection is reported in around 3–5/1000 live births and is now the commonest congenital infection.

Transmission and incubation period

- Transmission is only from human to human and is most commonly via urine and saliva, although CMV may be detectable in many other body fluids.
- The median duration of excretion of CMV in urine in those infected congenitally/post-natally is around 4 years, and 95% of congenitally infected babies are still excreting virus at 1 year of age.
- Congenital infection is thought to be transmitted from maternal blood via the placenta and is 40 times commoner following 1° infection in the mother during pregnancy than in those who have serological evidence of previous CMV infection.
- Perinatal/post-natal acquisition may be through cervical secretions during transition through the birth canal but is more commonly due to

ingestion of infected breast milk. Rates of transmission are higher in premature and low-birthweight neonates and in those fed fresh breast milk, as opposed to frozen or pasteurized milk.
- Infection via blood transfusion was common prior to the routine use of leuco-depleted and CMV-negative blood in high-risk subjects.
- Incubation has been predicted to be around 4–8 weeks, based on studies in the settings of perinatal, post-transplant, and blood transfusion-acquired infection.
- In the case of congenital infection, it is uncertain whether there is a maternal incubation, followed by a fetal incubation period, which has implications for the diagnostic timing of the amniotic fluid.

Clinical features and sequelae

Congenital

- Congenitally infected infants are broadly categorized into those who are symptomatic or asymptomatic at birth. Around 90% of babies with congenital CMV are asymptomatic at birth, and the major concern in these babies is the 5–10% risk of developing hearing loss during the preschool years.
- Around 10% of congenitally infected babies have symptoms of CMV disease at birth, including petechiae due to thrombocytopenia, blueberry muffin rash due to extramedullary haemopoiesis, IUGR, hepatosplenomegaly, and hepatitis/jaundice. CNS features are common, including microcephaly and intracranial calcification, along with ocular abnormalities, including chorioretinitis, optic atrophy, and strabismus.
- SNHL is one of the commonest manifestations of congenital CMV infection. It can be unilateral or bilateral, fluctuates, and is progressive up to around 7 years of age. Half of babies with SNHL and CMV infection identified at birth will have no other clinical findings of CMV. SNHL may, however, be delayed in onset in around 30%, and progressive in 50%, of cases. SNHL is therefore reported by 5 years of age in around 35% of those with symptoms at birth, and about 10% of those babies with no disease noted at birth. Overall CMV probably contributes to 25% of all SNHL.
- Long-term neurological disability (excluding SNHL) is reported in around 50% of those with, and <5% of those without, symptoms identified at birth.

Post-natal

- Post-natal disease is now most commonly seen in VLBW infants on NNUs, who received CMV-infected breast milk from their mothers. It presents as pneumonitis, hepatitis, hepatosplenomegaly, lymphadenopathy, GI disease, thrombocytopenia, and a sepsis-like syndrome.
- Long-term sequelae in these babies do not, according to current literature, seem attributable to CMV infection.

Immunocompromised children

- Immunocompromised patients (usually bone marrow or organ transplant) present with generalized systemic symptoms (often referred to as CMV syndrome) or organ-specific disease (including hepatic, pulmonary, and GI manifestations, and occasionally CMV encephalitis). In the transplant group, CMV can also have indirect effects on outcomes, such as graft rejection, and risks of other opportunistic infections.

Diagnosis

Direct methods

- Direct tissue culture of body fluids has traditionally been the gold standard for identifying infection; confirmation of a positive result may take up to 3 weeks, making this method impractical for early diagnosis.
- PCR amplification of viral DNA offers a rapid alternative with similar sensitivity and specificity; methods utilizing immunofluorescent or immunoperoxidase-labelled monoclonal antibodies directed against the early antigen of CMV may also be used.
- Urine or saliva PCR is positive in up to 100% of infected individuals (although intermittent detection has been reported) and remain the diagnostic samples of choice for congenital infection.
- Isolation of CMV from a specimen acquired within the first 3 weeks of life is necessary to discriminate between congenitally and post-natally acquired infection.
- Blood PCR is only positive for CMV in around 80% of babies with CMV disease at birth. Recent data would suggest that blood samples should be taken within the first 10–14 days of life to completely exclude post-natal infection.
- Detection and quantification of virus in blood (using PCR or methods detecting the presence of CMV antigen) are important for monitoring and detecting CMV viral load early in the transplant setting. Most children are now screened weekly post-transplantation by serial blood CMV PCR.
- Identification of CMV by PCR in the amniotic fluid may establish whether antenatal transmission has occurred. Samples should ideally be acquired at least 7 weeks after maternal symptoms (if present), and after 21 weeks' gestation, to minimize false negative reports.
- Dried blood spots (Guthrie card) taken shortly after birth may be used retrospectively to confirm the presence of congenital CMV using PCR. Blood viral load is always lower than urine and saliva. The sensitivity and specificity of this method currently varies widely between laboratories, depending on the extraction methods used, the amount of starting material, and the part of the CMV genome being amplified. If dried blood spots are negative on testing for CMV PCR, congenital CMV is not excluded.

Serology

- Serology is of limited use in those under 1 year of age but may be helpful as a first step in diagnosis in older children. IgM measurement may indicate 1° infection but is only positive in around 70% of congenitally infected infants; false positive results are not uncommon, particularly during pregnancy.
- The use of IgG avidity is helpful in identifying 1° infection in adults, particularly during pregnancy, but there are no published data on CMV IgG antibody maturation in younger children. High-avidity (stickiness/efficacy) IgG shows the presence of a more mature immune response. This implies an established infection that was not recently acquired.

Management and treatment

- Congenitally infected babies should be fully evaluated for signs of disseminated and CNS CMV disease.
- Baseline investigations should include FBC, LFT, clotting (in the presence of hepatomegaly or hepatitis), ophthalmologic review, and formal audiological assessment. Renal function should also be assessed prior to starting treatment with ganciclovir. Cranial ultrasound, carried out by a skilled operator, is sufficient in the 1° assessment of an asymptomatic baby with confirmed congenital CMV infection. MRI should be performed for all symptomatic babies and is increasingly being used in asymptomatic babies, particularly if mild abnormalities on cranial ultrasound.
- Follow-up investigations should include paediatric neurodevelopmental follow-up, audiology, and ophthalmic assessments. In the UK, it is currently recommended that both symptomatic and asymptomatic babies have 6-monthly hearing assessments until 3 years old, then annual checks until 6 years old; in symptomatic babies, yearly ophthalmic follow-up until 5 years old, as late-onset chorioretinitis has been reported. Completely asymptomatic infants do not require ophthalmic follow-up after the baseline assessment.
- Antiviral treatment with the nucleoside analogue ganciclovir, given twice daily IV for 6 weeks, has been shown to decrease progression of SNHL and improve neurodevelopmental outcome in those with CNS disease if started early in neonatal life. A randomized study comparing 6 weeks to 6 months of valganciclovir, the oral prodrug of ganciclovir, in babies with symptomatic congenital CMV disease suggests that 6 months of treatment results in improved audiological and neurodevelopmental outcomes at 2 years of age. In the UK, the only clear indication for treatment in congenital CMV infection is currently symptomatic CNS disease.
- CMV viral load, FBC, and liver and renal function should be assessed regularly during treatment to assess treatment efficacy, and monitor disease progression and treatment side effects.
- Therapeutic drug monitoring can also be performed to guide management and is essential in treatment failure; however, there are

very limited pharmacokinetic data on ganciclovir and valganciclovir in premature infants and older children.
- There is at present no clear evidence for the use of antiviral treatment in post-natally infected neonates. Treatment may, however, be considered in those with severe liver disease or pneumonitis where other conditions have been excluded and the risk of treatment is balanced by the severity of disease.
- In transplant recipients and other immunocompromised children, CMV infection and disease should be screened for regularly, and pre-emptive therapy started if a positive blood CMV PCR is found, according to local protocols, in order to prevent the significant morbidity and mortality associated with CMV in these groups. Alternatively, CMV prophylaxis should be commenced and continued until the child is considered at lower risk of CMV disease.
- Side effects of standard antiviral drugs are significant, and the risks and benefits of treatment need to be discussed with families. The commonest side effects relate to bone marrow suppression (mainly neutropenia), which usually reverses on termination of therapy. The theoretical risk of longer-term side effects identified in ganciclovir and valganciclovir animal models, which include carcinogenicity and impaired fertility, is not fully evaluated in the clinical setting—no evidence has been found in limited follow-up studies.

Prevention

- Advice to CMV-seronegative pregnant women to avoid contact with potentially infected secretions in younger children has been shown to decrease transmission in the research setting. However, in most countries, women are not offered routine antenatal serological screening for CMV, as it is currently of unproven benefit for the widespread prevention of CMV disease in neonates.
- Currently, neonatal screening is not routine; however, a recent study has shown that early detection of congenital CMV infection and enhanced hearing follow-up is feasible and may enable early audiological input to maximize hearing in the prelinguistic stage.
- Antiviral treatment may also prevent hearing deterioration and lead to improved neurological function at 2 years of age.
- Preventive strategies using antiviral agents in the post-transplant period have significantly decreased morbidity and mortality attributable to CMV in this patient group.
- An effective vaccine against CMV does not currently exist, although a number of vaccine candidates are currently undergoing clinical trials.
- Randomized antenatal studies are under way of both valaciclovir and immunoglobulin in pregnant women with 1° infection, aiming to reduce vertical transmission.

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Chapter 62

Dermatophytoses: tinea capitis, corporis, pedis, and unguium

Introduction

- Dermatophyte infections are common in childhood.
- They are caused by a group of keratinophilic fungi generally causing superficial infections of the skin, hair, and nails.
- In the immunocompromised host invasive infection can occur.
- The dermatophytes are referred to as *anthropophilic, zoophilic*, or *geophilic,* depending on whether their 1° source is human, animal, or soil.
- Anthropophilic dermatophytes produce mild chronic inflammation.
- Zoophilic and geophilic dermatophytes provoke a marked inflammatory reaction.
- Infections tend to become chronic, if not treated.
- Asymptomatic carriage is relatively common.
- The clinical picture and management depend on the site involved.
- The organisms responsible vary with climatic region.

Tinea capitis (scalp ringworm)

Name and nature of organism

- *Trichophyton tonsurans*, the most prevalent anthropophilic species, is common in Europe and North America.
- *Microsporum canis*, the most prevalent zoophilic species, is found worldwide.
- *Trichophyton violaceum* and *Trichophyton soudanense*, anthropophilic organisms endemic in West and Central Africa, are increasingly reported from countries with immigration from these regions.
- *Trichophyton schoenleinii*, an anthropophilic species, causes favus, a clinically distinct form of tinea capitis, endemic to the Middle East and South Africa.

Epidemiology

- The prevalence varies between countries.
- Commonest in Afro-Caribbean children and those living in urban areas.
- Reported in 2.5% of south-east London schoolchildren.
- Disease is commonest in 3–7 year olds.

- The prevalence has increased in the past 2–3 decades.
- In North America and the UK, *T. tonsurans* is responsible for up to 90% of cases of tinea capitis, whereas previously *Microsporum* spp. predominated. This shift towards anthropophilic species has been attributed to tourism and a change in migration patterns.
- *T. soudanense* and *Microsporum audouinii* are becoming increasingly common in France, and an increase in cases of *T. schoenleinii* has been reported from the US and Spain.
- *M. canis* is still the most important organism in Europe, with the highest incidence in the Mediterranean and Eastern Europe.
- The main reservoirs for *M. canis* are cats, dogs, and a number of other mammals.

Transmission and incubation period

- Tinea capitis is highly transmissible.
- Transmission is by passage of spores (arthroconidia) or infected hairs by close, often head-to-head, contact.
- Tinea capitis frequently spreads among family members and classmates. Household contacts should be screened both for tinea corporis and capitis (present in 50% of cases).
- Viable spores can be isolated from hats, hairbrushes, combs, razors, and unwashed towels.
- The incubation period is unknown.

Clinical features and sequelae

- There are a wide variety of clinical presentations: patchy scaly alopecia (hair loss), generalized diffuse scaling of the scalp resembling dandruff, scattered pustules associated with scaling or patches of alopecia with broken-off hairs (so-called 'black dots').
- **Kerion** is an inflammatory boggy abscess—like a mass with matted hair and pus draining from several openings. Often initially misdiagnosed as a bacterial abscess, it is usually painful, associated with regional lymphadenopathy, and can heal with scarring alopecia.
- **Favus** (Latin for honeycomb) is a particular presentation, caused by *T. schoenleinii*, characterized by yellowish, circular, cup-shaped crusts (scutula), through which the hairs protrude, grouped together to give a honeycomb appearance.
- **Dermatophytid** is a pruritic papular 'id' eruption that sometimes accompanies treatment initiation. It is considered a hypersensitivity reaction to dermatophyte and should not be confused with a drug reaction. Topical corticosteroids can be used for symptomatic relief.

Diagnosis

- Diagnosis based on clinical presentation with scale and bald patches may be inaccurate and should be confirmed by microscopy and culture of hairs and scalp scale.
- Samples of scale are collected using a blunt scalpel or an edge of a microscope slide, and placed in paper card packs. Samples of affected hair can be obtained by plucking or using a sterile plastic single-use brush. Collected samples are mounted in a 10–30% potassium

hydroxide (KOH) solution, and dermatophytes are identified as hyphae or spores viewed under light microscopy.
- Fungal cultures allow accurate identification of a causative organism but can take up to 3–4 weeks for results to become available.
- Kerion sampling can be difficult, and negative cultures are not uncommon.
- Woods lamp (UV light) examination of the affected area can sometimes aid in identifying *Microsporum* spp. infection, as it produces a greenish fluorescence.
- A PCR sequencing assay for dermatophytes has been developed but is not widely available.

Management and treatment

- Topical treatment alone is insufficient to eradicate symptomatic infection.
- The treatment protocol should reflect the local epidemiology and target the most likely culprit organism.
- Griseofulvin, a fungistatic, given daily for a period of 6–8 weeks, is usually successful and has been the treatment of choice for decades. Give with a fatty meal, and continue for 1–2 weeks after clinical resolution.
- Griseofulvin is the treatment of choice for *Microsporum* spp.
- Terbinafine (an allylamine) and itraconazole (an azole) are as efficacious as griseofulvin for *Trichophyton* spp. infections. Terbinafine, a fungicidal, is preferable for *Trichophyton*, as a short treatment for 2–4 weeks is sufficient.
- There is no suspension formulation of terbinafine available. A granule formulation has been licensed for use in children over 4 years of age in the US.
- Itraconazole and fluconazole are alternate agents for treatment of *T. tonsurans* and *Microsporum* spp.
- Additional topical treatment with 2% ketoconazole and 1% selenium sulfide shampoo twice per week or topical fungicidal cream once daily for a week may aid in reducing the carriage of viable spores.
- Carriers should also be given a 2-week course of topical therapy.
- Glucocorticoid therapy in kerion might reduce itch and discomfort but has not been shown to improve cure rates or scarring.
- Cultures should be repeated after completed therapy. Treatment failures are usually caused by non-compliance, reinfection, reduced absorption of drug, or fungal resistance.

Prevention

- As symptomatic children are likely to have been infected for some time, isolation is not necessary, but treatment should be prompt.
- Hats, combs, hairbrushes, etc. should not be shared. Combs and hairbrushes should be cleansed with disinfectant.
- If the infecting agent is *M. canis*, an animal source should be sought and treated.
- Household contacts should be screened and treated, if affected.

Tinea corporis (body ringworm)

Name and nature of organism

- *Trichophyton rubrum* is the commonest cause.

Epidemiology

- Commonest in pre-adolescent children.
- Of physician visits for tinea corporis in the US, 46.0% were in those <15 years old.
- Most often in hot, humid climate.

Transmission and incubation period

- Direct contact with an infected person or animal (dogs, cats, guinea pigs, rabbits, and cattle).
- **Tinea corporis gladiatorum** refers to infection as a result of contact sports such as wrestling and judo.
- Transmission can occur through indirect contact with contaminated items such as clothing, towels, bedclothes, and chairs handled by infected people.
- Incubation period of 2–4 weeks.

Clinical features and sequelae

- Pruritic, round or oval, red scaly patches, often with central clearing, giving rise to an **annular** appearance. Fusion of plaques produces gyrate patterns.
- In tinea corporis gladiatorum, the disease is often on the head, neck, and arms, the areas likely to come into contact with the infected skin of participants in close contact sports.

Diagnosis

- Usually clinical. If any doubt or unresponsive to treatment, take skin scrapings for microscopy and culture.

Management and treatment

- Except for chronic or widespread disease, topical therapy is the first-line treatment.
- Topical terbinafine, applied as a 1% cream, gel, or solution once or twice daily for 7–14 days, results in clinical cure rates ranging from 75% to 84%.
- Treatment with a combination topical antifungal/corticosteroid cream is best avoided, as it can prolong the course of therapy for months. It suppresses the inflammation, but the infection may not be cleared.
- If unresponsive or widespread disease is present, use an oral antifungal agent.

Prevention

- Clothing, towels, bedding, etc. should be carefully washed and not shared with infected individuals. Exclusion from school is not necessary.

Tinea pedis (athlete's foot)

Name and nature of organism

- *T. rubrum* and *Trichophyton interdigitale* are the commonest causes.

Epidemiology

- There has been a global increase in tinea pedis due to urbanization and use of sports and fitness facilities.

Transmission and incubation period

- Spread by sharing infected towels, socks, etc., as well as walking barefoot on an infected surface.
- Incubation period is 2–3 weeks.

Clinical features and sequelae

- Typically dry scaling or maceration, cracking, and fissuring of the skin in the webbing between the toes, associated with pruritus.
- Less commonly, there may be a more diffuse scaling pattern, involving the sole and side of the foot (moccasin type). May also have vesicles and blisters.

Diagnosis

- Usually clinical, with microscopy and culture if unresponsive to treatment.

Management and treatment

- Topical treatment is usually adequate, the most effective agent being terbinafine. Other topical agents, such as azoles, butenafine, and tolnaftate, are also effective. Relapse is common.
- Of oral treatments, griseofulvin has been the traditional mainstay, but newer treatments, such as terbinafine and the azoles, have a higher cure rate. On the basis of limited comparative data, terbinafine appears the most efficacious.

Prevention

- Avoidance of occlusive footwear and careful drying of feet after washing, especially between the toes.
- Use of powder to prevent maceration, antifungal powders.
- Infected feet should be covered when walking in public places.

Tinea unguium (onychomycosis)

Name and nature of organism

- Onychomycosis refers to nail infection caused by fungi, including dermatophytes, non-dermatophyte moulds, and yeasts.

Epidemiology

- Onychomycosis in children is relatively uncommon with prevalence rates of 0.5–2.6%.
- Predisposing factors include occlusive footwear, immunosuppressive conditions, diabetes mellitus and Down's syndrome.
- Toenail onychomycosis is most commonly due to dermatophytes (*T. rubrum*), whereas fingernail onychomycosis is more likely to be caused by yeasts.

Clinical features and sequelae

- Onychomycosis is classified clinically as distal and lateral subungual onychomycosis (DLSO), superficial white onychomycosis (SWO), proximal subungual onychomycosis (PSO), candidal onychomycosis, and total dystrophic onychomycosis.
- In DLSO, infection starts at the distal end of the nail bed, often laterally, and spreads proximally, causing hyperkeratosis and onycholysis (separation of the nail plate from the nail bed). *T. rubrum* is the cause in the majority of cases. Tinea pedis nearly always affects the surrounding skin.
- SWO is less common and affects the nail plate, rather than the nail bed. The surface of the nail is white and flaky. Tinea pedis is not usually present. It is usually due to *Trichophyton mentagrophytes* var. *interdigitale*.
- *Candida* infection of the nail can either cause paronychia (swollen, tender, and red proximal nail fold), distal nail infection, or total dystrophic onychomycosis (grossly thickened and hyperkeratotic nail; associated with chronic mucocutaneous candidiasis or APECED syndrome).

Diagnosis

- Other causes of dystrophic nails that are clinically indistinguishable from onychomycosis include psoriasis, eczema, trauma, and congenital dystrophies.
- In children, only 15% cases of nail dystrophy are of fungal origin, and laboratory diagnosis is therefore required to establish a presence of fungus.
- Subungual debris taken from the most proximal part is the most likely to yield viable hyphae.

Management and treatment

- As the nail plate in children is thin and grows faster than in adults, topical treatment can be used. However, it should only be used for SWO or very limited DLSO. The main preparations used are tioconazole and amorolfine.
- Systemic drug therapies for treatment of onychomycosis are currently not licensed for use in children, although the efficacy and safety profiles of terbinafine, itraconazole, and fluconazole appear similar to those in adult population.
- Oral therapy with terbinafine or itraconazole has higher cure rates than griseofulvin. Both terbinafine and itraconazole are retained in the nail plate after treatment cessation.

- Itraconazole can also be administered intermittently in pulses; 5mg/kg/day of itraconazole for 1 week every month is recommended for 2 months for fingernail infection, and 3 months for toenail infection.
- Terbinafine should be given for 6–8 weeks (fingernails) or 3–4 months (toenails).
- Combination therapy with both oral and topical drugs may result in faster clearance and improved cure rates.

Prevention

- Exclusion from school is not necessary.
- Tight footwear and trauma to the nails predispose to tinea.

Future research

Recent research advances in the molecular biology and genetics of dermatophytes will enable the study of the pathogenicity, host, and environmental adaptation mechanisms and allow the development of better therapeutic approaches. RCTs are needed to assess the optimum treatment duration with systemic antifungals in children.

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Chapter 63

Diphtheria

See also Chapters 13, 35, 42, 44.

Name and nature of organism

- An illness that may involve almost any mucous membrane and the skin and is caused primarily by toxigenic strains of *C. diphtheriae*, an aerobic Gram-positive, non-spore-forming pleomorphic rod.
- Main toxin is an exotoxin that consists of an active A domain and a binding B domain, which facilitates entry of toxin A into the cell. The A subunit inhibits protein synthesis, which has pathological consequences for many cell types.
- Toxin production (toxigenicity) occurs only when the bacillus is itself infected (lysogenized) by a specific virus (bacteriophage) carrying the genetic information for the toxin (tox gene).
- Non-toxigenic strains of *C. diphtheriae* can cause respiratory tract infections, as well as (more rarely) cases of endocarditis or other forms of invasive disease.

Epidemiology

- Epidemiology has been markedly altered by the advent of vaccination in developed countries.
- In resource-poor countries, diphtheria remains a serious problem, with major outbreaks occurring in Africa, Latin America, and Asia; in addition, states of the former Soviet Union have been reporting large outbreaks in the 1990s, only controlled by widespread immunization of both adult and child populations.
- According to WHO health statistics, a total of <5000 cases of diphtheria are currently registered worldwide per year, of which <50 occurred in Europe and North America.
- Although diphtheria is preventable by vaccination, the disease is thought to persist because of regional variations in vaccine compliance, inadequate booster regimens, and immunosenescence.
- Humans are the sole reservoir of *C. diphtheriae*.
- Peak season for respiratory disease is autumn and winter in the northern hemisphere.
- Unimmunized individuals are more prone to severe disease. However, even immunized persons may become asymptomatic carriers or have mild disease. Therefore, infection control precautions need to be taken, even with immunized individuals who have been exposed to an index case.

- Immunity to diphtheria depends mainly on the presence of antitoxin antibodies (IgG), and levels ≥0.1IU/mL are associated with long-term protective immunity.
- If untreated, the mortality rate may be as high as 20% in developing countries

Transmission and incubation period

- Spread of the organism is mostly from respiratory droplets or contact with skin lesions.
- Incubation period is 2–5 (range 1–10) days.

Clinical features and sequelae

- Early symptoms of pharyngeal diphtheria are generally non-specific. Fever is not a major feature of the disease, even though patients frequently appear toxic and with cardiovascular instability during the illness.
- Early on, the pharynx may appear slightly injected; within 1–2 days, patches of exudate appear and may form a leathery-looking membrane covering the oropharynx. This membrane is highly adherent; attempts to remove it will result in bleeding.
- The neck may appear swollen and indurated, with enlargements of the anterior cervical lymph nodes (so-called 'bull neck appearance').
- Major risk of this infection is respiratory failure due to obstruction of the upper airway, which may require surgical intervention. Pneumonia and lower respiratory tract obstruction may also occur, presumably if the membrane gets dislodged accidentally.
- Although clinical toxicity is not uncommon, bacteraemia is rare with toxigenic isolates.
- Toxin-mediated 2° damage to other organs may occur, especially the myocardium (myocarditis/cardiomyopathy is a leading cause of death due to arrhythmias and heart failure), the kidneys (proteinuria), and the peripheral nervous system (peripheral neuropathy, motor more than sensory, generally several days to weeks after the onset of infection). Many of these symptoms have been ascribed to the effects of the diphtheria toxin.
- It is important to remember that 1° sites, other than the oropharynx, may be involved; respiratory tract, conjunctivae, and vaginal infections have all been reported.
- Cutaneous infections are characterized by chronic non-healing ulcers, often associated with *S. aureus* or GAS infections. Common sites of lesions are the hands, feet, and/or lower legs.

Diagnosis

- Diagnosis of diphtheria is usually made on the basis of clinical presentation, since it is imperative to begin presumptive therapy quickly. Specimens should be obtained for culture from the appropriate site(s): oropharynx, nose, skin, or other mucosal site. Ideally, material from below the membrane or the membrane itself should be submitted for culture, as these materials have the highest yield. Alerting the laboratory of the possibility of diphtheria is critical, as the organism requires a special medium (tellurite) for growth.

Management and treatment

- For patients with respiratory diphtheria, there is a substantial risk of rapid decompensation. For this reason, the mainstay of therapy for respiratory diphtheria is the IM or IV administration of 10 000–100 000IU of equine diphtheria antitoxin (the dose depending on the extent of the infection) when cases are suspected, even prior to bacteriological confirmation. This treatment is not without risks, as allergic reactions to horse proteins are not uncommon; skin testing for sensitivity to equine proteins is generally recommended.
- Antimicrobial therapy should also be administered. Generally, macrolides (clarithromycin) or benzylpenicillin for 14 days is recommended. While treatment with antibiotics probably reduces toxin production, helps to eradicate the organism, and reduces carriage, it is not a substitute for antitoxin therapy and is an adjunctive therapy. *In vitro*, other macrolides are equally active against *C. diphtheriae* and thus could be also used for treatment and prevention. Disease does not necessarily confer long-lasting immunity; therefore, convalescent patients should receive active immunization.
- In general, two follow-up cultures are recommended, following completion of therapy, to confirm eradication. Should either of these cultures be positive, a new 14-day course of appropriate therapy should be initiated.
- Patients should receive toxoid immunization in the convalescent stage of the disease, because clinical disease does not always induce adequate levels of antitoxin.
- Isolation of index cases is very important, as is informing local public health officials.
- Droplet precautions should be used with any patient with suspected diphtheria or carriers with pharyngeal diphtheria, until confirmation of negative cultures after antibiotic therapy has been completed. Contact precautions are recommended for patients with cutaneous diphtheria.

Prevention

- The mainstay of prevention is through active immunization with diphtheria toxoid-containing vaccines, beginning in infancy. Periodic booster doses are required to maintain immunity in adulthood. In some countries, regular booster doses, given every 10–20 years, are recommended. National guidelines should be followed when making decisions on immunizations of adolescents and adults.
- Immunization of previously unimmunized asymptomatic carriers are also recommended; for those who have been immunized, but have not received a booster within 5 years, a booster should be administered as well.
- Interestingly, although few would doubt the efficacy of active immunization, there has never been a carefully controlled diphtheria vaccine clinical trial demonstrating effectiveness.
- While some bacterial conjugate vaccines (e.g. Hib, pneumococcus, meningococcus) contain small amounts of diphtheria toxoid (e.g. in the form of CRM197 protein) as protein carriers, these vaccines should not be viewed as substitutes for diphtheria immunization.
- **For close contacts**, the following steps are recommended:
  1. Surveillance for 7 days
  2. Attempt to culture the organism from the oropharynx
  3. Initiation of antimicrobial prophylaxis with clarithromycin or penicillin for 7 days if cultures remain negative. Those with positive cultures should be treated for 10 days with erythromycin as the first-line treatment of choice
  4. Those whose immunization status is incomplete or unclear should promptly receive a dose of toxoid appropriate for their age.

Future research

- Development of humanized monoclonal antibody against diphtheria toxin.
- In an era when a high proportion of adults have diphtheria toxin antibody levels likely below protective levels due to waning immunity, the importance of good surveillance should be emphasized in most European countries.

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Chapter 64

Enteroviruses (including rhinoviruses) and parechoviruses

See also Chapters 10, 14, 29, 30, 71, 102.

Name and nature of enteroviruses

- Enteroviruses are RNA viruses with a positive single-stranded genome of approximately 7kb. The positive-sense genome can direct translation straight from its genetic material, and the viral RNA is capable of acting as infective material in isolation.
- The translation machinery of infected cells is hijacked, such that protein synthesis becomes almost entirely dedicated to viral protein synthesis. The viral RNA encodes four structural capsid proteins and seven non-structural proteins; the capsid proteins define the virus type.
- The current classification (see http://www.picornaviridae.com) defines 12 species (*Enterovirus A–H, J*; *Rhinovirus A–C*), based on capsid sequence homology.
- The enterovirus and rhinovirus species include more than 100 different types (strains), encompassing the historic division into Coxsackie A, Coxsackie B, polio, and echoviruses. Newer enterovirus types are named with sequential numbers (onwards from enterovirus EV68).

Epidemiology

Enterovirus and rhinovirus species are responsible for more episodes of human infections than any other pathogen. Humans are the only natural hosts for the species *Enterovirus A–D* and *Rhinovirus A–C*. Enteroviruses are environmentally stable and are widely prevalent. They can be found on surfaces and in (waste) water.

Enterovirus A–D

- Most enteroviruses have a worldwide distribution, but disease phenotypes may vary regionally.
- Enteroviral infections are associated with seasonal summer outbreaks in some years, on a background of year-round infection.
- Recent UK data, based on laboratory-confirmed clinically significant enterovirus infections, found an annual incidence of 2.7/100 000, with a 7-fold higher incidence in children and infants <3 months accounting for a quarter of all disease. These data, based on voluntary submissions to the PHE database, underestimate the true burden of disease.

- Prevalence studies indicate that some subtypes are stable, whereas others fluctuate in prevalence, with epidemics occurring when a virus moves back into a non-immune population. Particular types may be absent for decades, then suddenly produce new outbreaks. Enterovirus 71, for example, has been associated with cyclical outbreaks with considerable morbidity and mortality in the Asia Pacific region.
  - In the 1998 Taiwan epidemic, the peak incidence was 37.1/100 000 in children aged 6–11 years.
  - China: a study of 7 million HFMD cases reported 500–900 deaths annually during 2010–2012, predominantly among young children. Overall, the case fatality, case severity, and severe case fatality rates were 0.03%, 1.1%, and 3.0%, respectively. Illness severity and death were strongly associated with EV71 and inversely related to age.
  - Vietnam and Singapore: serological studies showed a prevalence of neutralizing antibodies of up to 80% around age 5.
- Another example is EV-D68 which caused outbreaks of severe respiratory infection in the US and Canada during 2014.

Rhinovirus A–C

- Rhinovirus infections are prevalent worldwide and throughout the year, with a peak during autumn. They are the commonest cause of viral infection and responsible for more than half of all common colds.
- An Edinburgh study of the disease burden of respiratory viruses in hospitalized patients found that rhinoviruses were the leading cause of disease in immunocompromised patients.

Transmission and incubation period

Enterovirus A–D

- Enteroviruses are stable for several days at room temperature and are resistant to alcohol-based cleaning products. They are inactivated rapidly by heat (>56°C) and dilute chlorine-based products.
- Enterovirus A–D are acid-resistant, and therefore can pass the human stomach and replicate in the gut.
- Spread is primarily faecal–oral, but transmission through fomites or droplets has been described, and transmission is higher with overcrowding and poor hygiene.
- The incubation period for most infections is 3–10 days. Transmission is difficult to break, because patients shed the virus before they are symptomatic, and asymptomatic shedding can continue from the throat (for weeks) and the stool (for months) after infection.

Rhinovirus A–C

- Infection is transmitted by contact or aerosols through the intranasal and conjunctival, but not oral, route.
- The virus may be detected on the hands during infection and transferred from upper respiratory secretions, and efficient transmission can occur hand-to-hand or via other surfaces.

Natural history of infection

Enterovirus A–D

- Enteroviral infection, following oral entry, leads to local invasion of the pharynx and alimentary tract, followed by haematological spread of the virus. Congenital infection may occur this way.
- Symptoms may be determined by the tropism of the enterovirus. For example, infections with a neurotropic virus manifest with CNS symptoms.
- The virus is typically cleared by an antibody response, with levels of the virus starting to decrease after about 7 days.
- Immunopathology: cellular damage is thought to have both a viral cytopathic and a host immunopathological component, although the relative contribution of each remains unclear.
- *In vitro* infection of cell cultures and murine models provide evidence for a strong role for cytopathic effects in neurological damage, pancreatitis, and myocarditis.
- Murine models indicate that activation of innate immune responses is mediated via pattern recognition molecules such as TLR3.
- The adaptive immune system is thought to be important in the control of enteroviral infection. A humoral response is associated with viral clearance, but the $CD8^+$ T-cell response may contribute to long-term inflammatory damage following encephalitis.

Rhinovirus A–C

- Asymptomatic infection is common—present in a third of children in one study. It may reflect a prodromal phase, an asymptomatic infection, or a prolonged shedding phase after a symptomatic infection. Frequency of rhinovirus detection is similar in children hospitalized with respiratory infections and in healthy children.
- Rhinovirus is a significant upper and lower airway pathogen. In upper airways, direct cytopathology is not observed, and symptoms are driven by the immune response. It is unclear whether cytopathology or host immunopathology are responsible for symptoms in LRTIs.
- The virus enters cells after binding surface receptors, including ICAM-1. Rhinovirus is detected by pattern recognition receptors, including TLRs, RIG1, and MDA5, which can stimulate an NFκB-driven immune response.

Clinical features and sequelae

- Clinical features of the seven enterovirus species causing human disease are summarized in Table 64.1.

Enterovirus A–D

- Enteroviruses are associated with a wide range of clinical presentations, including mild URTIs, herpangina, conjunctivitis, HFMD (see Chapter 71), meningitis, and rarely with flaccid paralysis, pleurodynia, and encephalitis. Most infections are self-limiting and mild, but serious, and sometimes fatal, enteroviral disease continues to pose a serious problem as no effective treatment exists.
- Symptoms, in part, reflect the particular viral species and subtype, though there is considerable overlap.

Table 64.1 Classification of enteroviruses

Species	Types	Notes on clinical manifestations
EV-A	Coxsackie viruses A2–8, A10, A12, A14, A16	EV-A is associated with maculovesicular rashes, particularly HFMD in infants and young children, mild URTIs, conjunctivitis, pharyngitis, and herpangina
		A16, A10, A5 associated with HFMD
	EV71, 76, 89–91	EV71—causes HFMD (see Chapter 71) and outbreaks of severe disease in the Asia-Pacific region
EV-B	57 types	EV-B is responsible for most serious infections (except polio), including aseptic meningitis in infants and young children, neonatal sepsis, chronic enteroviral meningitis in agammaglobulinaemic children, and more rarely with myocarditis and pleurodynia (Bornholm disease)
	Coxsackie B viruses 1–6	Pharyngitis often the presenting feature—typically injected and sometimes with exudate
	All echovirus types	Severe disease associated with focal pneumonitis, meningitis (B5), pleurodynia (B3 and B5), myocarditis, and pericarditis (B5)
	Coxsackie A9	Rarely fatal; hepatic necrosis with some echoviruses; echovirus E3 associated with wandering myoclonus; E6 with myocarditis; E9 is highly prevalent, causing a febrile illness with a petechial exanthem or aseptic meningitis. Coxsackie A9 is associated with meningitis
	EV69, 73–75, 77–8, 100–1	
EV-C	14 types	EV-C includes polioviruses and other types rarely associated with severe disease
	Coxsackie A viruses (A1, 11, 13, 17, 19–22, 24)	A24 associated with haemorrhagic conjunctivitis
	Poliovirus types PV 1–3	Poliovirus infection is mostly asymptomatic but can cause meningitis and acute flaccid paralysis (see Chapter 96)
EV-D	Three types—EV68, 70, 94	EV68—outbreaks of respiratory illness
		EV70—epidemic haemorrhagic conjunctivitis
		EV94—flaccid paralysis
RV-A, B	>100 serotypes	Epidemiology and clinical spectrum similar for RV-A and B
RV-C		RV-C variably reported as causing more severe disease than RV-A or B, with frequent viraemia, and a more potent trigger of asthma exacerbations. There is a stronger association between early life infection and later development of recurrent wheeze

HFMD, hand, foot, and mouth disease.

- Asymptomatic infection: serological studies indicate that there is a high level of unrecognized infection. Overall, approximately 50% of infections are asymptomatic, rising to 90% for some such as Coxsackie A16 in those <5 years.
- Non-specific febrile illness: this is the commonest manifestation of enterovirus infection, with abrupt onset of fever with headache. Sore throat, without any observable inflammation, and conjunctivitis may be present. In infants and young children, the clinical picture typically includes fever, minor URTI symptoms, mild vomiting and loose stools, irritability, and minor macular rash; recovery usually occurs within a week.
- GI symptoms are common; this is unsurprising, given the tropism of enteroviruses for the gut.
  - Typical symptoms include diarrhoea, vomiting, constipation, and abdominal pain, but, in most cases, GI symptoms form only part of the illness. Rarely, more serious sequelae occur, including intussusception, hepatitis, pancreatitis, and peritonitis.
- Skin exanthems: enteroviruses cause a range of exanthems: macular, maculopapular, petechial, or morbilliform. Large blotchy papules are often seen in babies, around 10–20 on the trunk and body.

Rhinovirus A–C

- Upper respiratory infections include the common cold and AOM.
- Lower respiratory infections: bronchiolitis is the commonest clinical presentation in hospitalized children with rhinovirus. Although frequently detected in children hospitalized with pneumonia, it is difficult to tease apart the role of rhinoviruses from bacterial pathogens.
- Rhinoviruses are triggers of asthma exacerbations. Symptomatic rhinovirus infection in infancy is associated with later development of recurrent wheeze and, in the case of RV-C, with asthma.

Neurological manifestations: meningitis

- Meningitis is the commonest neurological manifestation, most often diagnosed in the neonatal period and in infants and young children. Meningitis is most often caused by EV-B.
  - CSF findings are typical for a viral meningitis, including proportionately lower neutrophils, higher lymphocytes, slightly raised protein, and normal glucose and lactate.
  - Enteroviral detection in CSF is more likely in patients with a greater CSF leucocytosis.
  - Enteroviral meningitis is generally self-limiting, with resolution of symptoms within 1–2 weeks.
  - The prognosis is much better than for bacterial meningitis, and follow-up studies of developmental outcome inconsistently report a mild impairment in a minority of children.
  - Appropriate advice for parents is that their child has had meningitis and that the great majority of children after viral meningitis are completely normal, but some more subtle effects on school learning cannot be ruled out. Long-term routine clinic follow-up is not warranted in the absence of clinical concerns, but early referral to a psychologist for detailed assessment may be useful if the child has any schooling difficulties years later.

Neurological manifestations: encephalitis—enterovirus 71

- This type has been associated with epidemics of severe disease. Typically, EV71 causes self-limiting HFMD in children under 5, but a proportion of children develop neurological complications, caused by invasion of a part of the brainstem where the autonomic nervous system (vagus nucleus) is regulated, leading to hypertension, tachycardia, and often fatal neurogenic pulmonary oedema and vasomotor collapse.
- From the late 1990s onward, there have been large outbreaks (up to 1.5 million cases) of severe disease in the Asia-Pacific region, including China, Malaysia, and Vietnam. Long-term neurological and neurodevelopmental sequelae have been described after EV71 encephalitis and cardiopulmonary failure.

Neurological manifestations: flaccid paralysis

- The tropism of poliovirus for the anterior horn cells explains the paralysis seen in polio infections. Rarely, non-polio enterovirus infections cause paralysis.

Other manifestations

- Herpangina—a painful blistering eruption of the mucosa at the rear of the palate and around the tonsilar fauces, typically caused by EV-A.
- Pleurodynia (Bornholm disease)—an epidemic disease with fever and acute inflamed, painful intercostal muscles. Spasmodic, sometimes severe, pain is experienced in the upper chest or abdomen, lasting minutes to hours, exacerbated by deep inspiration. There may be associated muscle tenderness. Children may also experience anorexia, nausea, vomiting, headache, and sore throat.
  - The course may be biphasic, with episodic pains recurring after the initial febrile episode, lasting a couple of weeks overall.
  - Although many enteroviruses have been described as causing pleurodynia, EV-B types are the commonest, particularly Coxsackie B3 and B5.
- Myopericarditis—though many enteroviral types have been occasionally implicated, EV-B types are the commonest causes of myocarditis.
  - Manifestations range from arrhythmia to ventricular failure and death. In neonates, the disease can be particularly severe. Active young teenagers can develop acute chest pain or heart failure, and may be diagnosed late.
- Haemorrhagic conjunctivitis—both EV70 (EV-D) and Coxsackie virus A24 (EV-C) cause epidemics of haemorrhagic conjunctivitis.
  - The illness is spread by direct inoculation to the eye, rather than by haematogenous spread, following oral entry. Eye pain, photophobia, blurred vision, and erythematous congestion are seen. Resolution by day 7 is typical.
- Enterovirus infection and diabetes—susceptibility to type 1 diabetes is known to have a strong genetic component, with linkage to HLA polymorphisms, but an environmental infectious trigger of autoimmunity to pancreatic β cells is suspected.
  - Enteroviruses, particularly Coxsackie virus B4, may act as such a precipitant. Although several studies have identified genomic enteroviral RNA in the blood of patients with type 1 diabetes, as yet, there is no convincing evidence of a direct link between enteroviral infection and diabetes onset.

Neonatal disease

- Neonatal disease may arise transplacentally during maternal viraemia, or by oral inoculation during labour or in the neonatal period. There is often a history of recent maternal viral illness.
- Most neonatal infections are not clinically significant, but a minority causes a severe sepsis-like illness, resembling disseminated HSV disease, with fever, poor feeding, abdominal distension, irritability, rash, and hypotonia. Blood indices include neutrophilia and thrombocytopenia, although with typically lower CRP than in bacterial sepsis.
- Respiratory, GI, hepatic, cardiac, and CNS complications can follow, and, in meningo-encephalitis, CSF pleocytosis does not always develop, although white matter changes are generally seen on cranial imaging.
  - A worse prognosis is associated with prematurity, maternal illness at time of birth, onset of symptoms during the first week of life, and absence of transplacental transfer of maternal antibody. Death is commoner in babies with acute hepatic failure and coagulopathy, particularly if myocarditis is also present. Long-term sequelae are commoner in those with encephalitis.
  - EV-B types, including echovirus E11 and Coxsackie viruses B2–B5, are most often responsible for symptomatic infection, with B4 associated with more severe disease.

Diagnosis

- Reverse transcriptase PCR (RT-PCR) is now the most commonly used diagnostic tool for entovirus and rhinovirus disease, and has replaced the use of virus isolation for clinical diagnostics.
- Stool (rectal swabs) and upper respiratory tract secretions (throat swabs or aspirates) provide useful samples for enteroviral detection. CSF, vesicle fluid, pericardial fluid, myocardial biopsy, and blood can also be tested. As enteroviruses may be shed asymptomatically or post-infection in respiratory secretions and stool, caution should be exercised in interpreting positive stool enterovirus PCR results.
- The usefulness of serological tests for enteroviruses is limited by the heterogeneity of the antibody response, which is type-specific but may cross-react. Serology is rarely helpful as a screening tool.

Management and treatment

Enterovirus A–D

- Enteroviral infections are generally self-limiting and require no specific treatment other than supportive care. However, although there is a need for specific antiviral treatment of severe disease, there is currently very limited evidence to support the use of any available treatment.
- IVIG has been used as supplementation therapy, with limited effect in neonates and agammaglobulinaemic patients. There is no evidence for its use in other severe enteroviral conditions, including severe

EV71-associated HFMD, although its use is widespread and mentioned by national and WHO guidelines.
- Pleconaril is one of a number of antivirals that target the relatively conserved VP1 capsid protein and block the unfolding of RNA. It has good *in vitro* activity against enteroviruses and good oral bioavailability, but, despite initial promise, clinical experience showed only a modest effect in adult meningitis and no effect in a small RCT in infants. The drug is not currently available, but a trial in enteroviral disease is ongoing. Rupintrivir and vapendavir have shown anti-enteroviral activity *in vitro* and are being clinically evaluated.
- Interferon beta—in a small trial of adult patients with dilated cardiomyopathy and persistent myocardial viral replication by enterovirus or adenovirus, a 6-month course of Interferon beta was associated with enteroviral clearance in all patients, and haemodynamic improvement in 14 of 22 patients. A larger randomized, placebo-controlled study was then started. However, there are no paediatric data on the role of Interferon beta.

Rhinovirus A–C

- No specific antiviral agents are available.
- A trial of pleconaril nasal spray is under way but has not been reported.
- Phase 2 trials of vapendavir found it was safe and efficacious at reducing symptoms during rhinoviral exacerbations of asthma in adults.
- A Cochrane meta-analysis of *Echinacea* does not support its use for treatment or prevention.

Prevention

Enterovirus A–D

- Prevention should be aimed at breaking the cycles of oro-faecal, droplet, and fomite/surface transmission.
  - Frequent handwashing of children and adult caregivers and applying hygienic measures when changing diapers, particularly in nurseries/day-care centres, prevent transmission of enteroviruses.
  - Frequent cleaning of toys and surfaces that are touched and shared by children, also in particular in nurseries/day-care centres.
- Continued clinical and laboratory surveillance of enteroviral disease is required, so that appropriate measures can be implemented early in outbreaks of severe disease, as seen, for instance, in Singapore with EV71 where early reporting from childcare centres of HFMD led to local actions to contain further spread, including closure and cleaning.
- Inactivated vaccines for EV71 have been developed in China and have shown 95% protection against EV71-associated HFMD in three recently published phase 3 trials. Regional implementation and follow-up studies will show whether it also provides protection against severe disease.

Rhinovirus A–C

- Hand-to-hand transmission of rhinoviruses can be reduced by improved hand hygiene, particularly in children.
- Masks can reduce transmission of respiratory viruses.

Future research

- Virus biology—it is unclear why some enterovirus types are associated with more severe disease, whether this is mediated by host or viral genetics or immune pathology.
- Virus epidemiology and surveillance—the significant impact of outbreaks of EV71 in the Asia-Pacific region emphasizes the importance of understanding the epidemiology, so that future epidemics can be anticipated.
- Vaccines—➔ see Prevention, p. 531.
- Treatment—the usefulness of pleconaril and other antivirals is a field of active research.

Human parechoviruses

- *Parechovirus* is another genus of *Picornaviridae*. Seven types cause human disease: *human parechovirus 1* to 7 (HPeV1–7).
- Parechoviruses are environmentally stable and widely prevalent. After replication in the gut, the virus is shed in stool, and infection is transmitted by the faecal–oral route.
- HPeV1 causes clinically apparent infections in early childhood after the protective effect of maternal antibody has waned, with a median age at infection of 18 months, particularly in late summer to early winter; almost all adults have antibodies against HPeV1. HPeV1 seropositivity is the highest, followed by HPeV3, 4, and 6.
- Mild GI and respiratory symptoms are commonest. Although rare, severe disease has been described, for instance, an outbreak where six patients developed flaccid paralysis. Myocarditis and encephalitis have also been described.
- Neonatal infection is characterized by a severe sepsis-like syndrome, clinically similar to severe enteroviral infection, which can require intensive care. HPeV3 is associated with more severe disease.
  - High fever, marked CNS irritability and seizures, and a rash or generalized redness can be presenting features. The CRP typically remains low.
  - Although CSF pleocytosis rarely develops, meningo-encephalitis is common, and white matter changes are commonly evident on cranial imaging. Neurodevelopmental outcome can be poor. Myocarditis is seen rarely.
  - There have been several outbreaks on neonatal units of necrotizing enterocolitis and pneumonia in association with HPeV1.
- Diagnosis is best made by RT-PCR from blood, stool, respiratory samples, or CSF. As with neonatal enterovirus infections, treatment of serious disease with IVIG has been tried, although further data are needed to support this approach.

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Chapter 65

Rhinovirus

Name and nature of organism

- Rhinoviruses are non-enveloped RNA viruses with a linear, single-stranded, positive-sense genome. The single gene is translated to a protein which is further processed into four structural, and seven non-structural, proteins.
- Rhinoviruses are classified in the genus *Enterovirus* in the family *Picornaviridae*. Three species A, B and C include ~160 rhinovirus types. Antigenic diversity among virus types is high.
- Most rhinoviruses (species A and B) use intercellular adhesion molecule-1 as their cellular receptor, and a minor part uses low-density lipoprotein receptor. The recently recognized species C rhinoviruses are not cultivable by standard methods, and their receptor is unknown.
- Rhinoviruses replicate primarily in the nasopharyngeal and nasal epithelium, but they can spread to the lower respiratory tract. Rhinovirus infection is perhaps the commonest of all acute infections in humans. There is no animal reservoir.

Epidemiology

- Rhinoviruses circulate in the population around the year. In temperate climates, epidemic seasons are in the autumn (September to November) and spring (May), but infections with lower frequency are seen also during other seasons.
- Several different rhinovirus types circulate simultaneously in communities. An infection induces the production of secretory and serum antibodies that are partially protective against the same virus type, but not against other types. Because of the high number of rhinovirus types, recurrent infections are common.
- Illnesses caused by rhinovirus species B are usually mild and not as frequent as those caused by species A or C.
- Rhinovirus infections are commonest in young children. Rhinovirus can be detected in more than half of children with symptoms of acute respiratory tract infection and also in a substantial proportion of children without symptoms. Children have typically several rhinovirus infections per year, and adults at least one infection per year.
- Rhinoviruses cause a wide range of clinical presentations, but the majority of cases in children and adults are URTIs such as the common cold. Subclinical infections do occur, but chronic carriage is not seen in immunocompetent individuals.

- The annual incidence of hospitalization associated with rhinovirus infection is five per 1000 children under 5 years of age, according to studies in the US. The rate of hospitalization is highest in infants younger than 6 months of age. The most frequent clinical manifestations in hospitalized children are bronchiolitis, recurrent wheezing, asthma exacerbation, pneumonia, and a non-specific febrile illness. Children with a history of wheezing have an increased risk of hospitalization.

Transmission and incubation period

- Rhinoviruses are secreted in large quantities from the nose. Virus shedding is highest during the first days of symptoms and continues usually for 1–2 weeks. The shedding may be longer in infants, and immunodeficient persons may shed rhinoviruses for extended periods.
- Hand-to-hand contact, or hand contact via fomites, followed by self-inoculation to the nose or conjunctiva, is considered to be an important mechanism of transmission. Direct transmission via large or small droplets can also occur. Transmission is efficient between close contacts in families with young children and in day-care centres with large groups of children. A proportion of rhinovirus infections remain asymptomatic.
- The incubation period is usually 1–4 days.

Clinical features and sequelae

- Common cold, otitis media, and rhinosinusitis.
  - Rhinoviruses are the most frequent causative agents of the common cold in all age groups. Typical symptoms in children are nasal obstruction and discharge, sore throat, cough, poor feeding, and fever. Symptoms, such as rhinorrhoea and cough, usually last for 1–2 weeks.
  - A large proportion of otitis media cases in children occur in association with a rhinovirus infection. AOM develops during the course of the viral infection and is often a viral–bacterial co-infection.
  - URTI caused by rhinovirus is frequently associated with rhinosinusitis which is, in most cases, self-limiting. The predominant symptoms are nasal congestion and mucopurulent rhinorrhoea. In uncomplicated rhinosinusitis, ultrasound or X-ray findings are non-specific, and thus they are not recommended. Severe symptoms suggest a concomitant bacterial sinusitis.
- Bronchiolitis and recurrent wheezing.
  - Rhinovirus is, after RSV, the second most frequent causative agent of bronchiolitis in infants. The signs and symptoms include increased respiratory rate, respiratory difficulties, wheezing or crackles in auscultation, poor feeding, and fever. The risk of developing asthma in the future is higher after rhinovirus bronchiolitis than after RSV bronchiolitis.

  - Rhinoviruses cause the majority of recurrent wheezing illnesses and asthma exacerbations. The clinical presentation is expiratory obstruction and wheezing, in association with symptoms of an acute respiratory tract infection. Children with risk factors for asthma (atopy, parental asthma) are at increased risk of wheezing illnesses caused by rhinovirus.
- Pneumonia.
  - Rhinoviruses can cause sole viral pneumonia, but often pneumonia is a viral–bacterial co-infection caused by rhinovirus and *S. pneumoniae* or other bacteria.
  - Rhinovirus-associated pneumonia cannot be clinically differentiated from pneumonia caused by other agents.
- Chronic infection in immunocompromised subjects.
  - Rhinoviruses have been reported to cause chronic and severe infections in prematurely born infants and in individuals with primary immune deficiencies or lung transplantation.
- Asymptomatic infections and co-infections.
  - A substantial proportion of healthy children (10–30%) are positive for rhinovirus at the time of sampling. This is due to frequent infections by different rhinovirus types, part of which remain subclinical or cause mild symptoms that are not recognized, and shedding of the virus after (or before) symptomatic infection.
  - AOM or pneumonia can develop as co-infections with rhinovirus and pneumococci or other bacteria. By using multiplex PCR, rhinovirus may be detected simultaneously with another virus or viruses. The specific role of rhinovirus in viral co-infections is unclear.

Diagnosis

- The detection of rhinovirus is based on RT-PCR in upper or lower respiratory tract samples. Nasal or nasopharyngeal specimens taken with flocked swabs of synthetic material are preferable. Most PCR methods amplify a conserved part from the 5′ non-coding region of the genome. Enteroviruses are amplified in the same reaction, and they should be differentiated from rhinoviruses by specific probes or other methods. Quantitative PCR produces an estimate of the viral load, but its clinical implications are unclear. Multiplexed PCR methods are increasingly used for the detection of rhinoviruses and other respiratory viruses at the same time.
- Virus culture in cell lines is nowadays rarely used, because it is slow, has a low sensitivity for species A and B, and does not detect species C rhinoviruses.
- Antigen detection or serological methods are not available for routine diagnostic use. Rhinovirus genotyping can be made by sequence analysis, but it is not a routine method.

Management and treatment

- No antiviral drug is available against rhinoviruses.
- Treatment is supportive. Oxygen supplementation should be used, as needed, for patients with bronchiolitis or other LRTIs. Hospitalized infants often need feeding via a nasogastric tube.
- Antibiotics should not be used in uncomplicated URTIs, rhinosinusitis, or wheezing illnesses caused by rhinovirus. Pneumonia associated with rhinovirus is often treated with antibiotics, because bacterial co-infection is difficult to exclude. However, wheezing illnesses are rarely complicated by bacterial pneumonia.
- Inhaled salbutamol and inhaled or systemic corticosteroids are used in asthma exacerbations. Corticosteroids are not beneficial in infants with bronchiolitis. Salbutamol inhalations may be efficient in rhinovirus-induced wheezing. Administration by using an inhalation chamber is preferable to administration by a nebulizer.

Prevention

- No rhinovirus vaccine is available.
- Hospitalized patients should be placed in isolation, and hygiene precautions should be used.
- Handwashing with soap and water, with or without using alcoholic hand rubs, is effective for the prevention of transmission.

Future research

- Known for long as the common cold virus, rhinovirus has only recently been recognized to cause also severe illnesses and hospitalizations. A large new group of rhinoviruses (species C) was discovered in 2006, and the epidemiology and clinical importance of different rhinovirus types are still unclear. The pathogenesis of rhinoviral–bacterial co-infections, such as pneumonia, also needs to be better elucidated.
- Several candidate drugs against rhinoviruses have been studied, but thus far none of them has proved successful. The development of a rhinovirus vaccine is difficult because of the great antigenic diversity of rhinoviruses.

Further reading

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Chapter 66

Giardiasis

See also Chapters 21, 22, 42.

Name and nature of organism

- *Giardia* organisms are a group of pear-shaped, flagellated protozoans. They have a ventral disc, by which they attach to the duodenum and upper small intestine. They have two forms: the disease-causing trophozoite and the encysted form which is transmittable in faeces.
- *Giardia duodenalis* (= *lamblia* = *intestinalis*) is the species found in humans, and also described in other mammals, birds, and reptiles.
- *Giardia* are one of the most primitive eukaryotic cells.
- Ribosomal RNA analysis suggests that *Giardia* forms an evolutionary link from around 2 billion years ago at the divergence between prokaryotes and eukaryotes—really a very old infection!

Epidemiology

- *Giardia* is a ubiquitous organism that is found worldwide.
- The incidence and intensity of infection is greatest where sanitation and safe water supply are inadequate.
- Serological surveys have shown that adults in urban areas in developed countries have a seroprevalence of 18–24%, while, in rural areas in resource-poor countries, this is over 50%.
- In high-prevalence areas, children acquire infection early, reaching adult levels of seroprevalence by 6 months of age.
- Children excrete *Giardia* episodically and are often asymptomatic.
- In Europe and America, travellers returning from the tropics account for at least half of all patients presenting with *Giardia*.
- In the UK, there are around 500 reported cases/year in children, with the highest rates seen in the 1- to 4-year age group (13/100 000 per year).

Transmission and incubation period

- Giardiasis is spread by faecal–oral contamination.
- Infected people excrete cysts, which can survive for months in moist soil or water.
- The cysts can survive the chlorine levels in treated drinking water and in cold mountain streams.
- The cysts are killed by cooking, but contaminated raw or undercooked foods can be a source of infection.

- There can also be direct person-to-person contact from contaminated hands, which leads to increased prevalence in day-care and institutional settings. Carers changing nappies are at increased risk.
- Sexual transmission can occur through oral/anal sexual practices.
- Ingestion of between ten and 100 cysts is required to cause infection in humans.
- After ingestion, the host's gastric acid causes excystation, and each cyst produces two trophozoites.
- The trophozoites migrate to the duodenum and proximal jejunum where they attach to the mucosa by the adhesive ventral disc. They reproduce by binary fission or a very evolutionary basic form of sex. Multiplication is encouraged by the presence of bile, carbohydrate, and low oxygen concentration.
- Symptoms develop 1–2 weeks after ingestion (median around 7–10 days).
- Diarrhoea is thought to be caused by a number of mechanisms:
  - Direct physical injury of the mucosa
  - Formation of a physical barrier between the gut epithelium and the intestinal lumen
  - Release of parasitic products such as proteinases or lectin
  - Mucosal inflammation associated with T-cell activation and cytokine release
  - Associated bacterial overgrowth
  - Bile salt depletion.
- Some trophozoites transform to cysts and pass into the faeces to complete the life cycle.

Clinical features and sequelae

- Common symptoms are: nausea, vomiting, flatulence, abdominal cramps, diarrhoea, and weight loss.
- In contrast to bacterial or viral diarrhoea, the onset of the diarrhoea may be more gradual and relatively mild.
- Symptoms last 2–4 weeks, and, without treatment, most resolve spontaneously.
- Ten to 20% of people develop chronic infection, with persistent loose stool, steatorrhoea, malaise, and depression.
- Chronic giardiasis in children can present with weight loss or failure to thrive with malabsorption. There is no blood or mucus in the stool.
- *Giardia* and other parasites may be found in the stool of children with recurrent abdominal pain, and treatment relieves symptoms in some cases.
- Patients can present with reactive arthritis or an urticarial rash as part of a hypersensitivity reaction.
- Malnourished children have a high incidence of *Giardia* and other intestinal parasites. There is an association between frequent episodes of giardiasis and stunting and cognitive impairment.

- Children with hypogammaglobulinaemia are at increased risk of disease and are more difficult to treat than those with normal immunity.
- T-cell abnormality does not seem to increase susceptibility. In patients with HIV, *Giardia* rates are the same as, or lower than, in the background population. This contrasts with the much higher rates of *Cryptosporidium* infection seen in patients with HIV and other T-cell deficiencies.

Diagnosis

- The diagnosis is made by finding *Giardia* cysts or trophozoites in stool. Cyst excretion is intermittent. Trophozoites are only seen in diarrhoeal stool, but cysts can be found in asymptomatic carriers.
- Examination of a single stool has a sensitivity of 50–70%; with serial examination of three stools, sensitivities of up to 90% can be achieved.
- Higher yields can be obtained from duodenal biopsy or aspiration.
- Stool examination is labour-intensive and operator-dependent.
- ELISA tests for *Giardia* antigen in stool are reliable, with a higher sensitivity than microscopy for a single sample, and allow rapid screening of large numbers of samples.
- Serological tests in plasma are insensitive for the diagnosis of disease.
- PCR techniques have also been developed for the detection of *Giardia* in stool.
- However, in high-prevalence, resource-poor countries, microscopy continues to be the most readily available investigation and also allows the detection of other intestinal parasites.
- Endoscopy is rarely necessary for routine diagnosis, but, if it is to be done as part of investigations for malabsorption, samples should be collected to look for trophozoites.
- Apart from the presence of the trophozoites, the mucosal histology may show varying degrees of villous atrophy, crypt hyperplasia, or inflammation with polymorphonuclear leucocytes or eosinophils.
- Malabsorption can occur despite normal light microscopy findings.
- *Giardia* does not invade the mucosa, so eosinophilia or leucocytosis are not seen in the peripheral blood.

Management

- The drug for which there is most experience is metronidazole, given orally once daily for 3 days.
- Treatment can be repeated if the infection is not eradicated.
- Tinidazole has a similar efficacy to metronidazole (70–100% eradication) and the advantage of single-dose administration.
- Albendazole and mebendazole have lower reported efficacy (50–100%), but the advantage of covering for other intestinal parasites.
- Immunocompromised patients may require a longer course of treatment, and specialist advice is recommended.

Prevention

- Safe disposal and treatment of faecal matter to prevent contamination of food and water are the mainstay of prevention. The fact that *Giardia* is still seen in countries with sophisticated sanitation shows that these measures will not eradicate the organism completely but will considerably reduce the prevalence and intensity of infection.
- Breast milk from mothers in endemic countries contains *Giardia*-specific IgA, and exclusive breastfeeding does delay the appearance of infection in infants.
- Mass school-based treatment programmes are appropriate in high-prevalence areas and are of benefit both for the individual child and for the wider community by reducing transmission rates. Drugs with both antihelminthic and antiprotozoan activity, such as albendazole and nitazoxanide, are valuable, as many children will have multiple parasites.
- Vitamin A and zinc supplementation, given separately or together, reduce the frequency of *Giardia* infections in children.
- Returning travellers and migrants from high-prevalence countries contribute up to 85% of symptomatic disease in developed countries. Screening and treating migrants from high-prevalence countries may help to further reduce the incidence in developed countries.
- Simple handwashing is an important control measure in institutional settings.

Future research

- Despite extensive study of *Giardia* infection in mouse models and, to a lesser degree, in human *in vitro* systems, the most important antigens in inducing immunity are still unclear and may vary in different geographical regions.
- There are as yet no obvious candidate antigens for a human vaccine.
- A few animal studies on the induction of immunity have shown successful induction of specific immunoglobulin, but without clinically significant protection from infection.
- It seems unlikely that an effective vaccine will be developed in the immediate future.
- Better implementation of known effective preventive measures will continue to be the most important factor in disease control.

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Chapter 67

Gonococcal infection

See also Chapters 11, 30, 31, 37.

Name and nature of organism

- *N. gonorrhoeae* is an intracellular Gram-negative diplococcal bacterium.

Epidemiology

- Gonorrhoea is the second commonest bacterial STI in the UK.
- Humans are the only reservoir of infection.
- The source of the organism is the exudate/secretions from an infected mucosal surface.
- Childhood infection occurs as two distinct clinical entities:
  - Newborn infants
  - Children and adolescents.
- Infection in prepubertal children is commonly the result of child sexual abuse.
- The highest incidence of infection is in ♀ aged 16–19 years.
- It is difficult to obtain data on younger adolescents due to asymptomatic infection and reluctance to access health-care services.
- The highest rates of infection are in urban areas (e.g. London) and in black ethnic minority populations.
- Gonococcal infection often coexists with *C. trachomatis* infection.

Transmission

- Transmission is due to direct inoculation of infected secretions from one mucous membrane to another.
- The risk of acquiring infection varies between 20% and 50% after a single episode of vaginal intercourse.
- Infection of the newborn results from passage through the birth canal of an infected mother, although infection after Caesarean delivery has been documented.
- Prematurity and prolonged rupture of membranes increase the risk of the neonate acquiring the infection.
- Infection in children and adolescents occurs through sexual contact.
- Reinfection with the same strain is common, as protective immunity does not develop.

Incubation period

- Incubation is usually 2–7 days.
- Incubation in the neonate often <3 days, but occasionally symptoms do not develop until 2–3 weeks after delivery.

Period of infectivity

- Infectivity lasts for as long as no treatment is given and the discharge continues.
- Infectivity may occur with no or minimal symptoms, especially in ♀.
- In adults without treatment, infectivity can continue for 3–6 months.

Clinical features and sequelae

Newborn infants

- Prominent eyelid oedema, followed by chemosis.
- Discharge is initially watery but progresses to become mucopurulent.
- It can be unilateral or bilateral.
- Corneal ulceration, perforation, and blindness can occur without treatment.
- Scalp abscesses can occur with the use of fetal monitoring in an infected mother.
- Rarely, disseminated disease can occur, resulting in SA or meningitis.

Children and adolescents

- Involves mucous membranes exposed to sexual contact, e.g. genital tract, urethra, pharynx, and rectum.
- The clinical spectrum varies from asymptomatic infection (less common in prepubertal children) through vaginitis, urethritis, or cervicitis with discharge, to PID, epididymitis, and perihepatitis.
- Disseminated gonococcal infection is rare but can result in SA and skin lesions—classically necrotic pustules on an upper limb, with polyarthralgia or arthritis.
- The most significant long-term sequelae is salpingitis, leading to ♀ infertility.
- An intact complement system is required to eradicate the organism.

Diagnosis

- Microscopic examination, Gram stain, and culture of exudate from a swab is the gold standard.
- When culturing samples from non-sterile mucosal surfaces, a culture medium that inhibits the growth of normal flora and non-pathogenic *Neisseria* spp. must be used.
- NAATs are generally more sensitive than culture and offer testing on a wider range of specimen types.

- Positive NAATs from extragenital sites in low-prevalence populations must be confirmed with supplementary testing using a different nucleic acid target.
- Culture confirmation is essential in child sexual abuse cases for medico-legal purposes.
- Identification of *N. gonorrhoeae* should lead to screening for other STIs.

Management

- Antimicrobial resistance patterns are continuously changing, usually for the worse.
- Surveillance systems are in place, and it is important to understand local resistance patterns.
- Current recommendations involve using third-generation cephalosporins.
- Test of cure is recommended.

Newborn infants

- For an asymptomatic infant born to a clinically infected mother:
  - Use ceftriaxone or cefotaxime as a single dose.
- For uncomplicated ophthalmia neonatorum:
  - Topical treatment alone is inadequate
  - Use ceftriaxone as a single dose, if not jaundiced
  - If jaundiced, consider cefotaxime as a single dose or in a divided-dose regimen
  - Irrigate the eyes well with saline several times a day, until the purulent discharge subsides.
- If there is evidence of scalp abscess or SA, treatment should be continued for 7 days.
- For gonococcal meningitis, treatment should be 10–14 days.
- It is important to consider the possibility of coexistent *Chlamydia* infection.
- Investigation and treatment of the mother should be done through specialists in GUM.

Children and adolescents

- For uncomplicated infection:
  - Ceftriaxone or cefotaxime as a single dose, or
  - Cefixime orally for children >12 years.
- Disseminated infection should be treated for 7 days:
  - Treatment can be switched to oral after 24–48 hours, if suitable agent available.
- Involve GUM specialists to instigate contact tracing, if appropriate.
- Consider child sexual abuse at any age, but, in particular, for prepubertal children.
- Consider treating for *Chlamydia*.
- Dual therapy with third-generation cephalosporin and azithromycin may be considered in areas with reduced cephalosporin sensitivity.

Prevention of further cases

Newborn infants

- Where the incidence of gonorrhoea is high, antimicrobial eye drops have been used routinely after birth. Silver nitrate 1% has been used historically, with erythromycin or tetracycline used more recently.
- In low-prevalence areas, screening of high-risk pregnant women should be offered.

Children and adolescents

- Children require protection from adults who seek underage sex.
- Adolescents require sex education and accessible health services.
- Contact tracing by GUM specialist prevents further spread.

Further research

- The most cost-effective management of multiresistant gonococcal disease is yet to be determined.
- The role of routine antimicrobial eye drops in very high-prevalence areas needs to be reinvestigated.

Further reading

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Chapter 68

Haemolytic–uraemic syndrome

See also Chapters 66, 103, 105.

Introduction

- HUS is a rare disease, which can be hereditary or newly acquired. The disease may occur in children as well as in adults. There has been an enormous progress in the last decade in the understanding of the causes of HUS.
- The clinical condition of HUS is characterized by:
  - Coombs' negative microangiopathic haemolytic anaemia
  - Thrombocytopenia
  - Acute renal failure.
- Another thrombotic microangiopathy also presenting with haemolytic anaemia and thrombocytopenia is thrombotic thrombocytopenic purpura (TTP) which is often accompanied by neurological abnormalities and other signs of organ injury such as renal dysfunction. Clinicians should be aware that neurological involvement is present in a third of cases of HUS. Although there are similarities in the clinical presentation, pathogenesis, and treatment, HUS and TTP are different disease entities. The renal involvement in TTP is mostly a renal dysfunction. In the majority of TTP cases, there is an inherited or acquired deficiency in the enzyme ADAMTS13.

Classification

- *The classification of HUS is now aetiology-based*:
  - Shiga toxin-producing *E. coli* infection (STEC)-HUS
  - *S. pneumoniae* infection-related HUS (Sp-HUS)
  - Atypical HUS (aHUS) due to complement dysregulation
  - Diacylglycerol kinase–epsilon (DGKE) mutation-HUS
  - Deficiency in cobalamin metabolism
  - *Shigella dysenteriae* infection-HUS
  - Virus-associated HUS: HIV, CMV
  - Drug-associated HUS: calcineurin inhibitors, mammalian target of rapamycin (mTOR) inhibitors, vincristine, quinine, oral contraceptives, ticlopidine, clopidogrel, bleomycin, bevacizumab, interferon gamma
  - Associated with systemic diseases: SLE, antiphospholipid syndrome, scleroderma, malignant hypertension, malignancy

  - Associated with pregnancy: pre-eclampsia, HELLP (haemolysis, elevated liver enzymes, low platelets)
  - Associated with BMT: GVHD.
- The first three mentioned causes of HUS form the majority of cases and are discussed in more detail.

Shiga toxin-producing *Escherichia coli* haemolytic–uraemic syndrome

Epidemiology

An infection with STEC causes illness, ranging from mild (even asymptomatic) to life-threatening haemorrhagic colitis and HUS. It is a rare disease; the European Food Safety Authority (EFSA)/European Centre for Disease Prevention and Control (ECDC) reports 4000 STEC infections, mainly serogroup O157, in their 27 EU member states per year. STEC serotype O157 remains the most important cause of STEC-HUS worldwide. However, non-O157 STEC infections are also detected frequently and are able to cause HUS as well. The most prevalent serotypes causing STEC-HUS are O157, O26, O145, O111, and O103. The risk of developing HUS after an STEC O157 infection is reported to be 8–18%. The incidence of HUS after a non-O157 serotype infection is difficult to determine, due to a lack of routine screening, but is thought to be smaller. STEC-HUS is commoner in children and the elderly; boys and girls are equally affected. Enterohaemorrhagic *E. coli* (EHEC) is another term for STEC-causing disease in humans, but this term implies that the stools contain visible blood, which is sometimes not the case (6–10% non-bloody/no diarrhoea) and frequently not the case in infections caused by STEC that belong to other serotypes.

Transmission

The infectious process begins when contaminated food, water, or faecal material is ingested or by person-to-person spread. The number of organisms required to establish an infection may be as low as 100. The main reservoir of STEC is cattle. Appropriate hand, fruit, and vegetable washing, as well as adequate meat preparation and cooking, are the best measures to prevent disease.

Pathogenesis

The virulence factor common to all STEC is the exotoxin shiga toxin. The STEC found in HUS produces shiga toxin 1 (Stx1) and/or shiga toxin 2 (Stx2). Stx1 is only one amino acid different from the toxin produced by *S. dysenteriae*. Stx2 and Stx1 share 70% of the same amino acid pattern. Stx1 and Stx2 belong to the class of AB_5 toxins. The B subunits allow the toxin to bind to its receptor globotriaosylceramide (Gb3) on the host cells. Once bound to the cell, the A subunit is endocytosed and transported into the cytosol where it inhibits the protein synthesis. In the majority of HUS cases, Stx2-producing strains are found.

In human disease, when STEC enters the intestines, it elaborates Stx and a variety of adhesins. The most important adhesin is called intimin and found primarily in O157 and O26 strains. The gene for intimin and its receptor Tir, a type III secretion system, are encoded in the LEE pathogenicity island of the STEC. Localized inflammation and intestinal damage will occur; Stx1/Stx2 release will take place and will cross the damaged intestinal epithelial barrier. The inflammation process with cytokines and lipopolysaccharide (LPS), released together with the Stx bound to its receptor on human cells, will lead to thrombotic microangiopathy, and, as such, to HUS, especially in the renal microvasculature, the main target in HUS. Thrombotic microangiopathy may also occur in other organs such as the brain and heart.

Clinical presentation

- The spectrum of clinical disease mediated by STEC ranges from non-bloody diarrhoea to haemorrhagic colitis, HUS, and possibly death. The time from consumption of the STEC to diarrhoeal illness is about 3 days. Diarrhoea may turn bloody after 1–2 days in three-quarters of the patients and can lead to HUS in 5–7 days in 8–18% of patients. Death from STEC-HUS occurs in ~2–5% of patients. Early detection is critical.
  - There are cases of HUS with positive *E. coli* serotype serology, but without a history of diarrhoea (6–10%). When diarrhoea is present, it is often associated with vomiting, which explains why half of the patients on admission are dehydrated and hypovolaemic.
  - When oliguria/anuria is not recognized and the child is maintained on liberal volumes of hypotonic fluids, hypervolaemia, hypertension, and hyponatraemia may occur.
- Anaemia and thrombocytopenia precede renal failure, resulting in pallor and jaundice, and, when/if the platelet count is <20 000/mL, a petechial rash or overt bleeding can be noted.
  - While red blood cell transfusion is indicated, platelet transfusion is contraindicated, unless the patient needs surgery or is actively bleeding.
- Acute renal failure develops suddenly in three-quarters of patients.
  - It can be anuric or oliguric, rarely polyuric.
  - If the child is not anuric, the urine may be red/dark red in colour, either because of haematuria or haemoglobinuria 2° to haemolysis.
  - Due to diarrhoea, patients in acute renal failure can be hypokalaemic.
  - Hypertension in the acute phase is usually volume-related but can also be renin-mediated, particularly in the later stage of the illness.
- CNS symptoms or signs are present in up to 20–30% of children.
  - They can present non-specifically with irritability, confusion, or lethargy, or more dramatically with seizures and coma.
  - Seizures and other abnormal neurological signs may also reflect low serum sodium, ischaemia–hypoxia, hyperuraemia, hypertension, and/or cerebral oedema, rather than CNS vessel thrombosis.
- Diabetes mellitus has been reported in <5%.

- STEC may cause severe colitis, leading to toxic colitis and even intestinal perforation.
  - Rectal prolapse is common.
  - As a rule, patients infected with STEC are not febrile, because there is no bacteraemia, unlike with *Shigella* infection when children typically present with bacteraemia and shock; hence, they require urgent antibiotic treatment.

Investigations

- Coombs' negative anaemia with fragmented erythrocytes on blood film, low haptoglobulin levels, and thrombocytopenia are typical for HUS.
- Electrolyte disturbances are in keeping with acute renal failure.
- Polymorphonuclear leucocytosis correlates with the severity of renal disease—a high number of neutrophils at the beginning of the disease is a poor prognostic marker.
- Liver enzymes can be elevated at the beginning of disease.
- LDH is elevated due to haemolytic anaemia. Serum glucose levels need to be followed up.
- Urea and creatinine levels.
- When the urine output is maintained, a dipstick test shows the presence of blood and/or haemoglobin and proteinuria.
- Faecal samples (stool/rectal swab) for STEC culture (STEC-O157; sorbitol MacConkey agar with or without cefixime–tellurite), PCR Stx (preferably 1–3 cultures due to low inoculums), toxin EIA. Think of faecal examination of family members with GI illness at the same time.
- If available, serology for the detection of serological antibodies against serotype STEC (O157, etc,).
- Exclusion of TTP by measuring ADAMTS13 activity in serum can be necessary.

Treatment

- Supportive management is of key importance to this condition.
  - Meticulous correction and maintenance of biochemistry, fluid status, and acid–base balance are essential.
  - If, in some cases, the STEC infection is diagnosed early, i.e. before the presence of renal injury, early and vigorous volume expansion may help in the avoidance of severe renal injury.[1]
  - Patients with worsening uraemia, either in isolation or combined with acid–base, fluid, or biochemical disturbances that cannot be corrected, require renal replacement treatment; about three-quarters of patients will need dialysis, usually peritoneal dialysis.
- It is important to maintain good nutrition.
- Blood transfusion is indicated when haemolysis is ongoing and the haemoglobin concentration falls to <6g/L.
- Platelet transfusion should be avoided, if possible, as there is evidence it may aggravate the disease process.
- If hypertension develops, calcium channel blockers and/or β-blockers can be given. One should be careful to use an ACE inhibitor in the acute phase.

- Antimotility agents should be avoided, as, by reducing gut peristalsis, there is prolonged contact of the pathogenic bacteria with the intestinal mucosa. Antibiotics for gut decontamination are not recommended and have been shown in various multiple case control studies to have no beneficial effect.
- Vitamin E, methylprednisolone, and Stx-absorbing agents, as well as anticoagulation therapy, are not recommended.
- While plasma exchange is a key treatment in patients with TTP and some with complement-mediated HUS, its use in patients with STEC-HUS, as has been shown in the recent German outbreak in 2011, is not recommended. Many clinicians, however, use plasma exchange in children with overt CNS disease, but there is no evidence that this is an effective treatment.
- Although there has been no RCT, data from the German outbreak in 2011 do not support a benefit of the complement inhibitor eculizumab on the short-term outcome.

Histopathology

- The history, together with clinical and laboratory investigations, are often sufficient to make the diagnosis of HUS. Renal biopsy is rarely necessary, and mostly not possible, in the acute phase due to thrombocytopenia. If a renal biopsy is performed, the vascular pathological abnormalities are the same in all aetiologies of HUS: renal arteriolar and capillary thrombosis, with characteristic abnormalities in the endothelium and vessel wall.

Prognosis

- High neutrophil count (>20 000/mL) at presentation, anuria lasting >10–14 days, and the need for dialysis for >2 weeks are markers of a poor prognosis (either isolated proteinuria, hypertension, chronic renal failure, or their combination).
- Rectal prolapse, the severity of colitis, and younger age may also be weakly associated with a poor prognosis.
- The reported early mortality rate in the order of 1.5–5% is related mainly to neurological involvement.
- Renal function fully recovers in 80%, while 5% develop severe chronic renal failure. Patients who progress to end-stage renal failure can safely receive a renal transplant. STEC-HUS does not occur in the transplant kidney. The remaining 15% are left with varying degrees of chronic kidney disease such as proteinuria, decreased glomerular filtration rate (GFR), and hypertension. Even among patients with an apparent full recovery of the kidney function, there are reports of late development of proteinuria, decline in GFR, or hypertension, even decades later. Therefore, patients with HUS, especially those with an abnormal GFR, proteinuria, and hypertension 1 year post-disease, should have lifelong follow-up.
- Of children who develop diabetes mellitus, approximately a third will require long-term insulin treatment; the remaining two-thirds will recover.

Streptococcus pneumoniae haemolytic–uraemic syndrome

Epidemiology

Another infection causing HUS is HUS due to an invasive infection with Sp-HUS. This form has been reported in 5–15% of all childhood HUS, and in 40% of non-STEC HUS. The incidence of Sp-HUS, following an infection with *S. pneumoniae*, is estimated at 0.4–0.6%. Compared to STEC-HUS, patients with Sp-HUS have a higher morbidity (25–50%) and mortality (5–25%). This type of HUS often affects younger children, some as young as <2 years. The majority of Sp-HUS are associated with pneumonia (70%), meningitis (29%), and rarely with both. Since the introduction of vaccination, the serotypes associated with Sp-HUS are changing.

Pathogenesis

The current hypothesis is the desialysation of glycoproteins of red blood cells, thrombocytes, and endothelial cells by the enzyme neuraminidase produced by the bacteria, leading to the exposure of the Thomsen Friedenreich cryptantigen (T-antigen). Naturally occurring circulating IgM antibodies against this T-antigen can bind to the exposed T-antigen, resulting in the agglutination of red blood cells, thrombosis, and endothelial damage. The direct Coombs' test detects antibodies and the complement that coat erythrocytes and can be used as a screening test for Sp-HUS. A positive Coombs' test is found in 90% of cases of Sp-HUS, but there are no data on the rate of a positive Coombs' test in pneumococcal infections without HUS.

A new possible role in the pathogenesis is suggested for the complement regulator factor H.

Clinical presentation

The diagnosis of Sp-HUS is based on the combination of clinical and laboratory findings and the evidence of *S. pneumoniae* infection. In a critically ill child, making the right diagnosis can be challenging due to the similarities of laboratory and clinical findings that are seen in DIC.

Investigations

Besides the mentioned laboratory measurements in STEC-HUS, patients with Sp-HUS are more likely to have only slightly prolonged coagulation parameters and normal fibrinogen without active bleeding, in contrast to patients with DIC. In the majority of Sp-HUS patients, the direct Coombs' test is positive. Evidence of an infection of *S. pneumoniae* can be found in blood or cerebrospinal, pericardial, auricular, peritoneal, or pleural fluids. Serological neuraminidase levels can be elevated in the acute phase. The existence of neuraminidase can be addressed indirectly by performing a transferrin isolectric focusing test, in which the transient abnormal transferrin *N*-glycosylation pattern in the plasma of Sp-HUS patients indicates the presence of neuraminidase.

Treatment

These children must be treated with antibiotics, as the pneumococcal infection itself is often severe and life-threatening.

The treatment of Sp-HUS is mainly supportive. Due to the fact that anti-T antibodies are present in normal plasma and can aggravate the disease, blood products, such as red blood cells or platelets, should be washed and free of anti-T antibodies, and plasma should be avoided. There is not enough evidence to support treatment with plasmapheresis in Sp-HUS.

Prognosis

Overall, end-stage renal failure occurs in 10–16% of Sp-HUS patients, and the mortality rate is between 5% and 25%. Patients with meningitis have been reported to have a far greater risk of death. Patients with Sp-HUS and a severe period of acute renal failure should have follow-up for the control for hypertension, proteinuria, and renal function.

Atypical haemolytic–uraemic syndrome

Epidemiology

aHUS is uncommon, accounting for <10% of all HUS cases. aHUS can occur at any age and is, in fact, the major cause of HUS in adults. aHUS can be sporadic as well as have a familial occurrence. The disease can have relapses. The risk of end-stage renal disease or death is higher than in STEC-HUS. aHUS is known to have a high recurrence rate in renal transplantation. Nowadays, dysregulation in the alternative pathway of the complement system is known to be the cause of aHUS. Evidence for complement dysregulation is found in up to 70% of patients with aHUS.

Clinical presentation

aHUS can sometimes be difficult to diagnose. In children, the clinical presentation and laboratory results usually allow the diagnosis of STEC-HUS, Sp-HUS, cobalamin deficiency, or TTP to start adequate treatment. It is important to know that, in patients with aHUS, diarrhoea (most frequently non-bloody diarrhoea) is a presenting feature in 15–39% of patients. Neurological symptoms, one of the main characteristic symptoms in TTP, can occur in 8–30% of patients with aHUS.

Investigations

Proper investigations and an urgent evaluation are mandatory in any patients presenting with signs of HUS. It is crucial in children to rule out the presence of an STEC infection. In adults and children, ADAMTS13 activity should be measured to differentiate the disease from TTP. Complement diagnostics to be performed include: plasma C3, C4, C3d, factor H (FH), factor I (FI), membrane cofactor protein (MCP) expression on leucocytes, antibodies against FH, and DNA mutation analysis for the complement proteins FH, FI, MCP, FB, C3, and thrombomodulin. Be aware that normal C3, FH, and FI levels in plasma or a normal expression of MCP on leucocytes do not rule out an abnormal complement activation and, as such,

do not exclude a diagnosis of complement-mediated aHUS. The development of antibodies against FH is strongly associated with the presence of a homozygous deletion of the genes encoding for FH-related protein 1 and protein 3. Antibodies against FH are mainly observed in children. aHUS with end-stage renal failure going for renal transplantation should always be genetically tested for complement abnormalities.

Pathogenesis

The alternative pathway of the human complement system is mainly involved in aHUS. To prevent continued and unopposed complement activation, and resulting cell damage, the complement system is normally tightly regulated. The key regulators of the alternative pathway are FH, FI, and MCP (or CD46). These complement regulatory proteins are either constitutively present on the endothelial cell membrane or are bound by the endothelial glycocalyx. A loss-of-function mutation in a complement-inhibiting gene (FH, FI, MCP, thrombomodulin) or a gain-of-function mutation in a gene that encodes a complement activator (C3, FB) will lead to an unopposed activation of the complement system, resulting in the formation of the membrane attack complex on cell surfaces, especially of endothelial cells in the microcirculation of the kidney. As a result, endothelial cells are damaged and leucocytes are attracted, releasing oxygen radicals and proteinases, which can further damage the endothelium. This will eventually result in increased platelet adherence and the formation of microthrombi in the kidney, thus explaining the characteristic triad of aHUS. Recently, homozygous mutations in DGKE have been described in aHUS in infancy, which is possibly not linked to disturbances in the complement system but affects the coagulation pathway.

Treatment

Intensive plasma therapy was, until recently, the therapy of choice. This is still the case in the absence of availability of eculizumab. Currently, eculizumab, a humanized monoclonal antibody that binds to C5 and blocks the generation of the formation of the terminal membrane attack complex, has been approved and registered in 2011 for the treatment of aHUS. It is obligatory that patients receive meningococcal vaccination before the start of eculizumab and/or additional antibiotic prophylaxis. Optimal treatment protocols/guidelines are currently being developed.

Prognosis

Without treatment, the prognosis of aHUS is miserable, with 50% of patients progressing to end-stage renal failure and 25% dying during the acute phase of the disease. However, controlled clinical data of the use of plasma therapy are lacking. The risks of end-stage renal failure and recurrence after renal transplantation is dependent on mutational analysis, with FH mutations causing the greatest risk. It is assumed that anti-complement therapy will improve the outcome.

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Chapter 69

Haemophilus influenzae

Name and nature of organism

- *H. influenzae* is a small, non-motile Gram-negative coccobacillus and is an important cause of invasive bacterial infections in children and adults.
- *H. influenzae* can be differentiated, according to its capsular polysaccharide composition, into six serotypes (Hia to Hif).
- *H. influenzae* serotype b (Hib) possesses a polyribosyl ribitol phosphate (PRP) polysaccharide capsule, which is the major virulence factor for the organism and protects the organism from phagocytosis.
- *H. influenzae* strains that lack a polysaccharide capsule are classified as non-encapsulated (ncHi) or non-typeable (ntHi).

Epidemiology

- Currently, Hib causes an estimated 3 million cases of serious disease and 400 000 deaths annually worldwide.
- Prior to the introduction of routine vaccination, Hib was responsible for over 90% of invasive *H. influenzae* infections in young children and was a major cause of bacterial meningitis in this age group.
- Children <5 years were at highest risk from Hib disease, with the peak incidence in the second half of the first year of life when protective maternal antibodies waned.
- Asplenia, sickle-cell disease, malignancy, and antibody deficiency syndromes are associated with an increased risk of developing invasive Hib disease.
- In children <5 years, other risk factors for invasive Hib disease include low socio-economic status, lack of breastfeeding in infancy, and regular nursery or day-care attendance.
- Infections due to other *H. influenzae* serotypes and non-encapsulated *H. influenzae* are rare and summarized at the end of the chapter.

Hib conjugate vaccine

- The Hib conjugate vaccine induces both antibody production and immunological memory and is highly effective in preventing invasive Hib disease.
- The introduction of Hib conjugate vaccine into national childhood immunization programmes since 1990 has led to a rapid and sustained decline in the incidence of invasive Hib disease.
- This decline has been observed across all age groups, because the Hib conjugate vaccine not only protects against invasive disease, but also prevents carriage and, therefore, the onward transmission of the organism to unvaccinated older children and adults (indirect or herd protection).

- There is no evidence that other *H. influenzae* serotypes or other pathogens have replaced Hib as a cause of serious bacterial infections in children after the introduction of routine Hib immunization.
- In 2011, there were 2152 confirmed cases of invasive *H. influenzae* disease reported by 24 EU/European Economic Area (EEA) countries (overall incidence 0.58 cases per 100 000 population), but Hib was responsible for only 7% of cases, with only three EU/EEA countries reporting a rate of >1 per 100 000 in children under 5 years of age.
- Most cases of invasive Hib disease now occur in older adults, who often have respiratory co-morbidities, such as chronic obstructive pulmonary disease (COPD), and develop Hib pneumonia.

Transmission

- Humans are the only known reservoirs for Hib.
- In the pre-vaccine era, children <5 years of age were the 1° reservoirs of Hib, with nasopharyngeal colonization rates of 3–9%.
- Because the Hib conjugate vaccine also reduces carriage, vaccinated children are rarely colonized; instead, older children and adults are more likely to harbour the organism and may now act as 1° reservoirs for ongoing transmission of Hib to susceptible individuals.
- Person-to-person transmission occurs through respiratory droplet spread but may be acquired through contact with infected respiratory discharge.
- Carriers of Hib are infectious as long as organisms are present in the nasopharynx, which may be for a prolonged period, even without nasal discharge.
- Second episodes of invasive Hib disease in the same individual are extremely rare, with only four cases reported in the UK since 1992.
- In the pre-vaccine era, household (mainly <5 year olds and immunocompromised individuals) and day-care contacts had a higher risk of developing invasive Hib disease than the general population, although the risk was much higher in the former group—there are no studies on 2° infections after the introduction of routine Hib immunization.

Incubation period

- The incubation period is not known; however, susceptible individuals usually develop disease within 7 days of exposure to Hib.

Clinical features

- Children with invasive Hib disease may develop a range of clinical manifestations, particularly meningitis, septicaemia, and epiglottitis.
- The introduction of the Hib conjugate vaccine has altered the epidemiology and clinical presentation of invasive Hib disease in children, such that the median age at Hib disease has shifted from 6–12 months to 2–3 years, and meningitis (which used to account for 60–75% of cases in the pre-vaccine era) now accounts for around 25%, while bacteraemia now accounts for 50% of cases; the proportion of

cases presenting with epiglottitis and other invasive infections remain at ~15% and ~10%, respectively.

- **Meningitis** due to Hib is clinically indistinguishable from other causes of bacterial meningitis; symptoms of meningitis include fever, headache, photophobia, stiff neck, vomiting, and decreased mental status; severe cases may present with convulsions and coma; infants (<1 year) usually present with non-specific symptoms, such as fever, vomiting, refusal to feed, and irritability, but severe cases may develop hypotonia, bulging fontanelle, a high-pitched cry, and convulsions; in industrialized countries, Hib meningitis has a case fatality of ~5% but may be as high as 40% in developing countries. In addition, 10–15% of survivors will develop severe long-term complications (e.g. cerebral palsy, hydrocephalus, epilepsy, blindness, sensorineural deafness), and a further 15–20% will have minor long-term sequelae (e.g. partial deafness, behavioural and learning difficulties, speech and language problems).
- **Epiglottitis** is a life-threatening condition that is caused by infection of the epiglottis, aryepiglottis, and arytenoids; it usually occurs in children aged 5–10 years, who present very acutely with a short history of high fever, tachypnoea, inspiratory stridor, and excessive drooling.
- Other less common clinical manifestations of Hib disease include pneumonia, cellulitis, SA, OM, and pericarditis.

Diagnosis

- Epiglottitis is usually diagnosed clinically, but Hib may be isolated from blood cultures (or from culture of swabs of the epiglottis), if taken prior to administering antibiotics.
- Diagnosis relies on the isolation of *H. influenzae* from a normally sterile site (e.g. CSF, blood, joint or pleural aspirate, etc.) in a child with clinical symptoms and signs of infection.
- *H. influenzae* serotype can be confirmed by PCR; in most countries, this requires submission of the isolate to a national reference laboratory for confirmation and serotyping. Since Hib is now extremely rare in countries with established Hib immunization programmes, it is vital to ensure that any *H. influenzae* isolated from a sterile site is subjected to serotyping in a validated laboratory.
- Rapid antigen tests for Hib are available, but rarely used, and may be prone to false positive and false negative results, if not used appropriately.

Management and treatment

- Epiglottitis is an acute medical emergency; children presenting with acute airway obstruction usually require immediate intubation and ventilation.
- Third-generation IV cephalosporins, including cefotaxime and ceftriaxone, are the empiric treatment of choice for suspected invasive bacterial infections and are highly effective against all *H. influenzae*, including Hib.

- Adjuvant dexamethasone, especially if given before or with the first dose of antibiotic, will reduce the risk of long-term sequelae, including SNHL, in patients with Hib meningitis.
- Fully immunized children who develop invasive Hib disease should be assessed for possible underlying immune deficiency after recovering from their infection.

Prevention

- The Hib conjugate vaccine remains the most effective measure for preventing invasive Hib disease.
- By reducing carriage, the conjugate vaccine also helps reduce transmission to susceptible individuals of all ages, thus providing herd protection
- All children should be immunized in infancy (two or three doses in the first 6 months of life) and receive a booster dose in the second year of life.
- Unimmunized children aged >1 year require a single dose of the Hib conjugate vaccine for long-term protection.
- Rifampicin remains the prophylactic antibiotic therapy of choice among contacts of a case of invasive Hib disease, because it can eradicate nasopharyngeal carriage in >95% of recipients, is well tolerated, and has an excellent safety profile.
- Treatment courses of quinolones and azithromycin may be suitable alternatives.
- Among cases with invasive Hib disease, treatment with >2 days of IV cephalosporins should eradicate nasopharyngeal carriage; however, patients treated with shorter courses or those treated with other antibiotics should receive rifampicin prophylaxis before hospital discharge, in order to eradicate carriage.
- Children who develop invasive Hib disease, particularly if <2 years old, should have Hib antibodies checked after recovering from infection, in order to ensure adequate protection against future Hib infections.
- Children with Hib antibody concentrations <1mg/mL or whose antibody concentrations cannot be measured should receive a dose of Hib vaccine after recovering from the infection, irrespective of their previous vaccination history.
- All household contacts, including pregnant women, should be offered chemoprophylaxis if there is a vulnerable individual in the household. In the UK, a vulnerable person is defined as an immunosuppressed or asplenic person of any age or a child aged <10 years, irrespective of the vaccination status.
- All unimmunized and partially immunized children in the household should complete their 1° immunization.
- In the UK, local health protection teams need to be informed of all cases of invasive Hib disease, as they are responsible for contact tracing to provide chemoprophylaxis and vaccination to close contacts.
- Families of children attending the same preschool or 1° school as the patient should be informed to seek medical advice if their child becomes unwell.

Invasive infections due to other *Haemophilus influenzae*

- Non-encapsulated *H. influenzae* commonly colonize humans and are a well-recognized cause of non-invasive respiratory tract infection, including otitis media and sinusitis, in healthy children but are rarely responsible for invasive infections.
- Following the introduction of routine Hib vaccination, invasive infections due to non-encapsulated *H. influenzae* have become relatively more important and account for ~80% of all invasive *H. influenzae* cases in children.
- In Europe, non-encapsulated strains made up 77% of cases in 2011, with non-b serotypes causing 16% and serotype b 7%, although the serotype was unknown for 51% of cases.
- Pregnant women and neonates have a significantly higher risk of invasive non-encapsulated *H. influenzae* infections. Infection in pregnancy is associated with stillbirths, septic abortion, and premature birth. In neonates, non-encapsulated *H. influenzae* infections are ten times commoner than Hib, nearly always occur within 48 hours of birth, and are associated with a fulminant course of infection and high case fatality, particularly among premature infants.
- After the neonatal period, invasive non-encapsulated *H. influenzae* infections are relatively rare and usually occur in children with underlying medical conditions (40–70%), particularly immune deficiency; the case fatality rate is significantly higher than for Hib, particularly in the first 6 months of life.
- Invasive infections due to other capsulated *H. influenzae* (a, c, d, and f) are extremely rare and mainly due to Hif (~75%); they too usually occur in immunocompromised children.

What's new?

- Recent studies have shown that pregnant women have a significantly higher risk of developing invasive non-encapsulated *H. influenzae* disease, which was often associated with miscarriage, stillbirth, septic abortion, and premature birth.
- Invasive *H. influenzae* disease in neonates nearly always occurs within the first 48 hours of birth and is nearly always due to non-encapsulated *H. influenzae*.
- A 10-valent pneumococcal conjugate vaccine (Synflorix®; PCV10; PHid-CV; GSK Biologicals) has been licensed, which uses an outer membrane protein (protein D) present on the surface of all *H. influenzae* as its carrier protein for eight of the ten pneumococcal serotypes. Children immunized with this vaccine develop high concentrations of anti-protein D antibodies. The antibodies do not protect against carriage but may protect against otitis media, and it is not known whether they might protect against invasive disease.

What's next?

- The duration of long-term protection provided by the Hib conjugate vaccines remains uncertain—in particular, there are concerns that, because the Hib conjugate vaccine is so effective in reducing carriage, there will be fewer opportunities for natural boosting of immunity in children, which may result in waning of protective Hib antibody concentrations, as has recently been shown in adults.
- The reduction in carriage of Hib in vaccinated children could also open an ecological niche and encourage colonization by other potentially pathogenic organisms, including non-b-encapsulated and non-encapsulated *H. influenzae*, emphasizing the importance of continued long-term surveillance of invasive *H. influenzae* infections across all age groups.
- Further studies are also needed to define more clearly the burden of non-encapsulated *H. influenzae* during the antenatal and perinatal periods.

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Chapter 70

Viral haemorrhagic fevers

See also Chapters 13, 14, 34, 42.

Name and nature of organisms

- VHFs comprise a diverse group of febrile illnesses, often accompanied by haemorrhagic manifestations and multiple organ dysfunction. Many of them present a high case fatality rate. They are classified as biosafety level 3 and 4 pathogens. A few can be transmitted from person to person (contact with blood or tissues of viraemic patients), with a risk for nosocomial infections.
- Viruses associated with haemorrhagic fevers (HFs) are RNA viruses belonging mainly to four families: *Arenaviridae, Bunyaviridae, Filoviridae*, and *Flaviviridae* (Table 70.1). Most are zoonotic, meaning that, in nature, they are also found in animals.
- *Arenaviridae*: viruses are enveloped, bisegmented, single-stranded, round, oval, or pleomorphic, and average 120nm in diameter. They are divided into New and Old World arenaviruses.

Table 70.1 Viruses causing haemorrhagic fever in humans

Family	Virus	Association with	Risk group
Arenaviridae	Old World: Lassa*, Lujo	Rodents	4
	New World: Machupo*, Chapare, Junin*, Sabiá, Guanarito	Rodents	4
Bunyaviridae	Genus nairovirus	Ticks	4
	CCHF*		
	Genus hantavirus	Rodents	3
	Old World: Hantaan, Dobrava-Belgrade		
	New World: Sin Nombre, Andes*, other related		
	Genus phlebovirus	Mosquitoes	3
	Rift Valley fever		
Filoviridae	Ebola*, Marburg*	Unknown	4
Flaviviridae	Omsk HF, Kyasanur forest disease, Alkhurma	Ticks	4
	Dengue (serotypes 1–4), yellow fever	Mosquitoes	3

* Viruses can be transmitted from person to person.

- *Bunyaviridae*: viruses are enveloped, trisegmented, single-stranded, 90–120nm in diameter. Four of the five genera of the family include human pathogens, and three of them include viruses associated with HFs (Table 70.1).
- *Filoviridae*: viruses are enveloped, non-segmented, single-stranded, filamentous, 80 × 800–1000nm. Two viruses are included in the family: Ebola and Marburg. There are five types of Ebola virus: Sudan, Zaire, Côte d'Ivoire, and Bundibugyo, which cause disease in humans, and Reston, which causes disease in primates, but not in humans.
- *Flaviviridae*: viruses are enveloped, non-segmented, single-stranded, 50nm in diameter. Infection with dengue virus can lead to serious disease with haemorrhagic manifestations, known as DHF.

Epidemiology

Viruses causing HFs are geographically restricted to the areas where their host species live. Several modes of transmission have been reported. Very close attention is needed when travellers from endemic areas present with fever of unknown origin, and malaria is excluded.

Arenaviridae

- *Lassa virus*: the disease was first reported in 1969 when two missionary nurses died in Lassa town, Nigeria. The natural host is the Mastomys rat. Lassa fever is endemic in West Africa where tens of thousands of people die of the disease each year.
- *Lujo virus*: it has been described in 2008 in South Africa. The index case acquired the infection in Zambia, and 2° and tertiary cases followed the repatriation of the patient to a hospital in South Africa. Four of the five cases were fatal. Little is known of the epidemiology of this virus, but a rodent reservoir is likely.
- *South American arenaviruses*: each of these viruses is associated with a specific rodent host. Each virus is endemic in a specific country of South America: Junin virus in Argentina, Machupo and Chapare viruses in Bolivia, Guanarito virus in Venezuela, and Sabiá virus in Brazil. Argentine HF (Junin virus) is the commonest, although its incidence has declined since the application of a vaccine. A resurgence of Bolivian HF was noted in 2007–8. Imported cases are very rare outside the Americas. Laboratory-acquired infections have occurred.

Bunyaviridae

- *CCHF virus*: initially reported in the Crimean Peninsula, and later in Congo, it is the most widely distributed tick-borne viral pathogen, being endemic in specific foci in Asia, Europe (Balkans, Russia), and Africa. The geographic range reflects the distribution of Hyalomma ticks, the main vector of the virus. Since 2002, when CCHF emerged in Turkey, several hundreds of cases occur every year.
- *Hantaviruses*: the first isolation of a hantavirus (Hantaan virus) was reported in 1978 in Korea. Hantaan virus and Dobrava-Belgrade

virus cause in humans HF with renal syndrome (HFRS) in Asia and Europe, while Sin Nombre, Andes, and related viruses cause hantavirus pulmonary syndrome (HPS) in the Americas. Several other hantaviruses cause milder disease in humans, while others, including the recently identified shrew-borne hantaviruses, are not associated with disease in humans (at least at present). Thousands of hantaviral infections are observed every year, but few of them present as HF. Each hantavirus is associated with a specific rodent host (voles, mice, rats).

- *Rift Valley fever virus*: the virus was identified at the beginning of the 1930s in the Rift Valley region of Kenya. Currently, it is present in Africa and the Arabian Peninsula. It is mosquito-borne and affects humans and livestock.

Filoviridae

- *Ebola virus*: Ebola virus disease was first recognized in 1976 in the Democratic Republic of Congo. Bats are considered the natural host of the virus. Non-human primates and other mammals are also susceptible. The four pathogenic subtypes are found near rainforests in Central and West Africa. Sporadic Ebola outbreaks occur, which may be extensive with hundreds or thousands of cases, like the major outbreak in 2014 in West Africa (>4000 cases, 60% fatal). Imported cases are very rare but have now occurred, with high fatality rates. Laboratory-acquired infections have been reported.
- *Marburg virus*: the virus was first identified in 1967 during simultaneous HF outbreaks in Marburg and Frankfurt (Germany) and in Belgrade (Serbia) where the virus was introduced through imported monkeys from Uganda. Fruit bats are the reservoir of the virus. It is endemic in Central and West Africa. Sporadic cases and outbreaks occur, the largest of which was in Angola in 2004–5 (252 cases, 90% fatal). Imported cases are very rare. Two cases occurred in 2008, one in the Netherlands and one in the US, after a visit to a bat-infested cave in Uganda.

Flaviviridae

- *Omsk HF virus*: the virus was isolated in 1947 in the Omsk region of Russia. It is tick-borne and endemic in Western Siberia. Rodents, muskrats, and ticks act as reservoirs of the virus.
- *Kyasanur forest disease virus*: tick-borne. First isolated in 1957 from dying monkeys in south India. An average of 400–500 human cases of Kyasanur forest disease have been seen annually over the past five decades in India. A variant of the virus has been identified in China. A related tick-borne virus Alkhurma virus is endemic in Saudi Arabia and Egypt.
- *Dengue virus*: Mosquito-borne. Dengue is endemic in over 100 countries in tropical and subtropical regions of the world. WHO estimates there are 50 million cases of dengue fever per year, of which up to 500 000 are DHF. Imported cases of dengue fever are relatively common in Europe; DHF cases are also seen.

Transmission and incubation period

- *Lassa virus*: humans are infected by direct contact with rats or their excreta, by eating rats or contaminated food, by direct contact with blood or tissues of viraemic patients, or by inhalation of infected rodent excreta or aerosol produced by patients' cough. Symptomatic patients are considered infectious, and the urine may be intermittently positive for up to 2 months. Sexual transmission is possible, as the virus remains detectable in semen for up to 3 months post-symptom onset. The incubation period is 8–14 (range 3–21) days.
- *South American arenaviruses*: modes of transmission to humans are the same as for Lassa virus. Most cases occur between April and July, coinciding with an increase in agricultural activities that facilitate human contact with the rodent reservoirs. Person-to-person transmission has been documented for Machupo and Junin viruses. The incubation period is 6–14 (range 5–21) days.
- *Ebola and Marburg viruses*: during an outbreak, the index case usually had direct contact with an infected animal (non-human primate, other mammal, or bat). The virus is then transmitted to other persons through contact with the patient's blood, tissues, or body fluids during the late stages of infection or during preparation for funerals. Airborne transmission between humans is suspected, but not documented. Nosocomial infections are common. Laboratory infections have been reported. Sexual transmission has been reported 3 months post-onset of symptoms. The incubation period is 5–12 (range 2–21) days for Ebola, and 5–7 (range 3–13) days for Marburg.
- *CCHF virus*: it is transmitted through bites (or crushing) of infected ticks or by direct contact with blood or tissues of viraemic patients or animals. Symptomatic patients are considered infectious. Nosocomial outbreaks are frequent in endemic areas. The incubation period is usually 1–3 (up to 9) days following a tick bite, and 5–6 (up to 13) days following contact with infected blood or tissues.
- *Hantaviruses*: humans are infected by inhalation of aerosolized excreta of infected rodents or consumption of contaminated food or water. Person-to-person transmission is rare (Andes virus). The incubation period is 2–4 weeks (few days to 2 months) for HFRS, and 14–17 days for HPS. Persons with outdoor activities are at increased risk for acquiring the infection.
- *Rift Valley fever virus*: the virus causes large epizootics characterized by abortions among pregnant ruminants. Humans are infected by contact with aborted material, by consumption of raw milk of infected animals, or by mosquito bites.
- *Omsk HF and Kyasanur forest disease viruses*: they are transmitted to humans through tick bites. Omsk HF can be transmitted also by contact with urine, faeces, or blood of infected muskrats or by consumption of milk of infected goats and sheep. Incubation period is 3–8 days.
- *Dengue virus*: humans are infected by bite of *Aedes* mosquitoes, mainly *A. aegypti*. During the viraemic phase, humans infect the biting mosquitoes. The incubation period is 4–7 (range 2–15) days.

Clinical features and sequelae

- *Lassa fever*: most infections (80%) are asymptomatic or mild; 20% are severe or fatal. The case fatality rate among hospitalized patients is 15–20%, and maternal death is high, especially in the third trimester of pregnancy. Fetal and neonatal loss is >80%. Main early symptoms include fever, chills, malaise, headache, myalgia, and sore throat. Nausea, vomiting, diarrhoea, conjunctivitis, exudative pharyngitis, or cough may be present. In severe cases, hypotension, shock, encephalopathy, pleural effusion, and renal and circulatory failure may develop, progressing to severe haemorrhage. Hair loss may occur in convalescence. The most notable complication is acute hearing loss; sensorineural deafness occurs in 25–30% of cases and may persist for life. It does not appear to be associated with disease severity.
- *South American HFs*: gradual onset of symptoms—fever, malaise, myalgia, headache, back pain, and flushing of the face. Petechiae and haemorrhage develop after a few days, and neurological manifestations may follow with tremor of the hands and tongue, seizures, and coma. Blood loss is usually minor, but the haematocrit rises as capillary leakage increases. Case fatality rate is 30–40%. Convalescence is slow, but sequlae are not observed.
- *Ebola and Marburg*: the onset is sudden with flu-like symptoms. Prostration follows rapidly, with pharyngitis, vomiting, severe watery diarrhoea, conjunctivitis, and a measles-like rash. Neurological manifestations include severe lethargy, irritability, and confusion. Haemorrhagic manifestations develop after 4–5 days and may progress to severe blood loss from various systems and death. Case fatality rate is up to 90%. Pregnant women present with severe haemorrhages, and fetal loss is very common. Convalescence is slow and debilitating, and survivors may have prolonged amnesia.
- *CCHF*: the onset is sudden with fever, myalgia, dizziness, neck pain and stiffness, backache, headache, sore eyes, and photophobia. Nausea, vomiting, diarrhoea, sore throat, and petechial rash may also occur. Haemorrhagic manifestations develop after 5 days and may be extensive with ecchymoses and generalized bleeding of the gums and orifices. In severe cases, multi-organ failure develops. Case fatality rate is 5–30%.
- *HFRS and HPS*: HFRS is characterized by acute renal failure, while cardiopulmonary insufficiency is seen in HPS cases. In both syndromes, the prodrome phase presents with flu-like symptoms, followed by the hypotensive, oliguric, diuretic, and convalescent phases in HFRS, and by a rapidly progressive cardiopulmonary phase, diuresis, and convalescence in HPS. The hypotensive and oliguric phases are very critical in HFRS, and severe haemorrhages may occur. Pleural effusion, pulmonary oedema, and cardiogenic shock can be seen in HPS. In both diseases, diuresis is a sign of recovery. Case fatality rate is 12% in HFRS, and up to 60% in HPS.
- *Rift Valley fever*: clinical signs include hepatitis, retinitis, encephalitis, and haemorrhages. Case fatality rate is 0.5–2%.
- *Dengue fever/DHF*: most infections are asymptomatic or mild with flu-like symptoms, retro-orbital pain, and rash. Lymphadenopathy may

be present. DHF is a potentially fatal complication of dengue fever, associated with an altered immune response to sequential infection with different viral serotypes, leading to increased vascular permeability. DHF is often seen in children <15 years old and is characterized by thrombocytopenia and plasma leakage. Case fatality rate of DHF can exceed 20% in the absence of circulatory support, but it is <2% with appropriate management. Dengue shock syndrome is a DHF accompanied by hypotension leading to shock.

Diagnosis

- Diagnostic testing must be carried out in a designated laboratory with containment level 3 or 4 facilities.
- The diagnosis of a VHF should be considered in all patients returning from an endemic area and presenting with compatible symptoms, especially when malaria is excluded.
- In the first few days of illness: detection of viral nucleic acid by PCR; detection of viral antigens by immunofluorescence or ELISA; virus isolation from blood or tissue samples.
- Detection of IgM and IgG antibodies in serum by ELISA or immunofluorescence. IgM may be detectable very soon after symptoms onset. For dengue diagnosis, serological cross-reactions with other flaviviruses must be rigorously excluded.
- Differential diagnosis depends on the country of exposure and includes malaria, typhoid fever, leptospirosis, and rickettsiosis.
- Dual pathology is possible.

Management and treatment

- Seek specialist advice as soon as possible, and transfer the patient to a specialized unit with negative airflow, if appropriate.
- Symptomatic and supportive treatment is essential, particularly fluid and electrolyte balance, oxygenation and haemodynamic support, and replacement of coagulation factors and platelets.
- Renal failure with oliguria is a prominent feature of HFRS and may be seen in other VHFs, as intravascular volume depletion becomes pronounced. In HFRS, the management of oliguria may require haemodialysis or peritoneal dialysis.
- In severe VHF cases, management will be required for blood loss and shock.
- Monitor platelets and the haematocrit, and the viral load in blood and/or urine.
- Ribavirin is effective for treating Lassa fever, Argentine HF, and potentially CCHF.
- Convalescent immune plasma has been used, with beneficial effect, against Argentine HF. Specific hyperimmune globulin from the plasma of CCHF convalescents is used in Bulgaria.
- No specific therapeutic options exist currently for other VHFs.

Prevention

Lassa and other arenaviruses, Crimean–Congo haemorrhagic fever, Ebola, and Marburg

- Strict isolation and barrier nursing of the patients to minimize exposure of other persons and to prevent nosocomial transmission. Non-essential staff and visitors should be restricted.
- All persons entering the room must wear gowns, gloves, booties, and face shields/googles. Proper disposal after use is critical.
- Laboratory tests should be kept to the minimum necessary for clinical management. Samples must be appropriately labelled, and the laboratory should be alerted. Avoid glass containers. Disposable sharp objects should be placed in the specific box immediately after use. Autoclave before disposal.
- Protective measures of family members and relatives of an infected person.
- Protective measures during infected bodies management (sealed bag, disinfectants).
- Standard protocols for laundry, cleaning, and disinfection may be followed where there is no contamination by blood/body fluids. Safe and effective disinfection and decontamination procedures are required for material contaminated with blood/body fluids. Contaminated environmental surfaces should be cleaned with hypochlorite solution (5000 ppm available chlorine); a higher concentration (10 000 ppm available chlorine) should be used when contamination is heavy. When possible, contaminated material and samples should be double-bagged and autoclaved or incinerated.
- Contact tracing: all persons who had contact with a symptomatic case must be identified and risk-assessed. Those with close contact must be monitored by daily temperature checks for 21 days following the last contact with the index patient.
- Post-exposure prophylaxis with ribavirin has not been studied but should be considered for high-risk contacts.
- Vaccines are currently not available, except for Argentine HF (used since the 1990s, resulted in decrease in the incidence of the disease) and for CCHF (inactivated suckling mouse brain-derived vaccine used in Bulgaria for prophylaxis of defined risk groups).
- Prevention of naturally acquired cases in endemic areas: control of rodents—rodent-proof storage containers; control of ticks with insecticides—avoid tick bites (application of insect repellents containing DEET, proper clothing); wearing gloves and other protective clothing to avoid contact with blood or tissues of livestock.
- Immediate report to the public health authorities about any suspected case—early warning system.
- Follow the international rules for transportation of laboratory specimens.

Dengue and haemorrhagic fever with renal syndrome/ hantavirus pulmonary syndrome

- Control of infection procedures when managing patients.
- Contact tracing is not required.
- A dengue vaccine has shown around 50% protection in recent clinical trials.
- Prevention of naturally acquired cases in endemic areas: control of rodents, rodent-proof storage containers, mosquito control, and avoidance of mosquito bites (application of insect repellents, bed nets).

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Chapter 71

Hand, foot, and mouth disease

See also Chapters 34, 64.

Name and nature of organism

- HFMD is caused by enteroviruses, mainly enterovirus 71 (EV71) and Coxsackie virus A16. Both most commonly associated with epidemics. Other Coxsackie viruses A5, A6,[1,2] A10, and B1–B5 have also been implicated.
- Enteroviruses are members of the *Picornaviridae* family; small (pico) non-enveloped RNA viruses.

Epidemiology

- HFMD is common in children, especially those aged 1–4 years. It has not been described in neonates or adults >65 years.
- Worldwide, the disease is endemic and occurs sporadically and in epidemics, especially in preschool childcare establishments.
- Epidemic HFMD is mostly seen in Asia (China, Malaysia, Japan, Taiwan, Hong Kong, Vietnam, Singapore, etc.), but, in the past 10 years, also in Australia, Europe (France, Denmark, Spain, Portugal, Hungary), and the US.[3,4]
- EV71 has been associated with severe neurological complications and even fatalities in infants and young children worldwide.[3]
- There is a bimodal seasonal pattern, with the disease being commonest in summer and late autumn/early winter.

Transmission and incubation period

- Transmission is either by faecal–oral route or droplet spread from nasal secretions, saliva, or blister fluid.
- Incubation period is 3–7 days.

Clinical features and sequelae

- HFMD usually starts with fever (mild to high) and sore throat.
- One to 2 days later, tender macular → vesicular → ulcer lesions 4–8mm develop across the tongue and buccal mucosa.

- Seventy-five per cent of cases develop a skin rash, usually 1 day after mouth lesions. The rash can be maculopapular, tender vesicular, or pustular in morphology (4–8mm in size). The rash is more commonly present on the hands than on the feet, and the dorsal surfaces are more often affected than the palms and soles. The rash can also develop on the buttocks, trunk, genitalia, face, and limbs.
- Classically, vesicles are seen along the sides of the fingers, which is virtually diagnostic of HFMD.
- The illness usually resolves in 2–3 days without complication. In some patients, the disease could last for 1 week.
- A small proportion of infected children rapidly develop severe, and sometimes fatal, neurological and systemic complications over days, or even hours.[5]
- Rare features include aseptic meningitis, poliomyelitis-like acute flaccid paralysis, brainstem encephalitis, pulmonary oedema, and cardiorespiratory collapse.[4,5]
- Onychomadesis (shedding of the nail) can be seen ~1 month after atypical HFMD associated with Coxsackie viruses.

Diagnosis

- HFMD is typically a clinical diagnosis, and no tests are required.
- The virus can be cultured, and/or PCR performed.[5]
- Samples for laboratory investigation should be selected, according to the disease manifestations (e.g. throat, rectal, ulcer, serum, urine, CSF, vesicular fluid). Virus detection in samples from sterile sites is more reliable than that in samples from non-sterile sites. However, the viral load in sterile sites is frequently very low. The efficient approach may be to examine throat swabs plus swabs from at least two vesicles or from the rectum for patients with no vesicles.[5]

Differential diagnosis

- Viral infections: measles, rubella, VZV, HHV-6, HHV-7, parvovirus B19, dengue, flavivirus infections (especially HF), alphavirus infections, EBV, 1° HIV infection, and non-specific viral rashes.
- Bacterial infections: meningococcaemia, scarlet fever, leptospirosis, relapsing fever (*Borrelia recurrentis*), Lyme disease, syphilis, typhus, and other rickettsial infections.
- Other disorders: scabies, drug reactions, allergies, and paraneoplastic syndrome.
- Aseptic meningitis caused by other viruses and flaccid paralysis of the limbs.

Management and treatment

- As HFMD is usually mild and self-limiting, symptomatic treatment is all that is usually required.

Prevention

- Children should be isolated until the rash has settled. The virus may continue to be shed in stool for weeks after the infection; however, it is not practical to isolate them after the symptoms have settled.
- Strict personal hygiene should be encouraged, and sharing of cups, cutlery, etc. should be prohibited.
- The Vero cell-based EV71 inactivated vaccine with aluminum hydroxide (Sinovac EV71) was approved in China in April 2014.[6] Phase III clinical trial of the vaccine candidate showed ~95% efficacy rate against HFMD caused by EV71 in infants and young children 6–35 months of age.[7]

Further research

- No established antiviral treatments are available for EV71.
- Several recent studies have demonstrated the anti-EV71 activity of natural products and other compounds (Kappa carrageenan, WIN 51711capsid-binding inhibitor, monoclonal antibody E18, LVLQTM peptide, etc.).[3]
- *In vitro* and *in vivo* studies show that both ribavirin and IFNs might be useful, and RNA interference approaches are being explored.
- IVIG suggest a benefit, if given early.
- Milrinone might be helpful in patients with cardiac dysfunction.[5]
- A bivalent vaccine studies against both EV71 and Coxsackie virus A16 are ongoing in mice.[8]

What's next?

- Vaccines that combine several picornaviruses are under development.
- Phase 2 studies examining the efficacy of magnesium sulfate therapy in severe HFMD are planned (Available at: <https://clinicaltrials.gov/ct2/show/NCT01940250>).

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Chapter 72

Helicobacter pylori

See also Chapters 12, 13, 22.

Name and nature of organism

- *Helicobacter pylori* is a non-invasive Gram-negative spiral organism that colonizes the gastric mucosa. It preferentially colonizes the gastric antrum, although it may also be found throughout the stomach.
- It occupies an inhospitable niche, at a site free from other bacterial colonization, where it has to survive for very long periods at low pH. It is predominantly found within, and immediately beneath, the gastric mucous layer where there is less acid than in the gastric lumen, and little proteolytic enzyme activity.

Epidemiology

- *H. pylori* affects over 50% of the world's population, making it one of the commonest chronic bacterial infections.
- There are major differences in prevalence both within and between countries, e.g. 40% of 50 year olds are infected in the UK, compared to 85% of 2 year olds in resource-poor countries. In general, the prevalence increases with age and is strongly associated with poor sanitation and crowded living conditions.
- In resource-rich countries, the incidence has decreased in recent decades, most likely due to improved socio-economic conditions.

Transmission and incubation period

- Transmission is almost certainly by direct person-to-person spread, with close personal contact being essential.
- The organism has been cultured from vomitus and faeces; isolated reports have identified bacteria and DNA from the oral cavity.
- Bacterial DNA has been detected in biofilms in water storage systems, but there is no good evidence to support the existence of environmental or animal reservoirs.
- The striking feature of *H. pylori*-associated upper GI disease is the very long duration of colonization before the disease state develops. Typically, colonization occurs in childhood, but disease appears in adult life after decades of colonization/infection.

Clinical features and sequelae

- *H. pylori* is usually asymptomatic in children.
- Children should only be tested for *H. pylori* if they have clinical evidence of gastritis or duodenal ulcer disease, and not for mild recurrent abdominal pain.
- Colonization always causes gastritis but alone does not cause symptoms.
- *H. pylori* is the major cause of duodenal ulceration worldwide,[1] but infection only rarely leads to duodenal ulceration in childhood.
- The pathogenesis of *H. pylori*-associated duodenal ulceration is incompletely understood, although certain bacterial genotypes may be associated with disease expression.
- While it seems likely that these virulence determinants are associated with the development of disease, many subjects with apparently pathogenic strains of *H. pylori* within their stomachs remain symptom-free, and many ulcer patients harbour 'non-pathogenic' isolates.
- Long-term *H. pylori* colonization is a risk factor for the development of gastric carcinoma in adult life. Infection has also been shown to cause very rare gastric mucosal B-cell non-Hodgkin's lymphomas (MALTomas).
- There is no good evidence for a link between *H. pylori* and recurrent abdominal pain in childhood. Diagnosis of *H. pylori* should not form part of the investigation of abdominal pain in childhood, unless duodenal ulceration is suspected.
- Iron deficiency: there is evidence that refractory iron deficiency anaemia may be associated with childhood *H. pylori* in some populations and that eradication of *H. pylori* may improve response to iron therapy, but results of studies are inconsistent.[2]

Diagnosis

- Culture or histology from endoscopically obtained biopsies is the diagnostic gold standard. Endoscopy also establishes whether a duodenal ulcer is present. Gastric mucosal biopsies are cultured on selective enriched media in a microaerobic atmosphere at 37°C for 5 days. Success has also been reported from research projects culturing samples obtained from string tests, vomitus, and occasionally faeces.
- Serology: measurement of specific IgG by ELISA is a reliable diagnostic test, suitable for 1° diagnosis in older children and adults. It may be unreliable in younger children (<10 years), and almost certainly unreliable among the <5 year olds. It is not useful to check eradication or reinfection, as specific IgG levels may remain positive for 6–12 months after clearance of infection.
- Urea breath tests are widely used for non-invasive diagnosis of *H. pylori* in childhood, with sensitivities and specificities of over 95%. Both radio- (^{14}C) and stable isotope (^{13}C) versions exist; they rely on the ingestion of a labelled dose of urea, followed by breath collection 30–45 minutes later. A rise in isotopic ratio of the label (^{13}C or ^{14}C) in expired breath

indicates gastric urease activity, which, in humans, is diagnostic of *H. pylori* colonization.
- Faecal *H. pylori* antigen can be detected by ELISA and is a reliable diagnostic test in children.
- Both faecal antigen ELISA and urea breath tests are suitable means of checking eradication and reinfection.

Management and treatment

- Only children with evidence of gastric or duodenal ulcer disease, lymphoma, atrophic gastritis, and a confirmed diagnosis of *H. pylori* should be treated.
- There is no good evidence to support treating children with no symptoms, recurrent abdominal pain, or a family history of ulcer disease and positive *Helicobacter* serology.
- There are insufficient randomized controlled treatment trials in children.
- The organism is relatively protected from the host immune response; therefore, intensive eradication therapy is required.
- The ability of small surviving inoculates to recolonize means that the emergence of antibiotic-resistant strains is very likely. It is therefore important to ensure that, when treatment is offered, complete courses are given, appropriate protocols that account for common local resistance patterns are followed, and treatment is reserved for those patients who will benefit from eradication.
- First-line therapies include two antibiotics, combined with a PPI, for 1–2 weeks. In children, treatment is usually given for 2 weeks, although it is not clear whether the higher eradication rates outweigh the increased side effects and poorer compliance.
- In children, two antibiotics out of metronidazole, clarithromycin, and amoxicillin are used, along with omeprazole.
- Antibiotic resistance is significant. The limited data suggest resistance rates of around 50% for metronidazole and 10% for clarithromycin across Europe. Check country-specific protocols.
- In older children and adults, the same antibiotic regimens are used, but lansoprazole usually replaces omeprazole.
- Poor compliance is associated with a high risk of persistent infection that becomes increasingly difficult to eradicate with further courses of therapy.
- Second-line therapies for eradication failure include colloidal bismuth subcitrate in combination with two antibiotics and a PPI. There may also be a role for ranitidine bismuth subcitrate in combination with two antibiotics. The duration of second-line therapy varies but is usually for at least 2 weeks.
- Eradication should be confirmed by urea breath test or faecal ELISA 4 weeks after treatment has been completed.
- Patients with peptic ulceration and persistent *H. pylori* infection after second-line therapy require ongoing treatment. Ideally, they should be referred to a specialist centre for isolation of the infecting strain of *H. pylori* and antibiotic sensitivity testing, before embarking on further

targeted treatment, which may include sequential antibiotic therapy, including tetracyclines, in older children and adults. They should remain on PPIs until their *H. pylori* infection is eradicated.
- Reinfection is unusual in those aged >5 years in developed countries. It is not known how common reinfection after eradication is in resource-poor countries, but rates may be very high.

Prevention

- There is no good evidence that the systemic and local immune response seen in *H. pylori* colonization either leads to eradication of the organism or protects against recolonization after treatment. Vaccines have been developed in animal models but are unlikely to be used in humans in the foreseeable future.
- There are no consistent data to support the use of pro- or prebiotics to protect against *H. pylori* colonization.

Future research

- A more detailed understanding of the pathogenesis and disease expression is being developed year-on-year.
- The role of the host immune response in regulating chronic infection and the influence of chronic, often decades long, gastric inflammation on mucosal immune regulation are important to our understanding of all GI inflammatory disease.
- The evolution of the *H. pylori* genome that occurs over decades within one stomach may also influence disease outcome.

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Chapter 73

Hepatitis A and E

Hepatitis A

Name and nature of organisms

Hepatitis A virus (HAV) is a non-enveloped, positive-stranded RNA picornavirus, ~27nm in diameter.

Epidemiology

- Hepatitis A occurs worldwide and is common in the Middle East, Africa, Asia, and Central and South America. Most people in these regions are infected when they are young children. Children from Europe who visit friends or relatives in these countries are particularly at risk of infection.
- The incidence of hepatitis A in developed countries has fallen dramatically over the past few decades. Seroprevalence in England and Wales increases with age: 4% in those aged 1–4 years, 9% in those aged 1–9 years, 26% in those aged 25–44 years, and 74% in those aged over 60 years. Seroprevalence is higher among those of non-white ethnicity.
- Travel is an important risk factor for hepatitis A infection, with the Indian subcontinent and the Far East being the areas of highest risk for UK travellers.
- Sporadic cases of HAV with no travel history are becoming increasingly common.[1]
- Blood-borne transmission of HAV can occur but is rare.

Transmission and incubation period

- HAV is excreted in bile and shed in stools of infected persons. Transmission is by the faecal–oral route.
- The incubation period of HAV is 15–45 days (average 4 weeks).
- Peak excretion occurs during the 2 weeks before the onset of jaundice. Patients are therefore infectious from 2 weeks before the onset of symptoms and may continue to be infectious for 1 week or more after. Children may excrete the virus for longer than adults, although a chronic carrier state does not exist.
- Person-to-person spread is the commonest method of transmission in developed countries. Children under the age of 6 years are particularly effective transmitters of hepatitis A infection. Transmission within households is very common and can occur in nurseries and 1° schools.
- Food-borne outbreaks and sporadic cases can occur due to contamination of food.

Clinical features

- Young children who are infected with HAV usually remain asymptomatic. The severity of symptoms increases with age.
- Typical symptoms of acute hepatitis are: general malaise, anorexia, nausea, vomiting, abdominal pain, arthralgia, and low-grade fever. Some children then develop jaundice, dark urine, pale stools, tender hepatomegaly, splenomegaly, or rash.

Diagnosis

- Both serological markers and molecular techniques are used in the diagnosis of HAV infection. Serological diagnosis is usually made during the acute illness by the presence of anti-HAV IgM, with anti-HAV IgG appearing shortly after the anti-HAV IgM. Viral RNA can be detected prior to the onset of symptoms and the production of anti-HAV IgM, and remains detectable many weeks after onset of symptoms. Anti-HAV IgM is rarely detectable 1 year after recovery, but anti-HAV IgG remains detectable giving lifelong immunity.

Management and treatment

- Hepatitis A is an acute self-limiting disease, and, in the majority of cases, no treatment will be required.

Management of the child with hepatitis A

- Advise good hygiene practices (to avoid faecal–oral spread).
- Exclude from school or nursery until 7 days after the onset of jaundice (or other symptoms if no jaundice).
- Identify possible source of infection.

Prevention

1° prevention

- Infection is prevented by good hygiene, especially handwashing, safe drinking water, and good food hygiene. Vaccination can be used to prevent hepatitis A in high-risk groups. The following children are recommended to receive hepatitis A vaccination:[2]

1. Anyone travelling to areas of moderate or high risk (Indian subcontinent, the Far East, and Eastern Europe) for prolonged periods, particularly if sanitation and food hygiene is likely to be poor
2. Patients with chronic liver disease
3. Patients with haemophilia.

Prevention of secondary cases

Prevention of 2° cases should be discussed with a consultant for communicable disease control.

- For household contacts identified within 14 days of exposure to the index case:
  - Offer hepatitis A vaccine to healthy contacts aged 1–50 years.
- Infants <12 months of age very rarely develop symptomatic hepatitis A infection. However, infants are at risk of developing subclinical infection and infecting others. If all those involved in nappy changing are vaccinated against hepatitis A, this should prevent the spread of infection.

- If it is not feasible to vaccinate all carers, infants aged ≥2 months can be vaccinated with hepatitis A vaccine or excluded from childcare settings until 40 days after exposure to hepatitis A.
- For household contacts identified >14 days post-exposure: discuss with a consultant for communicable disease control.

Management of contacts outside the household

Discuss with a consultant for communicable disease control.

- If the index case is a child cared for in a preschool childcare setting, then treat contacts working, or being cared for, in the same room as household contacts.
- If the index case attends a 1° school and the source of infection outside school has not been identified: assume infection acquired within school, and offer hepatitis A vaccine to classroom contacts.

Hepatitis E

Name and nature of organism

Hepatitis E virus (HEV) is a non-enveloped, spherical particle, ~30–34nm in diameter. The virus is a member of the *Hepeviridae* family.

Epidemiology

- HEV is a family of at least four closely related viruses referred to as genotypes 1 to 4 (G1–4), each of which has distinct host preferences and patterns of illness. HEV infection and the disease it causes—hepatitis E—are found worldwide.
- HEV is hyperendemic through much of the developing world where sanitation and food hygiene may be poor. Infections in the developing world are usually linked to G1 (South Asia, the Middle East, and Africa) and G2 viruses (Mexico). In these countries, the virus results in sporadic cases of hepatitis, but also in large water-borne outbreaks associated with faecal contamination of water. Data from hyperendemic regions indicate the clinical attack rates are highest among young adults.
- Cases in the developed world are mainly sporadic and are linked to G3 (Europe, North America, and Japan) and G4 viruses (South East Asia). The majority of HEV cases are acquired indigenously through the dietary route, although cases are also observed in travellers returning from HEV hyperendemic areas.
- A programme of enhanced surveillance of hepatitis E has been running in England and Wales since 2003 and shows the majority of cases to be acquired indigenously. Six hundred and ninety-one cases were reported in 2013, including 477 (69%) indigenously acquired infections. The demography of indigenous hepatitis E is striking, with the majority occurring in ♂ over the age of 50 years.

Transmission and incubation period

- The incubation period ranges from 15 to 60 days (average 40 days).
- In the developing world, the virus transmits enterically via the faecal–oral route. Infection is linked to the consumption of human sewage-contaminated food or water.
- Through the developed world, the virus transmits zoonotically. There is good evidence supporting the acquisition of HEV through the consumption of raw/undercooked deer, boar, and pig meat. Case control studies from England have indicated that HEV infection is linked to the consumption of processed pork.
- Reports of transfusion-transmitted hepatitis E demonstrate that the virus can be acquired parenterally. A recent study showed 1:3000 donations to be HEV RNA-positive and that asymptomatic infection among blood donors is widespread in England. A 42% transmission rate from HEV-containing blood components was demonstrated.
- Person-to-person transmission has been rarely described in relation to HEV infections.

Clinical features and sequelae

- The majority of infections, including those occurring in children, are asymptomatic. In symptomatic cases, the disease is usually mild. Symptoms typical of acute hepatitis E include jaundice, dark urine, pale stools, fatigue, loss of appetite, abdominal pain, fever, and nausea.
- Infections during pregnancy, especially in the third trimester, are associated with a 30% case fatality rate in mothers, with poor neonatal outcome. In a study of HEV-infected pregnant women, premature births were observed, as well as an increase in the probability of prenatal death. This has been reported in hyperendemic areas where G1 viruses circulate but does not appear to be a feature of G3 infections.
- Chronic HEV infection is increasingly recognized in immunosuppressed individuals, including children. Reports come from solid organ transplant recipients, patients with haematological disorders, and HIV-infected persons. These cases are, in the main, asymptomatic, with only mild liver enzyme derangement, although the long-term prognosis for individuals with chronic hepatitis E is poor. Chronic hepatitis E infection can result in rapidly progressive liver fibrosis and cirrhosis, with death due to decompensated liver disease.
- Acute HEV infection in patients with pre-existing liver disease has been associated with a poor outcome, with reported case fatality rates of up to 70%.

Diagnosis

- Both serological and molecular techniques are used in the laboratory diagnosis of HEV. In an acute HEV infection, peak viraemia occurs during the incubation period and early phase of disease. Viral RNA can be detected just before the onset of clinical symptoms in both blood and stool samples. HEV RNA does not persist, becoming undetectable in blood about 3 weeks after the onset of symptoms. Some reports suggest that the virus is shed in the stool for a further 2 weeks. HEV IgM is detected during the acute phase of the illness and can persist

for 4–5 months. HEV IgG appears shortly after IgM, and levels rise rapidly. Estimates of the duration of the IgG response and immunity to subsequent infection vary, but antibody has been detected up to 12 years after infection.
- HEV RNA must be measured when screening samples from immunocompromised individuals, as HEV antibody testing alone is not reliable in this setting. It should be noted that the development of an antibody response in these individuals is not always associated with viral clearance.

Management and treatment

- In the majority of hepatitis E cases, no treatment will be required, as these infections will clear uneventfully.
- Individuals with persistent HEV infection may require intervention. Data from the transplant setting have shown that a reduction in immunosuppression levels (in particular drugs that target T cells) led to viral clearance in 30% of cases. Clearance in this setting is usually associated with seroconversion, and frequently with transaminitis. Antiviral treatment should be considered for patients in whom alteration of immunosuppression has been either impossible or ineffective in achieving viral clearance.
- Antiviral treatment has been used successfully to treat chronic HEV infections. Treatment regimens vary and include interferon alfa and ribavirin as monotherapy or in combination. Ribavirin monotherapy is becoming the drug of choice, with viral clearance usually achieved within a few weeks. However, caution is needed, as IFN therapy is contraindicated in kidney transplant patients due to increased risk of acute rejection. In addition, to avoid ribavirin-induced haemolytic anaemia, the dose should be adjusted, according to renal function.

Prevention

- Prevention in endemic regions is best achieved by reducing faecal–oral transmission through the provision of clean drinking water and good sanitary infrastructure.
- In the developed world, ensuring meat products are thoroughly cooked and appropriately handled will be good measures for reducing transmission.
- The issues of introducing appropriate strategies to prevent the transmission of HEV through blood are currently being discussed.
- A hepatitis E vaccine (Hecolin®) has been licensed for use in China in those aged between 16 and 65 years. The vaccine, also known as HEV 239, is a 26kDa protein encoded by ORF2 of HEV G1. In a phase 3 trial, ~113 000 participants were randomly assigned to receive either three IM injections of the vaccine at 0, 1, and 6 months or hepatitis B vaccine as a placebo. Follow-up of around 97 000 participants who received all three doses indicated a protective efficacy rate of 100% (95% CI 72.1 to 100.0). Hecolin® was well tolerated, with local reactions at the injection site being the main adverse event associated with its use. The data also showed that, despite being based on G1 virus, the vaccine provided protection against G4 infections. However, there are limited or no

data available on the safety and immunogenicity of the vaccine among children, pregnant women, and in specific groups such as individuals with chronic liver disease and immunocompromised patients. The long-term efficacy of the vaccine, duration of protection, and the need for a booster dose have not been determined. In addition, the efficacy of the vaccine when administered post-exposure or in controlling disease outbreaks remains unknown.

Future research

- To better define HEV seroprevalence rates, using improved and validated immunoassays.
- More comprehensive studies are needed to understand chronic HEV infections in the immunosuppressed population. Questions still remain on how common these infections are, what the outcome in these patients is, and whether G1 and G2 infections also result in chronic HEV.
- More studies are needed on the safety and immunogenicity of the Hecolin® vaccine among specific groups. In addition, more data are needed on the efficacy of the vaccine against G2 and G3 infections.
- Further studies are needed to understand the food and environmental routes of HEV transmission.

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Chapter 74

Hepatitis B

Name and nature of organism

- HBV is a global health problem and can cause a wide spectrum of liver disorders, including acute hepatitis, fulminant hepatitis, chronic hepatitis, liver cirrhosis, or HCC.
- HBV is a prototype member of the *Hepadnaviridae* family.
- The virus comprises a partially double-stranded DNA, DNA polymerase with reverse transcriptase activity, and hepatitis B core antigen (HBcAg), all surrounded by hepatitis B surface antigen (HBsAg).
- Eight genotypes of HBV have been defined (A–H), and each genotype has a unique geographical distribution. Infection with different genotypes may have different clinical course and outcomes.

Epidemiology

- HBV has a worldwide distribution. An estimated 2 billion people (a third of the world population) have serological evidence of HBV infection, with an estimated 400 million people chronically infected with the virus.
- HBV is the tenth leading cause of death worldwide, causing up to 1 million deaths a year.
- High-prevalence regions include sub-Saharan Africa, most of Asia, and the Pacific islands. Low-prevalence regions include most of Western Europe and North America.
- Prevalence of chronic hepatitis B in children in England is estimated as 4.6 per 100 000. Approximately half are UK-born.

Transmission and incubation period

- Incubation period for acute infection ranges from 40 to 160 days, (average 90 days). Evidence of viraemia has been demonstrated as early as 6 days after exposure.
- Humans are the only natural reservoir of HBV.
- The main routes of transmission are parenteral or percutaneous exposure to infected blood or other body fluids, and include:
  - Sexual transmission (vaginal or anal intercourse)
  - Sharing of needles or other equipment by injecting drug users
  - Needle-stick injuries
  - Perinatal transmission from mother to child
  - Human bites (rare).

- In areas of high prevalence, transmission is predominantly perinatal from mother to child, although horizontal transmission between young children may occur.
- In low-endemicity countries, most infections are acquired in adulthood by sexual transmission or sharing of blood-contaminated needles and equipment by IV drug users.
- Transmission through breastfeeding is extremely rare. Mothers with HBV infection are advised that it is safe to breastfeed their babies.
- The risk of developing chronic infection depends on the age at which the infection is acquired. Chronic infection occurs in 90% of those infected at birth, in 20–50% of those infected between the ages of 1 and 5 years, in 6–10% of those infected >5 years of age, and <5% at older ages.

Clinical features and sequelae

Acute infection

- Hepatitis without jaundice is the predominant clinical presentation of acute hepatitis B infection (90% children, 50–70% adults).
- Most cases are asymptomatic or subclinical.
- Symptomatic acute hepatitis B, characterized by malaise, poor appetite, and jaundice, is mostly a disease of older children and adults (33–50%). It produces typical illness in only 5–15% of children between 1 and 5 years of age, while newborns generally do not develop any symptoms at all.
- Rarely (<1%), acute hepatitis B infection has a fulminant presentation. Newborns infected vertically from an anti-HBe antibody-positive mother have an increased risk of developing fulminant hepatitis B infection, typically at age 2–4 months.
- Blood tests: liver enzymes, especially transaminases, are markedly elevated. HBsAg is the first viral marker to appear in the blood. Hepatitis B envelope antigen (HBeAg) may appear early but is usually cleared rapidly. Hepatitis B core IgM (IgM anti-HBc) is a helpful marker in the diagnosis of acute hepatitis B.
- In acute hepatitis B, HBsAg clears, and its antibody (anti-HBs) appears within 6 months of disease onset. The seroconversion from HBeAg to anti-HBe antibodies is associated with a reduction in the viral load and is the first step toward clearance of infection. Virus elimination is characterized by clearance of HBsAg and production of anti-HBs antibodies.

Chronic infection

- Chronic hepatitis B infection is defined as persistence of HBsAg in the serum for 6 months or longer.
- Surface antigen-positive carriers are subdivided, according to eAg and eAb status. Children who are eAg-positive are highly infectious or 'high-risk' carriers, whereas those who are eAg-negative (usually anti-HBe-positive) have a lower risk of transmission ('low-risk' carriers).

- Children with chronic hepatitis B infection are usually asymptomatic, unless complications, such as cirrhosis or HCC, arise.
- Occasionally, extrahepatic manifestations, such as papular acrodermatitis, lymphadenopathy, and nephrotic syndrome related to membranous glomerulonephritis, occur. These manifestations are more often seen in children.
- Chronic hepatitis B has three phases, which may be determined by eAg/eAb status and serum aminotransferase enzymes. Level of HBV DNA, measured by PCR, provides supportive information and now provides more accurate and direct measurement of viraemia. Presence of eAg has been used previously as a surrogate marker of viraemia.
  1. *Immune-tolerant phase* with high viral replication: HBeAg-positive, high HBV DNA levels, and normal level of aminotransferases. This pattern is mainly seen in children infected at birth who are usually asymptomatic. It may persist for decades. However, some children proceed to the next phase.
  2. *Immune-active phase* with elevated aminotransferases and marked inflammation, which, if persistent, may lead to fibrosis. A sudden elevation of aminotransferases may lead to spontaneous seroconversion where HBeAg production ceases and anti-HBe is produced. This is not usually associated with any symptoms and leads to the next phase of inactive disease. However, if immune clearance is ineffective, persistent necro-inflammation leads to progressive liver disease and risk of complications.
  3. *Inactive carrier state* with normalization of aminotransferases, presence of e antibody, reduction in HBV DNA, and improvement in hepatic inflammation.

There remains a risk of resurgence of viraemia and inflammation, termed eAg-negative chronic hepatitis, with similar risks to the eAg-positive immune-active phase. In the absence of this, in ~1% each year, the inactive carrier state is followed by the loss of sAg and the development of sAb. Infection is not completely eradicated, however, as HBV covalently closed circular DNA (cccDNA) remains integrated in the host genome.

Cirrhosis and hepatocellular carcinoma

Chronic HBV infection is associated with a 15–25% risk of progression to cirrhosis or HCC over several decades. Risk factors include persistent high HBV viral load, prolonged immune activation phase, increasing age, and ♂ gender. Development of HCC is not wholly dependent on pre-existing cirrhosis being present. Seropositivity for HBsAg is one of the most important risk factors for the development of HCC. In areas of high endemicity of hepatitis B, >95% of HCC are HBsAg-seropositive. Although rare in childhood, it may complicate eAb-positive carriers, as well as eAg-positive. The prognosis of HCC is poor.

Diagnosis

Diagnosis is dependent on serology. Serological testing for hepatitis B antibodies and antigens indicates whether the child has acute or chronic HBV

infection, is a high- or low-infectivity carrier, and has natural immunity or immunity from vaccination. Table 74.1 summarizes the interpretation of serological tests in hepatitis B.

Table 74.1 Interpretation of serological test results for HBV

Status	Anti-HBc	Anti-HBc IgM	HBsAg	Anti-HBs	HBeAg	Anti-HBe
Acute infection	+	+	+	−	+/−	+/−
Chronic infection (high infectivity)	+	−	+	−	+	−
Chronic infection (low infectivity)	+	−	+	−	−	+
Recovery (natural immunity)	+	−	−	+/−	−	+/−
Immunity (after vaccination)	−	−	−	+	−	−

- Following confirmation of the diagnosis, HBV is a notifiable disease to PHE. Contact identification is required, and consideration given to the mode of acquisition which should include the possibility of sexual transmission.
- Most children with chronic hepatitis B in areas of low endemicity are either new migrants or vaccine failures. They should be referred to a specialist paediatric centre, so that all the family may be supported, counselled, screened, and immunized. Annual review should include hepatitis B serology and hepatitis B DNA viral load, LFTs, α-fetoprotein, and abdominal ultrasound. This will detect evidence of seroconversion, progressive liver disease, and/or HCC, and allow consideration of antiviral therapy.
- The incidence of HCC in children with chronic hepatitis B is low.

Treatment for hepatitis B infection

Acute HBV infection is usually self-limiting, and supportive treatment alone is adequate. Treatment strategies focus on the management of chronic HBV infection. HBV genotyping is not used to influence treatment decisions.

- The ultimate goal of treatment is to eradicate HBV infection and thereby reduce the associated morbidity and mortality. This long-term aim is difficult to achieve with currently available therapies. The short-term aims are to:
  - Reduce viral replication
  - Minimize liver injury
  - Reduce infectivity.

- Two different approaches to treatment are used:
  - Immunomodulation with interferon alfa
  - Reduction of viral load with antiviral agents such as nucleos(t)ide analogues (NAs).
- Consensus guidelines for treatment in children have been published but vary considerably. They require frequent revision, as new evidence and therapies rapidly emerge.
- Children with HBV infection often have mild or asymptomatic disease and remain in the immunotolerant phase, with minimal ALT elevation, despite high levels of circulating HBV DNA. Treatment with IFN or NAs during this phase is considered to be ineffective.
- In children with immune-active disease (ALT more than twice the upper limit of normal and active histology), both interferon alfa and lamivudine have been shown to be effective in inducing the loss of HBeAg and the normalization of serum ALT levels.
- Conventional interferon alfa is given subcutaneously three times a week for 6 months. However, pegylated IFN (peginterferon) is given once weekly and is in routine use in adult practice. All IFN-based therapies are limited by side effects, though children tolerate treatment better than adults. The main side effects are fever, flu-like symptoms, and bone marrow suppression. IFN is contraindicated in children with decompensated liver disease, cytopenia, severe renal or cardiac disorder, and autoimmune disease. The advantage of IFN treatment over NAs is a defined duration of therapy of up to 48 weeks. Response occurs in ~30%.
- Lamivudine is well tolerated, with similar response rate to IFN. Its most significant limitation is the development of viral resistance with prolonged use. Hence the risks and benefits of long-term therapy in children should be considered before treatment is started.
- More recent, improved NAs are superseding lamivudine as potential first-line therapies in adult practice and are being evaluated in children.
  - Tenofovir has good efficacy and a higher barrier to resistance. It is licensed for use in children over 12 years of age. Paediatric therapeutic studies are in progress. It may have a role in treating those in whom IFN-based regimes are not tolerated, contraindicated, or unlikely to be effective.
  - Entecavir is licensed for use after 2 years of age and has similar efficacy to tenofovir. Paediatric therapeutic studies are in progress. Like tenofovir, it may have a role when IFN-based therapies are not tolerated, contraindicated, or unlikely to be effective.

Prevention

- Public health measures for reducing transmission of HBV include: public information about the modes of transmission, promotion of safe sex, needle exchange programmes, and screening of high-risk groups (including pregnant women).
- Universal precautions should prevent exposure to blood or body fluids in health-care settings.

- Treatment of infected women during the third trimester of pregnancy with an oral antiviral agent may reduce viraemia, and hence the risk of perinatal transmission.

Vaccination

- Many countries around the world have introduced universal immunization against HBV in their national schedule. In Europe, 44 out of 52 WHO member states have introduced the vaccine. The UK is an area of low endemicity and has adopted a policy of selective immunization of high-risk groups, combined with universal antenatal screening.
- HBV vaccine is recommended as pre-exposure prophylaxis in:
  - Injecting drug users and their children
  - Homosexual men
  - Individuals who change partners regularly
  - Close household family contacts of carriers of hepatitis B
  - Families adopting children from high- or intermediate-prevalence areas of HBV
  - Foster carers
  - Haemophiliacs and other children receiving regular blood or blood products, and their carers
  - Children with chronic liver disease or chronic renal failure, including those on haemodialysis
  - Health-care workers who have direct contact with blood, bloodstained body fluids, or patient tissues
  - People travelling to areas of high or intermediate prevalence of hepatitis B
  - Inmates of custodial institutions
  - Staff and children with learning difficulties in residential homes.
- 1° immunization is three doses at 0, 1, and 6 months. Individuals at continuing risk of infection should be offered a single booster once only, 5 years after the 1° course. Measurement of anti-HBs is not required either before or after this dose. The route of immunization is IM (not in the buttocks). The dose varies, according to the manufacturer, but is lower in children.

Infants born to hepatitis B-infected women

- Post-exposure vaccination is recommended for babies born to infected mothers (HBsAg-positive). These babies should be given an accelerated course of four doses of the vaccine (0, 1, 2, and 12 months).
- Babies born to highly infectious mothers (HBsAg plus no HBe antibody) should also receive hepatitis B immunoglobulin (HBIG) within 24 hours of birth, together with active immunization with an accelerated course of vaccination.
- Infants should be tested for HBsAg at 1 year of age. This testing can be carried out at the same time as the fourth dose of vaccine is given and will identify those who may have become chronically infected with hepatitis B. These infected infants need referral for specialist assessment and management.

- A single booster dose of hepatitis B vaccine should be given with the preschool booster immunizations (age 4–5 years). This will also provide the opportunity to check whether the child was properly followed up in infancy.

Other post-exposure prophylaxis

Any individual potentially exposed to hepatitis B-infected blood or body fluids should be offered protection against hepatitis with HBV vaccine, with or without HBIG.[1]

A common occurrence is a child receiving an injury from a needle found on the ground. In these circumstances, a course of HBV immunization is started, but immunoglobulin is not given. It is considered that immunization should be given within 7 days of exposure if it is going to give protection against the needle-stick injury.

Future research

- Characterization of prognostic factors and optimal treatment regimes.
- Improved strategies to prevent perinatal transmission: maternal antiviral therapy in pregnancy and optimal provision of immunization.

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Chapter 75

Hepatitis C

See also Chapters 4, 18, 75.

Name and nature of the organism

- Hepatitis C is a viral infection of the liver affecting all age groups. It may lead to an acute, symptomatic hepatitic illness or be asymptomatic. After infection, ~75% will have a persistent chronic infection. Chronic HCV infection may progress to chronic liver disease and cirrhosis, with an increased risk of developing HCC. Rate of progression is usually slow, occurring over decades. Susceptibility to progression is modified by genetic and host co-factors, and co-morbidity. Symptomatic disease and development of complications of chronic disease are rarely seen in children.
- HCV is a positive-strand, enveloped, single-stranded RNA virus, a member of the genus *Hepacivirus* in the family *Flaviviridae*.
- HCV has high heterogeneity, and widely divergent genetic strains have been identified. HCV is classified into seven distinct genotypes (1–7), of which subtypes are also classified (a, b, c).

Epidemiology

- HCV infection is a global problem. It is estimated that 2–3%, or 160 million, of the world population are chronically infected with HCV.
- Disease prevalence is estimated to be 0.4% in the UK and is low (<1%) throughout Northern Europe, Australia, and Canada. The rest of Europe has an intermediate prevalence of ~1%. High prevalence (5–10% or more) is reported in Africa, Latin America, and Central and South East Asia. It is especially high in Egypt, with an estimated prevalence of up to 20%.
- An estimated 200 000 people in the UK have chronic HCV infection—50% of whom are unaware that they carry the virus. There are variations in the prevalence between different groups (0.04% in blood donors, 1% in people attending genitourinary clinics, and up to 50% in IV drug users).
- The distribution of the seven HCV genotypes varies between geographical regions. Genotype 1 is the most prevalent worldwide and is common in Europe. Genotype 4 is predominantly seen in Egypt and parts of the Middle East and Africa. Genotype 3a is the most prevalent in European IV drug users. In the UK, genotypes 1a, 1b, and 3a predominate.

Transmission and incubation period

- The most frequent route of infection in adults in the UK is through sharing contaminated needles during recreational injecting drug use. Tattooing, body piercing, and acupuncture under unsterile conditions may also transmit infection.
- Transmission of HCV from infected blood products is almost 100% efficient. This was the most important mode of HCV transmission for children, until blood donors were screened for HCV in the UK from September 1991. Children with haemophilia were at high risk of infection, before plasma inactivation became standard in 1985.
- The risk of transmission of HCV through a needle-stick injury is around 3% and depends upon the level of viraemia (amount of HCV RNA in the blood).
- Risk of heterosexual transmission is low, HCV transmission occurring in <5% of monogamous relationships. However, homosexual activity is an important mode of transmission.
- Intrafamilial spread is uncommon
- The commonest mode of acquisition of HCV for children in the UK is perinatal transmission from an infected mother. The risk of vertical transmission is low (<5%) but increases if the mother has a high level of HCV RNA in the blood, is co-infected with HIV, or has early rupture of membranes. Transmission through breastfeeding is extremely rare, and mothers with hepatitis C can be encouraged to breastfeed their babies.
- Children adopted from abroad may have a higher incidence of HCV, reflecting the prevalence in their country of origin (see Chapter 29 on international adoption).
- The incubation period from exposure to detectable viraemia and antibody production is 6–12 weeks but is variable.

Clinical features and sequelae

- *Acute hepatitis C* infection is very rare in childhood.
- *Chronic hepatitis C* infection is defined as persistently detectable serum HCV RNA for >6 months. There may be little or no elevation of liver enzymes (ALT and/or AST).
- Chronic hepatitis C develops in 90% of vertically infected infants, compared to 60–80% of older children infected by blood products.
- Most children with chronic hepatitis C are asymptomatic. Hepatitis C in children seems to be a milder disease than in adults. Children with chronic hepatitis C usually have no clinical signs of chronic liver disease.
- *Long-term sequelae*: there may be a slow progression of hepatic fibrosis with age. Fibrosis due to hepatitis C is usually mild in children, but progressive disease develops in at least 30%. The levels of aminotransferases do not correlate with clinical severity. After 20–30 years of infection, ~10–20% develop cirrhosis. Of those with HCV-related cirrhosis, 1–5% per year will develop HCC.

- Risk factors for rapid progression are older age at infection, ♂ gender, heavy alcohol consumption, co-infection with HIV or hepatitis B, treatment with immunosuppression, and obesity. IL28B genotype also impacts on the risk of progression and treatment response.

Diagnosis

- Serological assays are used to detect human antibodies to HCV (anti-HCV). Third-generation EIA testing is estimated to have 98% sensitivity and is the most widely used screening test. Anti-HCV antibodies are usually detectable 12 weeks after exposure to the virus.
  - Anti-HCV antibody testing is not reliable in the presence of immunosuppression (HIV, immunosuppressive therapy), as false negative results may be obtained.
  - Anti-HCV antibody testing in infants up to 1 year of age may reflect the transplacental passage of maternal antibody, and therefore may be detectable in the absence of infection.
  - Anti-HCV antibody may persist for many years after resolved infection, and therefore does not always signify an ongoing infection.
- HCV RNA testing by PCR detects viraemia and thus confirms the presence of infection. It is therefore used to assess the presence of infection following a positive HCV antibody test.
  - HCV RNA testing is also indicated to assess the presence of infection where false negative or false positive anti-HCV antibody tests may occur, and in infants in the first year of life.
  - HCV RNA presence for >6 months defines chronic infection.
  - Serial testing of HCV RNA levels are used for monitoring response to antiviral therapy. Quantitative analysis is used to determine response and may guide the continuation or discontinuation of treatment accordingly. The lower limit of detection of the virus by the most sensitive commercial kits is <15IU/mL.

Management and treatment

- Children with chronic hepatitis C infection should be referred to an appropriate paediatric specialist, usually in hepatology or ID.
- Management includes the assessment and monitoring of the natural history, providing age-appropriate counselling and family support, and considering indications for drug therapy.
- Outpatient assessment includes clinical examination, determining the persistence of infection by HCV RNA testing, and assessing liver disease by liver enzymes and ultrasound scan. α-fetoprotein monitoring may permit early detection of HCC, although rarely occurring in childhood.
- Percutaneous liver biopsy may be indicated to assess those with clinical evidence of significant liver disease, with co-morbidity also being explored. A liver biopsy may also help inform the decision to start treatment or continue monitoring without treatment.

Drug therapy

- Treatment for hepatitis C is available for children. Efficacy depends predominantly on the HCV genotype.
- Aim of treatment is to achieve a sustained viral response (SVR), defined as undetectable serum HCV RNA 24 weeks after completion of therapy. SVR is associated with virtually no risk of rebound of viraemia and will prevent further progression of HCV-related disease.
- Conventional and licensed treatment for children is with a combination of peginterferon, given weekly by subcutaneous injection, and oral ribavirin twice daily, given orally as a suspension or in tablet form. Treatment duration is 24 weeks (genotypes 2 and 3) or 48 weeks (genotypes 1 and 4).
  - Response to treatment in genotypes 1 and 4 is ~50%, and 90–95% in genotypes 2 and 3.
  - Common side effects of peginterferon include flu-like symptoms, loss of appetite, change in bowel habit, and hair thinning. There may also be mood alteration. Thrombocytopenia and neutropenia are common and may require dose alteration.
  - Common side effects of ribavirin are haemolytic anaemia, with a drop of 20g/L being common.
  - Side effects are usually reversible when treatment is completed or discontinued.
- These standard regimens are now being supplemented with newer protease-based therapy. Triple-therapy regimes with a direct-acting antiviral, such as the protease inhibitors boceprevir, telaprevir, or simeprevir, together with peginterferon and ribavirin, are licensed for adults with genotype 1. Interferon-free regimes are also licensed for use in adults, with more than ten direct-acting antivirals now being available. Clinical trials in children are in progress.

Management of hepatitis C-positive mothers during pregnancy

- Elective Caesarean section or breastfeeding has no effect on transmission rates of hepatitis C, unless the mother is also HIV-positive. In general, HCV-positive mothers should be encouraged to have a normal delivery and breastfeed their infants.
- If the mother is HCV antibody-positive, but HCV RNA-negative, there is no risk of HCV transmission to the baby. If the mother is HCV RNA-positive, the risk of transmission is ~5% but increases in the presence of high maternal HCV viral load, early rupture of membranes, and the presence of co-infection with HIV.

Needle-stick injury

- Following a needle-stick injury from a known HCV RNA-positive patient, the recipient should be tested for HCV RNA after 6 weeks. If negative, repeat testing for HCV RNA and for HCV antibody should be performed at 12 weeks. If these are both negative, a final test for HCV antibody 6 months after exposure should be performed to rule out viral transmission.

Prevention

- Hepatitis C testing should be offered to high-risk groups and also to those with unexplained jaundice and abnormal liver enzymes.
- Following the identification of HCV infection, counselling and testing of offspring, close household contact(s), and sexual contacts should be considered.
- Universal precautions should be taken in all health-care settings to reduce the possibility of exposure to infected blood. These precautions are particularly important on renal dialysis units.
- Strategies to reduce new infections in IV drug users should concentrate on: stopping people initiating drug use, helping those who inject drugs to quit drugs, and harm minimization for those who continue to inject by teaching them to avoid sharing of injecting drug equipment and needle exchange.
- Routine antenatal screening for hepatitis C is carried out in some countries with high prevalence. In the UK, it is not currently mandatory, as part of the national antenatal screening programme, but is undertaken in some high-risk areas.
- No vaccine is available for HCV.

Future developments

- Detailed characterization of host factors that influence the risk of progression and treatment response will guide tailored antiviral regimes.
- Direct-acting antivirals with better tolerability (such as the polymerase inhibitor sofosbuvir and many others) will need to be evaluated, and their role in clinical practice determined, for both adults and children. It is likely these regimens will replace ribavirin and IFN-based therapy.

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Chapter 76

Herpes simplex virus 1 and 2

See also Chapters 4, 10, 11, 14, 20, 30, 31, 34, 38.

Name and nature of the organisms

- HSV 1 and HSV 2 are both members of the *Herpesviridae* family of DNA viruses.
- HSV 2 is a major cause of neonatal herpes simplex encephalitis (HSE), while HSV 1 is the commonest cause of childhood herpes disease. HSV spread is usually via the orolabial route.
- 1° infection usually occurs in childhood and adolescence, but relapses can occur at any time. HSV neurovirulence and latency are thought to influence disease in children.
- Neurovirulence is the affinity of HSV for neuronal tissue, through which the virus is propagated.
- The most likely portal of entry for HSV 1° infection appears to be via the mucous membranes, following which it ascends the peripheral nervous system.
- Following 1° infection, HSV has the ability to develop latent viral infection, usually in the trigeminal or dorsal root ganglion.
- During this latent period, restricted viral replication takes place, and certain areas of the HSV genome have been described that may account for this ability to replicate without apoptosis and maintain a latent infection in the dorsal root ganglion.
- HSV can reactivate from latency and cause recurrent disease by travelling to areas innervated by this route, e.g. recurrent cold sores or genital herpes.

Neonatal infection

Epidemiology

- Incidence differs between countries, and HSV infection is commoner in the US (1:3000–1:20 000) than in Europe (1:60 000), and the UK (1.65/100 000).

Transmission and incubation period

- Neonatal infection is usually transmitted from mother to child through viral shedding from the birth canal during delivery (85%).
- Transplacental infection is rare, and infection via an orolabial lesion from contact with a family member is uncommon.

- Maternal 1° infection with HSV at the time of delivery has the highest risk of transmission (25–57%), compared with recurrent maternal genital HSV (2%).
- The majority of infants with HSV are born to mothers who are asymptomatic.
- Other risk factors known to influence HSV transmission include:
  - Lack of maternal antibody
  - Increasing duration of rupture of membranes
  - Breeching of mucocutaneous barriers (e.g. use of scalp electrodes)
  - Mode of delivery (vaginal versus Caesarean in women with active shedding of HSV at delivery)
- The incubation period for neonatal HSV is 1–6 days.

Clinical features and sequelae

The clinical presentation in neonates can be broadly classified into three distinct forms with different outcomes, but overlap syndromes occur (Table 76.1):

- Skin–eye–mouth (SEM) disease
- Disseminated disease with or without central nervous system (CNS) involvement
- CNS disease.

Table 76.1 Clinical characteristics of the three main presentations of neonatal HSV (percentages for sequelae and mortality in children treated with high-dose aciclovir)

Type of disease	SEM	Disseminated	CNS
Frequency	45%	25%	30%
Symptoms	Vesicles on skin/mouth—scalp (sites of minor trauma) or conjunctivitis/keratitis	Sepsis-like Hepatitis/DIC Thrombocytopenia Pneumonitis ± CNS involvement ± skin lesions	Lethargy Fever Convulsions—focal CT/MRI abnormal
Age of onset	5–14 days	5–10 days	2–4 weeks
Sequelae	1–5%	15–30%	50%
Mortality*	0–1%	30–50%	15%

* Since longer course of high-dose aciclovir advocated.

Diagnosis

Sick infants presenting in the second week of life with raised transaminases and coagulopathy should prompt investigation of HSV disease and empiric starting of aciclovir treatment.

- Investigations should include:
  - Scrapping of the base of the vesicles, if present

- Surface skin lesion swabs, nasopharynx, mouth, conjunctiva, blood, and CSF for HSV DNA PCR
- FBC, LFTs, and clotting screen
- CSF for cell analysis and HSV PCR. CSF testing is an essential component of the diagnostic work-up; CSF should be tested as soon as it is safe to perform an LP in any child with suspected encephalitis. It is important to take enough CSF for local laboratory requirements; it is common that insufficient CSF volumes reach the laboratories for all the necessary tests. Children produce ~0.35mL/kg of CSF per hour, and it is safe to take up to 0.2mL/kg of CSF
- CT or MRI (better) of the brain should be considered in patients with CNS disease (plus EEG if CNS disease is suspected—temporal lobe spike and wave). The only urgent brain imaging available may be a CT scan, preferably with contrast, and will help exclude haemorrhage as a cause of the symptom complex but should not be performed solely to determine the safety of proceeding to an LP.

- Ophthalmological review to exclude HSV retinitis.

Management and treatment

- Neonates with HSV infection should be treated with high-dose IV aciclovir. Recommended duration of therapy is a minimum of 14 days for SEM disease, and a minimum of 21 days for disseminated and CNS disease (Table 76.2).
- A repeat CSF HSV PCR is recommended at the end of the course of therapy in patients with CNS involvement to confirm clearance of the virus.

Table 76.2 Treatment of HSE (assuming normal renal function and hydration)

Treatment for acute HSE		
Birth to 3 months	**All children >3 months**	
Aciclovir IV: 20mg/kg tds for 21 days	Aciclovir IV: 3 months to 12 years: 500mg/m^2 tds for 21 days Over 12 years: 10mg/kg tds for 21 days	
Prophylaxis against HSE recurrence		
Birth to 3 months	**Immunocompetent children >3 months**	**Immunocompromised children >3 months**
Aciclovir PO: 300mg/m^2 tds for at least 12 months Valaciclovir PO: Not recommended—no neonatal data	Aciclovir PO: 300mg/m^2 tds for 6–12 months *OR* 1340mg/m^2 bd for 6–12 months Valaciclovir PO: 1 month to 12 years 25–40mg/kg tds for at least 3 months	Aciclovir PO: 300mg/m^2 tds for at least 12 months *OR* 1340mg/m^2 bd for at least 12 months Valaciclovir PO: 1 month to 12 years 25–40mg/kg tds for at least 12 months

bd, twice daily; IV, intravenously; PO, orally; tds, three times daily.

Prevention

During pregnancy

- Suppressive treatment from 36 weeks of gestation onwards is recommended by some experts to reduce the emergence of lesions around the time of delivery and the need for a Caesarean section. However, this approach reduces, but does not completely eliminate, asymptomatic shedding, and its efficacy and safety in pregnant women have not been clearly established.

At delivery

- Caesarean section should be considered in women with prodromal symptoms or active lesions of genital HSV at the time of delivery. It should be performed within 4–6 hours from the rupture of membranes. Non-randomized studies have shown that neonatal transmission decreases (but is not completely eliminated) using this approach. Caesarean section should be supplemented with aciclovir therapy to the mother.
- Asymptomatic neonates born to mothers with a *1°* genital lesion, either vaginally or by Caesarean section, with risk factors (rupture of membranes >6 hours prior to delivery; fetal scalp electrodes; chorioamnionitis; cervicitis) should receive a full diagnostic evaluation for HSV if there is no serological evidence of past maternal infection. Treatment with IV aciclovir should be initiated, until the evidence of active infection has been ruled out.
- Asymptomatic neonates born vaginally to a mother with a *recurrent* genital infection can have HSV surface swabs (nasopharynx, mouth) taken at 24–48 hours to rule out active replication of the virus and may be monitored clinically at regular intervals in the first few weeks of life. Some clinicians will also treat these infants prophylactically with aciclovir.

After skin–eye–mouth disease

- Recurrence of symptoms after neonatal HSE are recognized, and, although most occur within 3 months of completing an initial course of IV aciclovir, late relapse is well recognized. Prophylaxis with aciclovir has been shown to prevent this significantly. While 6–12 months of antiviral prophylaxis is adequate for some children following neonatal HSE, late central or dermal flares may indicate that longer-term, or even lifelong, prophylaxis may be required. Findings from a small patient series proposed doses of 1340mg/m^2 of aciclovir given twice daily (total daily dose 2680mg/m^2), based on CSF penetration data, but a more recent, larger placebo-controlled RCT validated oral aciclovir given at 300mg/m^2 three times daily (900mg/m^2) as adequate at improving neurodevelopmental outcome.

Childhood infection

Epidemiology

- Most childhood infections are caused by HSV 1, whereas HSV 2 infection occurs in adolescents after the onset of sexual activity.

- Prevalence of HSV 1 seropositivity in children varies, according to the geographical location and social class status. In the UK, the presence of HSV 1 antibodies reaches 50–75% by adulthood.
- The vast majority of 1° infections in children are asymptomatic. In a study of 4000 children with HSV 1 seropositivity, only 12% had evident signs of 1° infection.
- The virus remains latent for life (HSV 1 trigeminal ganglia; HSV 2 sacral sensory neural ganglia) with possible episodes of reactivation and neural axonal spread ('cold sores' or genital herpes) and periods of asymptomatic shedding.

Transmission and incubation period

- Transmission of HSV 1 occurs through mucocutaneous contact, often with asymptomatic children who are shedding the virus.
- Patients with 1° gingivostomatitis shed the virus for ≥1 week.
- Patients with recurrent symptoms shed the virus for a shorter duration of 3–4 days.
- The incubation period is 2 days to 2 weeks.

Clinical features and sequelae

Gingivostomatitis

- Classical paediatric presentation of HSV 1.
- Prodromal symptoms include fever, nausea, malaise, and anorexia.
- This is followed by the appearance of numerous vesicles, which break down rapidly to enlarging erythematous lesions with central ulcerations covered by yellow–grey membranes.
- Lesions are painful and may coalesce.
- Main clinical problem is dehydration; rarely needs hospital admission.
- Areas involved may include the buccal mucosa, tongue, posterior pharynx, and gingiva. Commonly, satellite lesions are seen on the skin around the mouth.
- Healing occurs in 10–21 days.

Herpes labialis ('cold sores')

- Following 1° infection, one-third of patients have episodes of viral reactivation, consisting of orolabial lesions at the outer edge of the vermillion border.
- Fever or non-specific stressors can trigger episodes, which are usually preceded by a tingling or pain sensation at the site.
- Episodes last for 4–5 days, though HSV shedding is detected by PCR in between acute episodes.

Keratoconjunctivitis

- Follows auto-inoculation in a child with gingivostomatitis or herpes labialis.
- The episode presents with acute onset of pain, photophobia, and excessive lacrimation.
- This is followed by chemosis and periorbital oedema.
- The infection leads to corneal ulceration, with pathognomonic branching dendritic lesions of the cornea and blurred vision.
- Resolution of the episode takes up to 4 weeks.

- Recurrent infections may lead to corneal opacification and corneal blindness.

Herpetic whitlow (herpetic paronychia)

- Result of auto-inoculation in children with orofacial herpes infection.
- Characterized by the swelling of a finger (usually the thumb from sucking) and the appearance of one or several painful, clear, fluid-filled vesicles, later becoming opaque.
- Typically side of finger on the distal phalanx. Larger than vesicles seen in hand, foot, and mouth disease.
- Symptoms last for 1–2 weeks.

Eczema herpeticum

- HSV skin superinfection in patients with underlying eczema.
- In one-third of children, there is a recent history of herpes labialis in one of the parents.
- Vesicles appear in areas of recently healed atopic dermatitis but rapidly become 'punched-out' ulcers and can spread quickly destroying skin.
- Fever develops 2–3 days after the appearance of vesicles and usually lasts for 4–5 days.
- Toxic symptoms may be severe, and viraemia with visceral involvement has been reported.

Herpes gladiatorum—scrum pox

- Lesions present on the face, neck, or arm of children involved in contact sports such as wrestling or rugby.
- Viral inoculation results from close contact between injured skin and oral secretions.

Herpes simplex virus-associated erythema multiforme

- Disease characterized by an autoimmune response to HSV DNA fragments present in the patient's skin, with the development of distinctive cutaneous target lesions.
- Episodes usually follow an episode of herpes labialis and lasts for 10 days.
- Recurrences are common, and direct testing for HSV by culture or PCR is negative.

Central nervous system infection

- HSV is the commonest identified cause of severe encephalitis. In older infants and children, the classic features of HSE are: fever, encephalopathy, a deteriorating level of consciousness, focal seizures, or focal neurological abnormalities; however, the infective source is usually elusive.

Other infections

- A number of other manifestations of HSV have been described in the immunocompetent host, including pneumonitis, exudative tracheobronchitis, oesophagitis, hepatitis, recurrent aseptic meningitis, myelitis, and facial nerve (Bell's) palsy.

Diagnosis

- Diagnosis and typing of HSV can be readily performed by PCR assay of lesions and various body fluids, or via immunofluorescence or direct antibody (EIA or ELISA) testing, or viral culture.
- CSF PCR for HSV, as for neonatal HSV, is vital if CNS disease is suspected. HSV PCR is a highly sensitive and specific test (94 and 96%, respectively), *except* during the first 24 hours of the disease when as many as 10% of HSE CSF samples can be falsely negative. Serological testing is available but has limited diagnostic utility.

Management and treatment

- A variety of formulations are available for the treatment of HSV, including oral, topical, and IV aciclovir, oral valaciclovir and famciclovir, and IV foscarnet (Table 76.2). In addition to aciclovir, the following are important management considerations:
  - *Gingivostomatitis*: to adequately manage any pain, to ensure adequate hydration, and to promote healing. Especially for infants and small children, careful assessment for decreased feeding, short-term weight loss, and poor urine output are important. Dehydration can result insidiously, especially where reduced fluid intake is coupled with increased insensible losses from mouth breathing and drooling, particularly if the need for effective symptomatic relief is not appreciated. Topical local anaesthetics (washes, gels, sprays, lozenges, etc.) are widely used to provide some short-term symptomatic relief, which also help improve oral intake
  - *Skin infections*: there are few efficacy data available to recommend treatment in skin infection, except eczema herpeticum, which should be treated with IV aciclovir. Treatment of infections in immunocompromised hosts and burn patients should be considered because of the potential severity of symptoms
  - *CNS infections*: early initiation of treatment with high-dose IV aciclovir has shown to significantly reduce morbidity and mortality in patients with encephalitis.

Recurrence

- Recurrence of neonatal HSE can be as devastating as the original disease, and neonates remain prone to late recurrences of infection for months to years after their initial illness.
- It is thought that early-life infection impairs the development of an effective adaptive immune response, but prolonged antiviral prophylaxis can prevent recurrence.
- It is common for neonates who have had an initial HSE infection to develop recurrence of dermal flares.
- Some rare cases of recurrent childhood HSE may be due to an underlying immunodeficiency in the innate immune system, which is associated with a defective virus recognition, particularly in the TLR3/UNC93B pathways.

Future research

- A trial of dual antiviral therapy (aciclovir versus liposomal cidofovir) versus aciclovir monotherapy in infants with HSV disease is under way.
- The optimal management of the baby born to a mother with HSV lesions in different prevalence settings remains unknown, including the role of rapid diagnostics.

Further reading

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Chapter 77

Human immunodeficiency virus infection

See also Chapters 4, 20, 24, 55, 61, 62, 90, 95, 112.

Introduction

- The key to HIV pathogenesis is the impact of immunodeficiency through the loss of T-helper or $CD4^+$ cells and subsequent development of opportunistic infections and cancers. HIV also directly damages other cells, causing focal organ disease. AIDS is advanced HIV disease, defined by the presence of severe opportunistic infections or specific organ diseases, including cancers.
- More than 80% of HIV-infected people live in sub-Saharan Africa where the impact on HIV-related morbidity and mortality has been profound, with dramatic changes in population structures and demography.
- After years of little or no effective therapy against HIV, we have seen the advent of combination ART that has remarkably altered the outcome of those receiving treatment.
- The advent of ART and the associated benefits has meant that HIV has moved from being a fatal condition to a chronic one, and the impact on children has been that of increased survival into adulthood.
- A dramatic implementation of ART worldwide, where, by 2013, >10 million people living with HIV are receiving ART, represents the fastest scale-up of a lifesaving public health intervention in history.
- There are, however, important issues regarding adherence to therapy, stigma, and MDR that make the management of HIV more complex and different from other chronic conditions.

Causative organisms

- HIV is an enveloped RNA virus of the family *Retroviridiae*.
- There are two major types—type 1 (HIV-1) and type 2 (HIV-2). HIV-1 is, by far, the commonest and predominates outside West Africa.
- There are also several different clades or subtypes (designated A, B, C, D, E, F, G, H, J, and K) in different geographical regions.
- As HIV is a retrovirus, its life cycle involves integration into the target cell genome as a provirus, and the viral genome is copied during DNA replication to complete viral replication.
- Latent virus can persist in the cell reservoir of infected people for life.

Epidemiology

- Humans are the only known reservoir of HIV infection, although related viruses, perhaps genetic ancestors, have been identified in chimpanzees and monkeys (called simian immunodeficiency viruses).
- Established modes of HIV transmission include the following:
  - Sexual contact (vaginal, anal, or orogenital)
  - Mother-to-child transmission (MTCT) during pregnancy, around the time of labour and delivery, and post-natally through breastfeeding
  - Percutaneously through contaminated needles or other sharp instruments
  - Contaminated blood products.
- WHO and UNAIDS estimated that, in 2012, there were about 35.3 million people living with HIV/AIDS (about two-thirds living in sub-Saharan Africa), including 3.3 million children <15 years of age. An increase from previous years was observed, as more people are receiving lifesaving ART. There were 2.3 (1.9–2.7) million new HIV infections globally, showing a 33% decline in the number of new infections from 3.4 (3.1–3.7) million in 2001. At the same time, the number of AIDS deaths is also declining, with 1.6 (1.4–1.9) million AIDS deaths in 2012, down from 2.3 (2.1–2.6) million in 2005
- In Europe (Central and Western) and North America, there were an estimated 2.3 million people living with HIV/AIDS, of which 1.3 million were in the US.
- As a result of scaled up HIV prevention services and effective PMTCT programmes, new HIV infections among children have declined by 58% since 2000. Worldwide 220 000 children became newly infected in 2014 down from 520 000 in 2000.

Epidemiology of HIV infection in the UK

- In the UK and Ireland, the major risk factor for infection is vertical infection from women who acquired their infection in high-prevalence areas, particularly sub-Saharan Africa.
- A total of 1873 children in the UK were reported to the Collaborative HIV Paediatric Study (CHIPS, <http://www.chipscohort.ac.uk>) by the end of March 2014.
- The median age at first presentation of those born in the UK and Ireland (44%) has remained relatively constant at around 6 months. For children born abroad, it increased from <2 years up to 1991 to around 6 years from 2009 onwards. The majority of children with HIV in Europe are now teenagers, and most of them left paediatric care and transitioned to adult clinics.
- Children very rarely get sick, with the rate of hospital admission now around 0.1/child/year. Of around 1500 children under care, <5 children die each year.
- In the absence of the use of ART in pregnant women, vertical transmission rates of HIV-1 infection (MTCT) historically varied between 15% and 25% in US and Europe, and 25% and 35% in Africa. Risk factors for vertical transmission include maternal factors

(1° infection, advanced clinical disease, low CD4 counts, high viral load and presence of STIs/chorioamnionitis), mode of delivery (prolonged rupture of membranes, premature delivery), and breastfeeding.

- The introduction of universal routine antenatal HIV testing and the use of combination ART in pregnancy have reduced the vertical transmission rate in Europe to <1%. A higher proportion of women with undetectable viral loads during pregnancy are choosing to have normal vaginal deliveries, with very low rates of vertical transmission. There remain a few babies still born with HIV in Europe where either the mother has not integrated with antenatal testing and treatment or there have been system failures in the antenatal screening programme. Data on HIV in pregnancy and outcomes in the UK are available from the National Study of HIV in Pregnancy and Childhood (Available at: <http://www.nshpc.ucl.ac.uk>).
- The 2013 WHO guidelines recommend that countries at high HIV prevalence should provide all HIV-positive pregnant or breastfeeding women with a course of ART to prevent MTCT. A triple-drug antiretroviral regimen should be taken throughout pregnancy, delivery, and breastfeeding—continuing for life, regardless of the CD4 count or clinical stage. This strategy is called option B+, as compared with option B where the triple-drug regimen should be stopped 1 week after breastfeeding will be finished. Results from several African countries where this strategy has been implemented, such as Malawi, showed a major decrease in the number of infected children and in the number of women on ART.

Clinical presentation and differential diagnosis

- Updated guidance on the management of children with HIV can be obtained from the UK Children's HIV Association website (<http://www.chiva.org.uk>) and the PENTA-ID website (<http://www.penta-id.org>).
- HIV infection in children and adolescents causes a broad spectrum of disease manifestations and a variable clinical course. The management of HIV is complex and should only be undertaken as part of a clinical network with a recognized paediatric HIV specialist. In the UK, this will be through the Department of Health's Children's HIV National Networks).
- AIDS represents the most severe end of the clinical spectrum.
- Box 77.1 and Table 77.1 outline the CDC 1994 classification of HIV/AIDS in children, based on clinical and immune categories. In resource-limited settings, the WHO clinical staging classification (<http://www.WHO.org>) usually applies. Although slightly different, the concept behind the two classifications are very similar.
- Paediatric AIDS is defined by the appearance of a number of diseases which are mainly included in category C of the CDC classification.
- Opportunistic infections: PCP is the most commonly reported opportunistic infection, seen most often in infants where the mother was not known to have HIV in pregnancy. Without ART, it occurs most

Box 77.1 Revised HIV paediatric classification system—clinical categories

Category N: not symptomatic

Children who have no signs or symptoms considered to be the result of HIV infection or who have only one of the conditions listed in category A.

Category A: mildly symptomatic

Children with two or more of the conditions listed, but none of the conditions listed in categories B and C:

- Lymphadenopathy, hepatomegaly, splenomegaly
- Dermatitis
- Parotitis
- Recurrent or persistent URTI, sinusitis, or otitis media.

Category B: moderately symptomatic

Children who have symptomatic conditions, other than those listed for categories A or C, that are attributed to HIV infection. Examples of conditions in clinical category B include, but are not limited to:

- Anaemia (<8g/dL), neutropenia (<1000/mm^3), or thrombocytopenia (<100 000/mm^3) persisting ≥30 days
- Bacterial meningitis, pneumonia, or sepsis (single episode)
- Candidiasis, oropharyngeal (thrush), persisting (>2 months)
- Cardiomyopathy
- CMV infection, with onset before 1 month of age
- Diarrhoea, recurrent or chronic
- Hepatitis
- HSV stomatitis, recurrent (>2 episodes within 1 year)
- HSV bronchitis, pneumonitis, or oesophagitis
- Herpes zoster (shingles) involving at least two distinct episodes or >1 dermatome
- Lymphoid interstitial pneumonia (LIP)
- Nephropathy
- Persistent fever (lasting >1 month)
- Toxoplasmosis, onset before 1 month of age
- Varicella, disseminated (complicated chickenpox).

Category C: severely symptomatic—AIDS-defining disease

Children who have any condition listed in the 1987 surveillance case definition for AIDS, with the exception of LIP (which is a category B condition):

- Serious bacterial infections, multiple or recurrent
- Candidiasis, oesophageal or pulmonary (bronchi, trachea, lungs)
- Coccidioidomycosis, disseminated
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis or isosporiasis with diarrhoea persisting >1 month
- CMV disease with onset of symptoms at age >1 month (at a site other than the liver, spleen, or lymph nodes)

(*Continued*)

Box 77.1 (*Contd*.)

- Encephalopathy
- HSV infection causing a mucocutaneous ulcer that persists for >1 month; or bronchitis, pneumonitis, or oesophagitis for any duration
- Histoplasmosis, disseminated
- Kaposi's sarcoma
- Lymphoma
- *M. tuberculosis*, disseminated or extrapulmonary
- *Mycobacterium*, other species or unidentified species, disseminated (at a site other than, or in addition to, the lungs, skin, or cervical or hilar lymph nodes)
- *Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated (at site other than, or in addition to, the lungs, skin, or cervical or hilar lymph nodes)
- *P. jirovecii* pneumonia (PCP)
- PML
- *Salmonella* (non-typhoid) septicaemia, recurrent
- Toxoplasmosis of the brain with onset at >1 month of age
- Wasting syndrome in the absence of a concurrent illness, other than HIV infection.

Source data from Centers for Disease Control and Prevention. Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR* 1994;**43**:1–10.

Table 77.1 Revised HIV paediatric classification system 1994—immune categories based on age-specific $CD4^+$ T lymphocytes and percentages

Immunological category	Number/mL (%)		
	<12 months	1–5 years	6–12 years
1: no suppression	≥1500 (>25)	≥1000 (≥25)	≥500 (≥25)
2: moderate suppression	750–1499 (15–24)	500–999 (15–24)	200–499 (15–24)
3: severe suppression	<750 (<15)	<500 (<15)	<200 (<15)

Source data from Centers for Disease Control and Prevention. Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR* 1994;**43**:1–10.

frequently at around 2–4 months of age, often when the CD4 cell count is relatively high, and has a high mortality. In older patients, it can also occur when the CD4 count is below 200, which is considered as the cut-off to start PCP prophylaxis (Available at: <http://www.who.int/hiv/pub/guidelines/en/>).
- CMV may cause disseminated disease, especially early in life when it may accompany PCP infection. Atypical mycobacterial infection and cryptosporidiosis are seen in children with severe immunosuppression.
- Severe bacterial infections: the commonest organisms causing infection are *S. pneumoniae, H. influenzae*, and *Salmonella* spp.
- Failure to thrive: poor oral intake, HIV enteropathy, or 2° GI infection are all important factors that contribute to poor growth and weight gain.
- HIV encephalopathy: developmental delay or motor signs, such as spastic diplegia, are common presentations in the early years of life. Neuroimaging studies show cortical atrophy and sometimes basal ganglia calcification.
- Lymphoid interstitial pneumonia (LIP) causes widespread nodular miliary shadowing on chest radiographs. LIP is seen in 30–40% of vertically infected children and is often accompanied by persistent bilateral parotid enlargement (a good clinical sign of HIV infection). In most cases, it is asymptomatic and only diagnosed on radiological investigation where it looks like miliary TB in a child who clinically looks just far too well to have miliary TB! Recurrent pneumonia may occur in some children and subsequently result in bronchiectasis and chronic lung disease.
- Following the scaling up of ART, the incidence of all the mentioned infections have dramatically decreased, as well as the rate of hospitalization in both developed and developing countries.
- With the increased survival of the vertically infected population, it has been shown that neurological and psychiatric disorders are more common in this population.

Investigations

- In children >18 months, combination HIV-1/2 antigen antibody immunoassays (ELISA) are now recommended (Available at: <http://www.cdc.gov/hiv>) for HIV diagnosis and are highly sensitive and specific. Confirmation with HIV PCR is usually needed only when results are indeterminate. A positive HIV antibody test result in a child ≥18 months is usually indicative of infection.
- Due to the transplacental transfer of maternal antibody, the use of antibody-based assays for the diagnosis of HIV infection in infants is non-specific in the first months of life. The median time to loss of maternal antibody is 10 months, and, by 18 months, all infants will have lost antibody. Plasma HIV RNA or DNA PCR is therefore used to diagnose HIV infection in infants.

- Infants born to HIV-infected mothers should initially be tested by either an RNA or DNA PCR during the first 48 hours of life, with a second test 4–6 weeks apart (at least 2 weeks after any neonatal post-exposure prophylaxis (PEP) ART has stopped) and eventually a third test at 2–4 months of age. An infant is considered infected if two separate samples are positive, and uninfected with two or more negative results, one at >3 months of age, and provided that the mother is not breastfeeding.
- For initial assessment of a child newly diagnosed with HIV, see Table 77.2.

Table 77.2 Initial assessment of a child newly diagnosed with HIV

HIV parameters	HIV RNA PCR (viral load)
	Baseline HIV resistance test (plus maternal resistance if an infant)
	CD4 count
	HLA B5701
Haematology	FBC and film
	Sickle screen (if appropriate racial group)
	Ferritin
	Consider malaria film if recently arrived from endemic area
Biochemistry	U&Es, creatinine, total protein (globulin), Ca, PO_4, albumin, LFTs, lipids, glucose, amylase, thyroid-stimulating hormone (TSH), vitamin D
Serology	Hepatitis A IgG, HBsAg, anti-HBsAg, HCV IgG, syphilis serology, IgG for EBV, CMV, HSV, VZV, and toxoplasmosis
	In children >1 year: measles, mumps, rubella IgG
	Immunization responses: Hib, tetanus
	(<18 months, serology may reflect maternal antibodies and should be repeated)
Viral PCRs	Plasma CMV PCR should be undertaken in infants and children with advanced disease
	HCV PCR should be undertaken in infants at risk of exposure and those with advanced disease
Cultures	According to symptoms/travel history: stools/urine/throat swabs/blood cultures/malaria films/gastric washings also for TB (Mantoux test), IGRA testing (where available)/sexual health screen if sexually active
Clinical investigations	Formal ophthalmological examination for infants
	BP, urinalysis, height/weight/head circumference/pubertal stage/BCG scar
Radiology	Baseline chest radiograph
	Bone age if small for age
	Infants/children with neurological signs: MRI of brain

IGRA, interferon-γ release assay.

Management

- Therapy for specific opportunistic and other infections is discussed under the individual diseases in other chapters. Management will focus on prophylaxis, prevention, and ART.

Prophylaxis against opportunistic infections

(See <http://www.chiva.org.uk>)

- Prophylaxis with co-trimoxazole is highly effective at preventing life-threatening infections, such as PCP, and also reducing bacterial infections.
- Prophylaxis should be given to all HIV-infected infants, from diagnosis until their first birthday. In older children, prophylaxis should be given to all those with low CD4 counts (below 200–250 cells/mm^3 or 15%).
- Prophylaxis against other infections, including CMV, atypical mycobacteria, and fungal infections, has been suggested for those with very low CD4 counts.

TB case finding and anti-TB treatment

- HIV-infected children who have any of the following symptoms of poor weight gain, fever, and current cough, or contact history with a TB case, may have TB and should be evaluated for TB and other conditions. If the evaluation shows no TB, children should be offered isoniazid preventive therapy, regardless of their age.

Prevention of bacterial infection

- Immunization against *H. influenzae* and *S. pneumoniae* is recommended for all children with HIV infection.
- Prophylactic antibiotics may be beneficial in children with LIP and recurrent chest infections.

Immunization

- Children with HIV should receive all immunizations, including rotavirus vaccine, except for BCG vaccine.

Antiretroviral therapy

Updated guidance on ART can be obtained from the Paediatric European Network for the Treatment of AIDS website (2015 PENTA guidelines on the use of ART, Available at: <http://www.penta-id.org>) (Table 77.3).

When to start

Consider starting ART in all infants and children regardless of their age. Priority should be given to those with lower CD4 counts and higher viral loads.

What to start with

- Children should start combination ART always as triple therapy, usually a dual nucleoside reverse transcriptase inhibitor (NRTI) backbone, together with either a ritonavir-boosted protease inhibitor (most commonly lopinavir/ritonavir or atazanavir or darunavir if older) or a non-NRTI (either nevirapine or efavirenz if younger or older than 3 years of age).

Table 77.3 PENTA 2016 recommendations on ART initiation

	<1 year	1 to 3 years	3 to 10 years	>10 years
Clinical stage	ALL	ALL	ALL	ALL
Priority		WHO stage 3/4 or CDC category B/C CD4 ≤ 1000 cells/μl (≤ 25%)	WHO stage 3/4 or CDC category B/C *Age 3–5 years:* CD4 ≤ 750 cells/μl (≤ 25%) *Age 5–10 years:* CD4 ≤ 500 cells/μl	WHO stage 3/4 or CDC category B/C CD4 ≤ 500 cells/μl Sexually active

ALL, all children irrespective of immunological status; CDC, Centers for Disease Control and Prevention; WHO, World Health Organization.

- Preferred NRTI combination in Europe includes ABC/3TC if <12; otherwise tenofovir.
- The child's age, HLA-B*5701 status (denotes an increased susceptibility to severe allergic reactions with abacavir), previous drug exposure, resistance profile, available formulations, and likely adherence should be taken into account when constructing a first-line regimen.

Monitoring antiretroviral therapy

- The aim of ART is to achieve an undetectable viral load (<50 copies/mL of plasma) and CD4 reconstitution; the viral load and CD4 counts should be monitored, wherever resources are available, at least every 4–6 months once established on ART.
- More frequent clinical and laboratory monitoring is required in infancy, if adherence is poor, soon after starting or changing therapy, and when giving other medications such as antituberculous therapy.

When to switch?

- The best time to switch to second- and third-line therapy remains uncertain.
- Switching treatment when there are ongoing problems with adherence may lead to loss of efficacy of further classes of ART.
- Resistance testing should always be performed prior to switching regimens in order to choose the most effective background therapy.

Stopping treatment and treatment interruptions

- Treatment interruption is not recommended, and starting ART currently means lifelong therapy.
- Treatment interruption for a short period of time should be considered in case of major adherence or drug toxicity issues.
- Stopping non-NRTIs requires a substitution or staggered stop to reduce the risk of developing non-NRTI resistance.

Social/psychological management

- Caring for children with HIV requires an expert multidisciplinary team, ideally involving specialist paediatric nurses, psychologists, pharmacists, and others working together to support the family.
- Testing of mothers and children should always be provided with counselling. It can be performed by any competent professional who has adequate knowledge of the condition and the implications of a positive diagnosis.
- Disclosure of infection to paediatric patients is complex and usually occurs in a phased approach over many years.
- Adherence support requires a multidisciplinary approach.
- Adolescent issues need to tackled in close collaboration with adult services and should be part of a clearly planned transition programme into to adult services.

Prevention

- Reduction of vertical transmission: full updated antenatal and post-natal HIV guidelines are available on the British HIV Association website (Available at: 🔗 <http://www.bhiva.org>) or WHO website (Available at: 🔗 <http://www.WHO.org>):
  - Antenatal HIV testing should be universal and integrated into routine antenatal care
  - ART in pregnancy: national guidelines should be followed, but generally option B or B+ are the preferred approach including the use of triple-drug regimen throughout pregnancy and breastfeeding
  - Obstetric management of pregnancy and delivery: pre-labour Caesarean section (women on zidovudine monotherapy or on combination therapy, but detectable viraemia) or elective vaginal delivery (women on combination therapy, with no detectable viraemia)
  - Management of infants born to HIV-infected mothers: zidovudine monotherapy for 4 weeks or triple therapy as PEP (for infants born to untreated mothers or mothers with detectable viraemia).
- Infant feeding: exclusive formula feeding for all babies should be recommended in settings where it can be safely provided.

Future research

- Vaccine development has been very disappointing so far.
- Newer treatment strategies to minimize toxicity of long-term treatment, combined with optimal efficacy and reduced pill burden.
- Continued follow-up of vertically infected young people for long-term outcomes (growth, neurocognitive function, fertility, malignancy, and long-term drug toxicity).

Further reading

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Chapter 78

Helminthiases

Overview

Helminthiases (parasitic worm infections) are the commonest infections in people living in poverty in low- and middle-income countries. This chapter will focus on those causing multisystem disease.

- >1 billion people are affected worldwide, with children often suffering the most severe disease because they experience the highest-intensity infections, i.e. on average, they harbour the largest number of worms in any age group. Together the major human helminths cause >14 million disability-adjusted life years (DALYs) annually, indicating that helminthiases rank among the most important global infectious disease threats.
- Helminths frequently establish long-standing infections in children, and the resulting chronic inflammation and malnutrition can produce deficits in growth, physical development, and physical fitness.
- In some cases, chronic helminth infections produce intellectual and cognitive deficits, so that helminthiases also adversely affect childhood learning and education, and ultimately economic development.
- Helminths that cause multisystem disease often exert their effects through larval stages or eggs that migrate through human tissues. The unique inflammatory response to such tissue-invasive organisms usually results in host elevations in IgE and tissue and peripheral blood eosinophils. Therefore, eosinophilia is often a hallmark of infectious helminthiases causing multisystem disease.
- Some, but not all, tissue-invasive helminths release eggs into the GI tract, so that many of the diseases discussed here would have negative faecal examinations. Instead, a serological analysis that measures parasite-specific antibodies is often required for diagnostic confirmation.

The major helminthiases discussed here are cysticercosis, hydatid disease, schistosomiasis, strongyloidiasis, toxocariasis, and trichinellosis.

Cysticercosis

Causative organisms

- Cysticercosis is an infection of the muscles, brain, and eye, caused by the larval stages of the pork tapeworm *Taenia solium*.
- When the infection occurs in the brain, it is sometimes referred to as neurocysticercosis.

Epidemiology

- Cysticercosis is endemic in low- and middle-income countries where pigs are allowed to feed on human faeces (Fig. 78.1).
- Humans acquire the pork tapeworm *T. solium* by consuming uncooked or poorly cooked pork containing the larval stages. The resulting adult tapeworm produces few, if any, symptoms in the GI tract.
- Individuals infected with the pork tapeworm shed eggs, which can be accidentally ingested by other humans. Cysticercosis therefore results when humans inadvertently substitute for the pig in the parasite's life cycle.
- Endemic and hyperendemic areas:
  - Globally an estimated 1.4 million cases of epilepsy attributed to cysticercosis
  - Latin America, especially Mexico (and 40 000–160 000 cases in the US)
  - Eastern Europe
  - Sub-Saharan Africa, especially Burundi and elsewhere in eastern and southern Africa, as well as Cameroon
  - India, China, elsewhere in South East Asia.

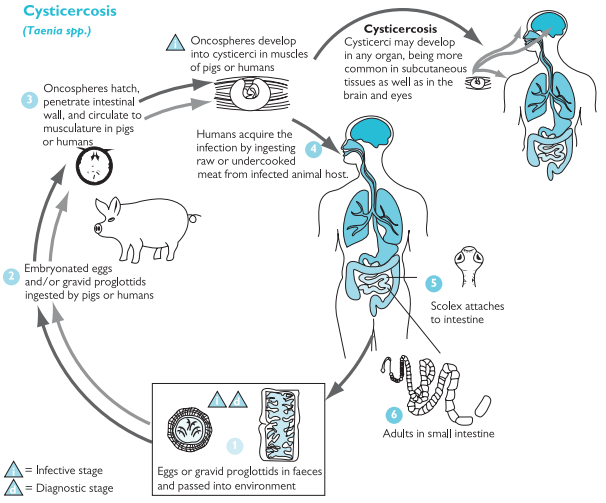

Fig. 78.1 Life cycle of *Taenia solium* and cysticercosis.
(From the Public Health Image Library of the US Centers for Disease Control and Prevention, <http://phil.cdc.gov>.)

Transmission and incubation period

- Accidental ingestion of *T. solium* eggs.
- Close personal contact with a tapeworm carrier or food handler.
- Eggs hatched following ingestion release oncospheres that enter the muscles, brain, eye, establishing space-occupying lesions within 2–3 months.

Clinical features and sequelae

- Neurocysticercosis—active disease:
  - Single or multiple cysts
  - Neuroimaging reveals ring of inflammation
  - Generalized tonic–clonic seizures
  - Partial seizures with generalization
  - Cerebral oedema and encephalitis with multiple cysts
  - Elevated ICP—rare.
- Calcified cysts of inactive disease—some controversy on whether active cysts may also be calcified.
- Other forms:
  - Ventricular and subarachnoid neurocysticercosis
  - Ocular cysticercosis—altered vision or ptosis
  - Muscle involvement.

Diagnosis

- Neuroimaging:
  - Cysts (0.5–2.0cm) on CT or MRI
  - Presence of scolex (head) pathognomonic
  - Surrounded by oedema and inflammation seen on CT with contrast and/or MRI.
- Confirmatory serodiagnosis: enzyme-linked immunotransfer blot for detecting anti-cysticercal antibodies.
- Resolution of multiple intracranial lesions on therapy or spontaneous resolution of a single, small lesion.

Management and treatment

- Anticonvulsant therapy:
  - Antiepileptic drugs
  - Continue anticonvulsants with calcifications.
- Corticosteroids to reduce inflammation, if required.
- Anthelmintics:
  - Not always required with single, resolving ring-enhancing lesion—albendazole or praziquantel.

According to new evidence-based treatment guidelines, 'albendazole plus either dexamethasone or prednisolone should be considered for adults and children with neurocysticercosis'. This approach reduces the number of active lesions on brain imaging studies, and long-term seizure frequency.

Prevention

- Sanitation, animal husbandry, meat inspection.
- Veterinary vaccine to prevent transmission to people.

Hydatid disease

Causative organisms

- Cystic echinococcosis.
- Larval tapeworm infection.
- *Echinococcus granulosus*.

Epidemiology

- Enzootic infection of dogs and sheep:
  - Dogs shedding tapeworm eggs ingested by sheep.
- Geographical distribution:
  - Globally 1.1 million cases with symptomatic disease in the liver, lungs, and CNS
  - South America (especially Chile, Argentina, Uruguay, Andean region)
  - Mediterranean (especially Turkey)
  - Central Asia and South Central former Soviet republics
  - China (especially western China, e.g. Tibet, Xinjiang provinces)
  - Selected areas in Africa
  - Australia
  - North America, sporadic cases among Inuit, also Arizona and New Mexico.
- High rates among indigenous populations.

Transmission and incubation period

- Accidental ingestion of eggs.
- Several years' incubation before detectable cyst appears in the viscera.

Clinical features and sequelae

- Single hydatid cyst in most cases.
- Liver (two-thirds of cases)—hepatic enlargement in right upper quadrant, pain, nausea, vomiting, cyst leakage with allergic manifestations.
- Lungs (one-fourth of cases)—leakage of cyst fluid—chest pain, cough, dyspnoea.
- Other organs, including the brain, kidney, spleen.
- Geographical variation in organ location.

Diagnosis

- Radiographic imaging (CT, MRI, ultrasound).
- Fluid-filled cysts.
- Sometimes daughter cysts—internal septations noted on radiographs.
- Confirmatory serology.

Management and treatment

- PAIR:
  - Puncture using ultrasound guidance
  - Aspiration of liquid
  - Injection of scolocidal agent (ethanol, hypertonic saline)
  - Re-aspiration.
- Albendazole:
  - Drug treatment used as adjunct with PAIR
  - Monitor liver function and blood cell counts with prolonged use.
- Surgical removal, including laparoscopic hydatid surgery, represents an alternative option.

Schistosomiasis

Causative organisms

- Urinary and urogenital schistosomiasis:
  - *Schistosoma haematobium*.
- Intestinal and biliary schistosomiasis:
  - *Schistosoma mansoni*
  - *Schistosoma japonicum*
  - *Schistosoma mekongi*.

Epidemiology

- Two hundred and fifty million infections worldwide. However, additional estimates indicate that the actual number of infected people could be twice that number.
- Ninety per cent of cases in sub-Saharan Africa.
- Urinary and urogenital schistosomiasis—*S. haematobium*:
  - Two-thirds of cases worldwide
  - Most in sub-Saharan Africa, some cases in Egypt and the Middle East
  - Water-borne infection transmitted from *Bulinus* snails (Fig. 78.2)
  - Highest-intensity infections in children, adolescents, and young adults
  - Important reproductive health problem for young women.
  - Risk factor for acquiring HIV/AIDS.

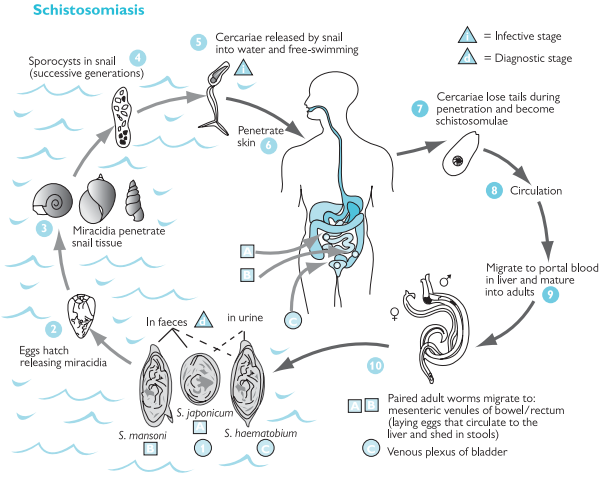

Fig. 78.2 Life cycle of human schistosomes and schistosomiasis.

(From the Public Health Image Library of the US Centers for Disease Control and Prevention, <http://phil.cdc.gov>.)

- Intestinal and biliary schistosomiasis—*S. mansoni*:
  - One-third of cases worldwide
  - Most in sub-Saharan Africa, some cases in Egypt and the Middle East
  - Only form of schistosomiasis in the Americas, 1–2 million cases, mostly in Brazil
  - Transmitted from *Biomphalaria* snails (Fig. 78.2)
  - Highest-intensity infections in children, adolescents, and young adults.
- Intestinal and biliary schistosomiasis—*S. japonicum* and *S. mekongi*:
  - Fewer than 1 million cases
  - Most in China and the Philippines (*S. japonicum*)
  - *S. japonicum* transmitted by *Oncomelania* snails (Fig. 78.2)
  - Highest-intensity infections in children, adolescents, and young adults.

Transmission and incubation period

- Freshwater contact with cercariae.
- Direct skin penetration by cercariae (Fig. 78.2).

Clinical features and sequelae

- Clinical manifestations caused by inflammation and granulomas elicited by parasite eggs in host tissues.
- Acute schistosomiasis—Katayama fever:
  - Heavy exposure to *S. japonicum* and *S. mansoni* infection
  - One to 2 months after exposure to cercariae
  - Fever, chills, cough, headaches
  - Lymphadenopathy, hepatosplenomegaly, eosinophilia
  - Transverse myelitis in returning travellers (rare).
- Chronic schistosomiasis:
  - Urinary/urogenital schistosomiasis caused by *S. haematobium*
  - Impaired child development and anaemia
  - Haematuria, dysuria, increased frequency
  - Hydroureter, hydronephrosis
  - Renal failure
  - Squamous cell carcinoma of the bladder
  - ♀ genital schistosomiasis—increased risk of HIV/AIDS.
  - Intestinal/biliary schistosomiasis caused by *S. mansoni, S. japonicum*, and *S. mekongi*
  - Impaired child development
  - Fatigue, abdominal pain, diarrhoea, bloody diarrhoea
  - Symmer's pipestem (periportal) fibrosis of the liver
  - Hepatosplenomegaly, oesophageal varices.

Diagnosis

- Urogenital schistosomiasis:
  - Eggs in urine (concentration required)
  - Serological tests (may not distinguish between current and past infection)
  - Urinary tract ultrasound
  - Sandy patches on colposcopic examination.
- Intestinal/biliary schistosomiasis:
  - Eggs in stool
  - Rectal biopsy for eggs

- Serological tests (may not distinguish between current and past infection)
- Ultrasound for periportal fibrosis.

Management and treatment

- Praziquantel.
- Several vaccine candidates entering clinical trials.

Strongyloidiasis

Causative organisms

- *Strongyloides stercoralis* is the major species.
- Only major helminth to replicate in human host (in association with hyperinfection).

Epidemiology

- Strongyloidiasis is a soil-transmitted helminthiasis (Fig. 78.3).
- ~30–100 million cases worldwide, with highest rates in low- and middle-income countries, especially tropical regions of the Americas, South East Asia, and sub-Saharan Africa.
- Foci also present in the US (Appalachia), Southern (Spain and south-west France) and Eastern Europe, Japan, and Australia.

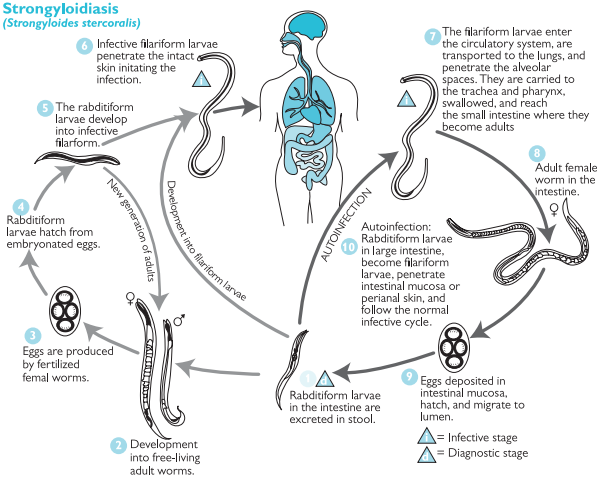

Fig. 78.3 Life cycle of *Strongyloides stercoralis* and strongyloidiasis.

(From the Public Health Image Library of the US Centers for Disease Control and Prevention, <http://phil.cdc.gov>.)

Transmission and incubation period

- Larvae in the soil penetrate through the skin (similar to human hookworm infection).
- Migratory route through human tissues to reach the intestine.
- Larvae can migrate through human tissues through the process of autoinfection, with clinical manifestations sometimes appearing after years or decades.

Clinical features and sequelae

- Chronic strongyloidiasis:
  - Enteritis
  - Diarrhoea or diarrhoea alternating with constipation
  - Inflammatory bowel disease
  - Urticaria
  - Larva currens (subcutaneous larval migration in the skin).
- *Strongyloides* hyperinfection:
  - In association with steroids used for treatment of other chronic conditions, such as cancer, autoimmune disease, but also human T-lymphotropic virus (HTLV)-1 (not so much HIV) and other underlying conditions
  - Severe diarrhoea
  - Ulcerative intestinal disease
  - Bronchopneumonitis
  - Larva currens
  - 2° bacteraemias and bacterial meningitis
  - Significant mortality rate.

Diagnosis

- Detection of larvae (not eggs) in stool:
  - Often requires multiple stool exams
  - Amplification techniques: nutrient blood agar cultures, Baermann concentration.
- Serological testing—ELISA:
  - Poor specificity in patients co-infected with other helminths (endemic areas).

Management and treatment

- Ivermectin:
  - Safety in young children (<15kg) not established
  - Taken on empty stomach with water (opposite for albendazole)
  - Prolonged or repeated therapy for hyperinfection
  - Combining with albendazole has been suggested for hyperinfection
  - Veterinary formulations for patients unable to take orally
  - Taper steroids in hyperinfection.
- Alternative drugs: albendazole and thiabendazole.
- Antibiotics for bacteraemia and/or bacterial meningitis.

Toxocariasis

Causative organisms

- The canine roundworm *Toxocara canis*.
- The feline roundworm *T. cati*, also other zoonotic ascarids.
- Larval migrans syndromes associated with eosinophilia and other sequelae.

Epidemiology

- The most common helminth infections in the US and Europe.
- High rates of infection in US among African American populations living in poverty.
- High rates of infection in Puerto Rico and among some Hispanic American populations.
- Endemic to Eastern Europe.
- Endemic to Brazil, Nigeria, and presumably other low- and middle-income countries.

Transmission and incubation period

- Accidental ingestion of *Toxocara* eggs.
- Environmental contamination of sandboxes and playgrounds.
- Co-infections with toxoplasmosis.

Clinical features and sequelae

- Visceral larva migrans (VLM):
  - Very young children and toddlers 1–4 years of age
  - Loeffler's pneumonitis—wheezing and asthma
  - Hepatitis—hepatomegaly
  - Lymphadenitis
  - Cerebritis—seizures
  - Eosinophilia.
- Ocular larva migrans (OLM):
  - Older children and adolescents
  - Larval tracks and granuloma on the retina
  - Retinitis or endophthalmitis
  - Strabismus.
- Covert toxocariasis:
  - Asymptomatic or partial features of VLM
  - Eosinophilia, wheezing, abdominal pain
  - Pulmonary dysfunction
  - Cognitive deficits.

Diagnosis

- VLM or covert toxocariasis—ELISA, high sensitivity and specificity, eosinophilia, elevated IgE and IgG.
- OLM—clinical diagnosis (low sensitivity of ELISA for OLM).

Management and treatment

- Covert toxocariasis or VLM sometimes self-limited.
- All three forms can be treated with albendazole.
- Corticosteroids sometimes helpful.
- OLM frequently requires additional surgical management.

Trichinellosis

Causative organisms

- *Trichinella spiralis* (worldwide), but at least eight other geographically restricted species, including *Trichinella britovi* in Eurasia, *Trichinella nativa* in the Arctic.

Epidemiology

- Worldwide distribution.
- Incidence has declined in North America, except among the Inuit in the Canadian Arctic and infections among hunters who consume bears.
- European outbreaks have occurred, and the disease still occurs in Eastern Europe.

Transmission and incubation period

- Occurs by ingestion of contaminated meat.
- Uncooked or undercooked pork for *T. spiralis* and other species.
- Incubation period of days to weeks before the enteral phase begins.

Clinical features and sequelae

- First, enteral phase, lasting days to weeks:
  - Diarrhoea, nausea, vomiting.
- Second, parenteral phase (muscle phase):
  - Fever
  - Periorbital oedema
  - Muscle pain and myositis
  - Carditis and ECG changes
  - Neurotrichinellosis—meningo-encephalitis (fewer than a quarter of cases)
  - Eosinophilia.

Diagnosis

- Clinical diagnosis and epidemiological history.
- Elevated creatine phosphokinase (CPK), LDH.
- ECG changes.
- Confirmatory serological tests.
- Muscle biopsy.

Management and treatment

- Analgesics/antipyretics.
- Bed rest.
- Monitor cardiac function.
- Corticosteroids.
- Albendazole × 8–14 days.

Prevention

- Prolonged freezing or cooking of pork and other meats.

Cutaneous larva migrans

- Caused by cat or dog hookworms—classically *Ancylostoma braziliense*. Larvae survive from dog faeces on beaches of Asia, Central and South America, and the Caribbean.
- In humans, larvae penetrate the skin but cannot migrate further. They migrate within the skin with a serpiginous track at a rate of 0.5–1cm/day for around 1 week, sometimes causing itching and local urticaria.
- Most commonly seen on the feet.
- Can be treated with topical thiabendazole, or oral albendazole or ivermectin. Does not typically cause systemic disease.

Future research

- There is an urgent need for further large clinical trials to determine the most cost-effective treatment of most helminthiases in children.
- Improved pharmacokinetic studies of anthelmintic drugs in young children
- Developments of new anthelmintic drugs and vaccines.

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Chapter 79

Epstein–Barr virus

See also Chapters 15, 44.

Name and nature of the organism

- EBV is an enveloped DNA virus, belonging to the family of human herpesviruses (HHV-4) and subfamily of γ-herpesviruses. Two strains EBV-1 and EBV-2 are recognized, and infection could occur with both strains.
- EBV is named after Anthony Epstein and his student Yvonne Barr, who discovered the virus in 1964 in cells cultured from tumour specimens sent to them from Uganda by Denis Burkitt. He postulated that there might be an infective component to the tumours he was treating (Burkitt's lymphoma), and he was right!
- EBV most commonly infects B lymphocytes but rarely is also capable of infecting squamous epithelial cells, smooth muscle cells, T cells, natural killer cells, plasma cells, and follicular dendritic cells.
- EBV is the commonest cause of infectious mononucleosis (IM).
- EBV is associated with various cancers. In addition to endemic Burkitt's lymphoma, EBV is implicated in certain types of Hodgkin's and non-Hodgkin's lymphomas, undifferentiated nasopharyngeal carcinoma (NPC), and a proportion of gastric carcinomas. These cancers affect several hundred thousand persons per year worldwide.
- EBV is often claimed to be associated with CFS, but there is little evidence to support this.
- EBV exhibits a lifelong latent infection in healthy carriers harbouring EBV in B-memory lymphocytes where no virus or viral products are expressed.
- Infectious virus is present in the saliva, but replication of both the virus and infected B cells expressing viral products is usually controlled by antibody, natural killer, and T-cell responses in healthy individuals.
- In acute infection, up to 20% of all circulating B cells may be infected.

Epidemiology

- EBV occurs worldwide, but the occurrence of EBV-associated tumours, endemic Burkitt's lymphoma, and undifferentiated NPC has distinct geographical patterns. Endemic Burkitt's lymphoma occurs in areas with holoendemic malaria, while NPC is commonest in Southern China.
- Humans are the only source of infection.
- More than 90% of the population will have been infected by the virus in childhood when it is most often asymptomatic. Infection during adolescence is much more likely to cause IM (glandular fever).
- No seasonal pattern is documented.

Transmission and incubation period

- Transmission is by close personal contact with healthy asymptomatic carriers, and spread is via saliva—'the kissing disease'. IM is common in adolescents—typically spreading in schools or colleges.
- The virus is viable in saliva for several hours outside the body, but transmission via fomites is unknown.
- The virus can also be isolated from blood, genital tract secretions, CSF, and breast milk, although these are not thought to play a role in transmission.
- The incubation period is 4–7 weeks, but the person will remain infected and infectious indefinitely after the symptoms have completely disappeared, in the same way as a normal, healthy, asymptomatic carrier.

Clinical features and sequelae

- As in other herpesviruses, the clinical features are divided into 1° infection (IM) and reactivation.
- The spectrum of disease is very wide, ranging from asymptomatic, through typical glandular fever to (very rarely) severe, prolonged, and occasionally fatal illness.
- IM (glandular fever) is typically associated with fever, exudative pharyngitis, cervical lymphadenopathy, headache, hepatosplenomegaly, hepatitis, and malaise.
- A non-specific maculopapular rash is seen in up to 10% of cases.
- Palatal petechiae may be observed.
- In acute EBV, facial oedema/fullness is seen across the nasal area.
- Apparently normal young children can develop a severe illness with high fever, widespread marked lymphadenopathy, and hepatosplenomegaly.
- If amoxicillin or ampicillin is given, some patients will develop a florid rash.
- Neurologic conditions attributed to EBV infection have included aseptic meningitis, encephalitis, and Guillain–Barré syndrome. These are usually only seen in severe cases.
- Rare complications include autoimmune haemolytic anaemia, thrombocytopenia, haemophagocytic syndromes, splenic rupture, orchitis, and myocarditis.
- IM doubles the subsequent risk of contracting multiple sclerosis and Hodgkin's disease, but a causal relationship in either case has not been established.
- In boys (classically aged 3–5 years) who develop an increasingly severe IM picture, with worsening hepatitis, encephalopathy, and marrow failure, urgently consider the possibility of X-linked lymphoproliferative syndrome (Duncan's syndrome) due to a defect in the *SAP* gene.
- In immunocompromised patients (congenital or acquired), reactivation of EBV may lead to severe symptomatic infection or B-cell lymphomas. EBV is also associated with PTLD, which may be either polyclonal or true malignant lymphoma.

Diagnosis

- Usually based on typical clinical features.
- The blood picture shows a lymphocytosis with atypical lymphocytes.
- The commonest serological test is based on the heterophile antibody test (Monospot or Paul Bunnell), in which the infected plasma agglutinates sheep erythrocytes. This test is specific, but not sensitive. False negative results occur in up to 25% in the first week, 5–10% in the second week, and 5% in the third. The antibody may not appear until the second or third week of illness. Of young children, up to 50–75% may have a negative heterophile antibody test.
- More useful is specific EBV serology. IgM antiviral capsid antigen (VCA) or anti-early antigen (EA) is useful to identify a recent infection, whereas a positive IgG anti-VCA indicates a past infection. Serum antibody against EBNA is only present weeks or months after the initial infection, so a positive anti-EBNA antibody test will exclude a very recent infection. A negative anti-EBNA with a high positive IgG anti-VCA is indicative of a recent infection.
- EBV viral load, determined by quantitative PCR, is now commonly used in the post-transplantation setting to detect early signs of EBV reactivation and disease, and prevention of PTLD.
- Differential diagnoses include:
  - Other viral causes (such as CMV) or toxoplasmosis, especially in heterophile-negative patients
  - HIV, which can mimic similar signs
  - Acute leukaemia. The blood results of EBV and leukaemia may be confused. A bone marrow examination may be necessary for clarification
  - Other causes of pharyngitis (*Streptococcus*, diphtheria, and respiratory viruses).

Management and treatment

- IM is generally self-limiting, and therefore only supportive and/or symptomatic treatments are used. Antipyretics and simple anti-inflammatory medications may reduce fever and pain.
- Antibiotics are not recommended. If they are used, ampicillin and amoxicillin should be avoided, as they are likely to produce a rash.
- Steroids have been effectively used for severe disease or massive pharyngeal swelling compromising the airway of the patient. However, a recent Cochrane review concluded that there was insufficient evidence to recommend steroid treatment for symptom control in simple glandular fever.
- Rest is important during the acute phase. Contact sports should be avoided, until the patient is fully recovered and the spleen no longer palpable to avoid splenic rupture.
- Aciclovir and penciclovir have shown similar activity against EBV in cell cultures, but clinical data are almost entirely missing.

Prevention

- There is no vaccine currently available, although a phase 2 trial of a recombinant subunit vaccine indicated that IM can be prevented, but not EBV infection itself.
- Patients with a recent 1° EBV infection should not give blood.
- Affected individuals do not need to be isolated, and there is no quarantine time.

Future research

- The prevalence of EBV-related cancers worldwide warrants work on laboratory assays to both detect and quantify the infection, which can be used as a tumour marker to support the clinical management of patients. International efforts are under way to establish a standard by which to calibrate EBV DNA measurement.
- The development of EBV vaccines to prevent or modify infection continues to progress, as does the development of immunotherapeutic strategies for the treatment of EBV tumours themselves.
- Gene expression profiling and proteomics aim to identify patterns of viral and human gene expression to correlate with the diagnosis, prognosis, and response to therapy.
- Search for new antiviral agents against EBV is ongoing.
- The clinical efficacy and the most appropriate treatment regimen of aciclovir and penciclovir should be established.

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Chapter 80

Influenza and parainfluenza

Influenza

Name and nature of organism

- Influenza viruses belong to the family *Orthomyxoviridae*, and they have a segmented RNA genome coding for ~10 proteins.
- Influenza viruses are classified into three distinct types: A, B, and C.
- The main surface antigens of the virus are haemagglutinin (17 known subtypes) and neuraminidase (ten known subtypes).
- Birds (waterfowl) are the natural reservoir of influenza A viruses.
- All known subtypes of haemagglutinin and neuraminidase have been found in birds, but few subtypes have been detected in humans.
- Influenza A viruses are divided into subtypes on the basis of their haemagglutinin and neuraminidase content (e.g. A/H1N1 or A/H3N2).
- Influenza viruses undergo constant antigenic adaptation because of point mutations in the viral genome ('antigenic drift').
- Major reassortment of gene segments from two different virus subtypes results in 'antigenic shift'. Such a shift may give rise to a new influenza pandemic if the progeny virus contains a haemagglutinin that is new to humans (usually originating from animal viruses).

Epidemiology

- Influenza viruses have a worldwide distribution.
- Epidemics of influenza A occur annually during wintertime in temperate regions of the northern hemisphere.
- Influenza A and B viruses cause large outbreaks. Most (~80%) seasonal influenza in Europe is due to influenza A, with B viruses causing major outbreaks every 3–4 years; influenza C viruses are responsible for minor respiratory illnesses.
- The severity of the epidemics varies substantially from year to year, depending on the antigenic variation of the circulating strains.
- Influenza attack rates are highest in young children.
- Since 1977, only A/H1N1, A/H3N2, and B viruses have been circulating among humans in epidemic proportions.
- A/H5N1 ('bird flu') viruses have continued to cause sporadic illnesses since 1997, but there have been no true epidemics.
- Depending on the definition used, four or five influenza pandemics have occurred during the past century (starting year): A/H1N1 (1918 'Spanish flu'), A/H2N2 (1957 'Asian flu'), A/H3N2

(1968 'Hong Kong flu'), A/H1N1 (1977 'Russian flu'), and A/H1N1 (2009 'swine flu´).
- Since 2013, new A/H7N9 viruses have been causing severe illnesses, mainly in China.
- The threat of a new influenza pandemic exists all the time.

Transmission and incubation period

- Influenza viruses are spread by virus-laden respiratory secretions from infected subjects.
- Viruses can be transmitted through aerosols, large droplets, or direct contact with secretions.
- Viruses attach to sialic acid-containing receptors on the cell surface of the respiratory mucosa.
- The average incubation period is 2 days (range 1–5 days).
- Virus shedding begins 1 day before the onset of symptoms, peaks at 2–3 days, and continues for 5–7 days after symptom onset.
- Longer periods of shedding are frequently seen in children and immunocompromised patients.

Clinical features and sequelae

- The clinical presentation varies from asymptomatic infection to severe lethal illness.
- The duration of illness is usually between 3 and 8 days.
- Abrupt onset of illness is a classic feature of influenza.
- Typical initial symptoms in adults and older children include fever, chills, malaise, headache, myalgia, cough, and sore throat.
- Most infants and young children with influenza have fever ≥39.0°C and rhinitis already during the early phase of the illness.
- Sepsis-like illness is the commonest reason for hospitalization of infants <6 months of age.
- In older children, common clinical manifestations leading to hospitalization include pneumonia, laryngitis, febrile convulsion, and wheezing.
- Myositis, myocarditis, encephalitis, and encephalopathy are infrequent manifestations of influenza.
- The most frequent complication in children is AOM, which occurs in 40% of children <3 years of age.
- Pneumonia and sinusitis are rarer complications in children.
- The disease may be very severe in immunocompromised children and in those with serious underlying illness, e.g. neurological diseases, HIV infection, cardiac disease, etc.
- Mortality due to influenza is low in children, but almost half of all influenza-related deaths occur in children without any underlying medical conditions.

Diagnosis

- Clinical diagnosis of influenza is extremely difficult in young children because of signs and symptoms that overlap with those seen during other respiratory viral infections.

- Viral culture is the gold standard for diagnosis (and it is also essential for surveillance purposes), but antigen detection and PCR-based assays are most useful for everyday clinical purposes.
- Several rapid tests are available that produce results within 15–30 minutes. They usually have high specificity, but their sensitivity varies (also depending on the quality of the specimen obtained).

Management and treatment

- Neuraminidase inhibitors oseltamivir and zanamivir are specific antivirals for the treatment of influenza.
- Rapid initiation of antiviral therapy is crucial for clinical efficacy.
- Oseltamivir reduces symptoms of influenza A by up to 4 days if started within 24 hours of symptom onset, but only by 1–1.5 days when started within 48 hours of the onset of symptoms.
- When started within 12 hours of symptom onset, oseltamivir reduces the rate of development of AOM as a complication by ~80%.
- Oseltamivir is administered orally (capsules or suspension), and, in Europe, it is currently licensed for children >1 year of age (but also to young infants during pandemics). There is currently an ongoing reassessment of the efficacy and toxicity of oseltamivir, as new data emerge.
- Zanamivir is administered by inhalation with the use of a specific device and can be used in children >5 years of age.
- Antiviral resistance patterns of influenza viruses vary between different drugs, viral subtypes, and geographical areas.
- A number of new antivirals are under study, including novel neuraminidase inhibitors, peptides, defensins, short interfering RNA (siRNA), nitazoxanide.
- Acetylsalicylic acid (aspirin) should not be used in children because of increased risk of Reye's syndrome.

Prevention

- Vaccination is the cornerstone of influenza prevention.
- The antigenic composition of the influenza vaccine is revised annually in order to accommodate the constantly occurring changes in the haemagglutinin antigens of the circulating viruses.
- Two main types of vaccines are currently available for children in Europe: inactivated vaccine (administered by injection) to children >6 months of age, and live-attenuated vaccine (intranasal spray) for children 2–17 years of age.
- The conventional trivalent vaccines consist of three antigens (two A viruses and one B virus).
- Recently, quadrivalent vaccines (containing two A viruses and two B viruses) have been produced.
- The clinical efficacy of the influenza vaccine varies between different seasons, depending on the degree of match between the strains included in the vaccine and the actual wild-type strains of influenza circulating in the community.

- In years with good antigenic match, the efficacy of the inactivated vaccine against virologically confirmed influenza is usually 70–80% in children; the efficacy of live attenuated vaccine is even higher in children.
- Vaccine recommendations vary between different countries, but, in developed countries, influenza vaccination is generally recommended at least for all children with certain chronic medical conditions.
- In several countries (e.g. the US, the UK, Canada, Finland), influenza vaccination is currently included in the routine vaccination programme for children.
- In certain situations (e.g. within households or for high-risk children), PEP with influenza antivirals can be used to prevent clinical illness.

Future research

- More data on the burden of illness and the cost-effectiveness of vaccination in different countries are needed to guide national vaccine recommendations in children.
- Development of vaccines with broader immunogenicity and more robust 'antigenic-drift-and-shift-proof' protection against the various circulating strains of influenza viruses is needed.

Parainfluenza

Name and nature of organism

- Parainfluenza viruses belong to the family *Paramyxoviridae* and have a single-stranded RNA genome.
- The viruses are classified into four types (1, 2, 3, 4) and two subtypes (4a, 4b).
- No clinically significant antigenic variants of parainfluenza viruses are known to exist.

Epidemiology

- Parainfluenza viruses have a worldwide distribution.
- Major outbreaks (especially by parainfluenza type 3 viruses) occur usually in the spring months, but infections may occur at almost any time of the year.
- Type 1 and 2 viruses often cause epidemics in the autumn of every second year.
- Almost all children will be infected by type 3 viruses, and most by type 1 and 2 viruses during their first years of life.
- Reinfections by the same virus type are common.

Transmission and incubation period

- Parainfluenza viruses are spread by respiratory droplets or by direct contact with secretions from an infected subject; also airborne infection is possible.
- Viruses enter the body via the nose or eyes, using sialic acid-containing membrane proteins as receptors.
- Virus replication is mostly limited to the respiratory tract; viraemia is extremely rare.

- The incubation period varies between 2 and 7 days, and it is probably dependent on the size of the inoculum.
- The duration of viral shedding is ~1 week, but type 3 viruses, in particular, may be shed for substantially longer periods.
- Virus shedding may begin several days before the onset of symptoms.

Clinical features and sequelae

- Type 1 and 2 viruses are among the most frequent causes of laryngitis and croup.
- Type 3 viruses are mostly associated with LRTIs (bronchiolitis and pneumonia) but may also cause laryngitis and croup.
- Type 3 viruses have been occasionally associated with aseptic meningitis.
- AOM and sinusitis are the most frequent complications of parainfluenza virus infections.
- Immunocompromised children have higher rates of disease and shed the virus longer.

Diagnosis

- For clinical purposes, antigen detection and PCR-based assays are most useful for laboratory diagnosis, but also viral culture can be used.
- The usefulness of serology is limited by substantial cross-reactivity between different types of parainfluenza viruses.
- Except for cases of laryngitis and croup during confirmed parainfluenza activity in the community, distinguishing parainfluenza infections from other viral respiratory infections on clinical grounds alone is very difficult in children.

Management and treatment

- Treatment is supportive; no specific antiviral therapy is available.

Prevention

- Vaccines against parainfluenza viruses (particularly type 3) are being developed but are currently not commercially available.

Future research

- Because of the substantial impact of parainfluenza virus infections on young children, the availability of effective vaccines and antiviral treatments would be worthwhile goals for research in this area.

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Chapter 81

Threadworms

Name and nature of organism

- *Enterobius vermicularis* is a small, white roundworm with a thread-like appearance. It is commonly referred to as the threadworm or pinworm. A second species *Enterobius gregorii* has been described in Europe, but, for all practical purposes, the morphology, life cycle, clinical presentation, and treatment are identical to *E. vermicularis*.
- The adult ♀ worm measures about 9–12mm in length and is much larger than the ♂ worm, which is ~2–5mm long.
- Humans are the only reservoir.
- Ingested threadworm eggs hatch in the duodenum. Within 5–6 weeks, the larvae develop into adult worms and live in the terminal ileum, appendix, caecum, and ascending colon. The ♀ worm can live for 4–6 weeks, and the ♂ worm for only 2 weeks. Threadworms do not multiply within the body. At the end of the life cycle, the gravid ♀ worms migrate to the perianal region (in girls, eggs may also be deposited around the vagina and urethra) where they deposit up to 10 000 eggs and die. This occurs usually during the night, as inactivity of the host causes the worms to migrate. The ♀ worm secretes a sticky mucus to attach the eggs to the skin, which causes intense itching. The eggs then embryonate to become infective within 4–6 hours.

Epidemiology

- Threadworm infection is the commonest helminth infection throughout the world, and the commonest parasitic infection of children in Europe.
- It is most frequent among preschool and school-aged children up to the age of 10 years. Western European studies indicate that up to 20% of children are affected at any one time.
- Children living in overcrowded conditions or in institutions are most affected. However, higher socio-economic status and good sanitation do not prevent from infection.
- Within a household, other family members, most often the mother and other children, are commonly infected.

Transmission and incubation period

- The commonest mode of transmission of eggs is via the hands, particularly underneath fingernails, from scratching the anal/perianal region.
- From contaminated hands, eggs may be passed directly into the mouth or indirectly via toys, food, etc. Ingestion of fresh eggs continues the cycle of infestation (or autoinfestation where a person ingests their own eggs).
- Transmission may also occur by exposure to viable eggs in soiled bed linen, house dust, or clothing. As the eggs are so small, it is possible to ingest them while breathing (e.g. when they become airborne after shaking contaminated linen).
- Reinfection is common and occurs either by autoinfestation or via contaminated fomites (eggs can survive in the environment for up to 3 weeks).
- Retro-infection can also occur when eggs hatch on the anal mucosa, and larvae migrate into the large intestine.
- The incubation period is 2–6 weeks.

Clinical features and sequelae

- Most threadworm infections are asymptomatic.
- The commonest symptom is pruritus ani—itchy bottom (worse at night)—which varies from mild itching to acute pain. Scratching of the perianal region may lead to excoriation of the skin and 2° bacterial infection.
- Some children present, because worms have been seen on the perianal skin or less commonly in stools.
- Persistent infestation can cause anorexia, weight loss, restlessness, irritability, enuresis, and insomnia.
- Vulvovaginitis with pruritus vulvae and mucoid vaginal discharge may also occur in young girls.
- Threadworm infestation can sometimes present with more serious GI tract symptoms and signs:
  - Symptoms resembling appendicitis without histological evidence of appendicitis can occur; there may also be an increased risk of true appendicitis
  - Eosinophilic colitis or gastroenteritis may rarely occur.
- Rarely, abnormal migration of the worms leads to ectopic disease, such as pelvic, cervical, vulvar, and peritoneal granulomas, which may be mistaken for other disease processes. Threadworms have also been found in the inguinal area, the prostate, the liver, and even the lungs.

Diagnosis

- On examination of the perianal area, there may be signs of excoriation from scratching and signs of localized 2° bacterial infection.
- Occasionally, adult ♀ worms (often described as 'small threads of slowly moving white cotton') may be seen in the perianal region, typically 2–3 hours after the child is asleep. It is unusual to see these during the day.
- Detection of eggs by microscopic examination of material collected using a moistened perianal swab is the preferred diagnostic method. This is more sensitive than, and has largely superseded, the use of transparent adhesive tape applied to the perianal skin.
- Microscopy of stool specimens is not recommended, because very few eggs are present in stool. The detection rate from faecal samples is only 5–15%.

Management and treatment

- Treatment is indicated if threadworms have been seen or their eggs detected.
- Treatment should also be given if the test result is negative, but symptoms are highly suggestive.
- The drug of choice is mebendazole, which can be given in children ≥6 months old. A second dose may be given 2 weeks later to eliminate possible re-infestation following the first dose. Mebendazole acts by inhibiting the uptake of glucose by the worm. It is poorly absorbed from the GI tract, and side effects are rare.
- Hygiene measures alone are preferred for those ≤6 months old.
- Alternatives treatments for children ≥2 years old are albendazole or pyrantel pamoate.
- As anthelmintics have no effect on threadworm eggs, treatment needs to be combined with strict hygiene measures to prevent reinfection. These measure include:
  - Good hand hygiene before each meal and after using the toilet
  - Having a bath or shower every morning to remove large amounts of eggs laid during the night
  - Frequent changes of underwear, nightclothes, and bedding
  - Keep fingernails short
  - Avoidance of nail biting and finger sucking
  - Wearing of close-fitting nightclothes to discourage night-time scratching
  - Avoidance of sharing towels/flannels
  - Cleaning, vacuuming, and damp dusting of surfaces in the home daily for several days after treatment of cases. Wash the cloth frequently in hot water
  - Disinfect bathroom surfaces daily
  - Make sure there is good ventilation, and reduce humidity in the house
  - Elimination of overcrowded living accommodation.

- It is recommended that all family members are treated simultaneously in order to minimize reinfection. Hygiene measures should continue for 6 weeks.
- It is not necessary to exclude children from school and other day-care facilities, as asymptomatic infection is often involved in transmission, and threadworm is generally a mild illness in childhood.

Prevention

- Maintenance of high standards of personal hygiene can reduce the risk of threadworm infection.
- Children should be taught to wash their hands with soap and water regularly, particularly after using the toilet and before eating or preparing food.

Future research

- None.

What's new?

- Piperazine, previously a treatment option for treating children over 3 months old, has been withdrawn because of its unfavourable risk–benefit ratio and concern that it may give rise to potentially carcinogenic N-nitroso derivatives.

What's next?

- None.

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Chapter 82

Kawasaki disease

See also Chapters 32, 33, 46, 105.

Introduction

Kawasaki disease is a self-limiting vasculitic syndrome that predominantly affects medium and small-sized arteries. It is the second commonest vasculitic illness of childhood (the commonest being Henoch–Schönlein purpura) and is the leading cause of childhood acquired heart disease in developed countries.

Pathogenesis

- Pronounced seasonality and clustering of Kawasaki disease cases have led to the hunt for infectious agents as a cause. However, so far, no single agent has been identified.
- The aetiology of Kawasaki disease remains unknown, but it is currently felt that one or more widely distributed infectious agents evoke an abnormal immunological response in genetically susceptible individuals, leading to the characteristic clinical presentation of the disease.

Epidemiology

- Kawasaki disease has a worldwide distribution, with a ♂ preponderance, an ethnic bias towards children of Asian ancestry, some seasonality, and occasional epidemics.
- The reported incidence of Kawasaki disease is rising worldwide, including the UK. The current reported incidence in the UK is 8.1/100 000 children <5 years old. This may reflect a truly rising incidence or an increased clinician awareness.

Clinical presentation

- The principal clinical features of Kawasaki disease are:
  1. Fever persisting for ≥5 days
  2. Peripheral extremity changes (reddening of the palms and soles, indurative oedema, and subsequent desquamation)
  3. Polymorphous exanthema
  4. Bilateral conjunctival injection/congestion
  5. Lips and oral cavity changes (reddening/cracking of lips, strawberry tongue, oral and pharyngeal injection)
  6. Acute non-purulent cervical lymphadenopathy.

- For the diagnosis of Kawasaki disease to be formally established, five of the six clinical features described should be present.
- Children with fewer than five of the six principal features can be diagnosed with Kawasaki disease when coronary aneurysm or dilatation is recognized by two-dimensional echocardiography or coronary angiography.
- The cardiovascular features are the most important manifestations of the condition, with widespread vasculitis affecting predominantly medium-sized muscular arteries, especially the coronary arteries. Coronary artery involvement occurs in 15–25% of untreated cases. Additional cardiac features include pericardial effusion, ECG abnormalities, pericarditis, myocarditis, valvular incompetence, cardiac failure, and myocardial infarction.
- Irritability is an important sign, which is virtually universally present, although not included in the diagnostic criteria.
- Another clinical sign that may be relatively specific to Kawasaki disease is the development of erythema and induration at sites of BCG inoculations. The mechanism of this sign is thought to be cross-reactivity of T cells in Kawasaki disease patients between specific epitopes of mycobacterial and human heat shock proteins.
- An important point is that the principal symptoms and signs may present sequentially, such that the full set of criteria may not be present at any one time. Awareness of other non-principal signs (such as BCG scar reactivation) may improve the diagnostic pickup rate of Kawasaki disease.
- Other clinical features include: arthritis, aseptic meningitis, pneumonitis, uveitis, gastroenteritis, meatitis and dysuria, and otitis.
- Infants may have few classic signs of Kawasaki disease and can present with persistent fever, signs of inflammation, and irritability—a difficult diagnosis to make. Infants also respond less well to IVIG.
- Relatively uncommon abnormalities include hydrops of the gall bladder, GI ischaemia, jaundice, petechial rash, febrile convulsions, and encephalopathy or ataxia, macrophage activation syndrome, and SIADH.

Differential diagnosis

Conditions that can cause similar symptoms to Kawasaki disease and must be considered in the differential diagnosis include:

- Scarlet fever
- Rheumatic fever
- Streptococcal or staphylococcal TSS
- SSSS
- Systemic JIA
- Infantile polyarteritis nodosa
- SLE
- Infections with adenovirus, enterovirus. EBV, CMV, parvovirus, influenza virus
- *M. pneumoniae* infection

- Measles
- Leptospirosis
- Rickettsial infection
- Adverse drug reaction
- Mercury toxicity (acrodynia).

Investigations

No diagnostic test exists for Kawasaki disease. However, in cases of suspected Kawasaki disease, the following investigations should be considered:

- FBC and blood film
- ESR
- CRP
- Blood cultures
- Anti-streptolysin O titre and anti-DNase B
- Nose and throat swab—bacterial and viral, and stool sample for culture (superantigen toxin typing if *S. aureus* and/or β-haemolytic streptococci detected). Measles is best tested for with a saliva swab
- Renal and liver function tests
- Coagulation screen
- Autoantibody profile (ANA, extractable nuclear antigen (ENA), rheumatoid factor, antineutrophilic cytoplasmic antibody (ANCA))
- Serology (IgG and IgM) for *M. pneumoniae*, enterovirus, adenovirus, measles, parvovirus, EBV, CMV
- Urine microscopy, culture, and sensitivity
- Dip test of urine for blood and protein
- Consider serology for *Rickettsiae* and leptospirosis if history is suggestive
- Consider CXR
- ECG
- Two-dimensional echocardiography to identify coronary artery involvement acutely and monitor changes long-term
- Coronary arteriography has an important role for delineating detailed anatomical injury, particularly for children with giant coronary artery aneurysms (CAAs) (>8mm; or, for infants, Z-score for internal coronary artery diameter >7mm, based on Montreal normative data—available at: http://parameterz.blogspot.co.uk/2010/11/montreal-coronary-artery-z-scores.html>) where stenoses adjacent to the inlet/outlet of the aneurysms are a concern. Note that the procedure may need to be delayed until at least 6 months after disease onset, since there could be a risk of myocardial infarction if performed in children with ongoing severe coronary artery inflammation.

Management and treatment

The treatment of Kawasaki disease is summarized in Fig. 82.1 and comprises:

- IVIG at a dose of 2g/kg as a single infusion over 12 hours (consider splitting the dose over 2–4 days in infants with cardiac failure)

- IVIG should be started early, preferably within the first 7–10 days of the illness. However, clinicians should not hesitate to give IVIG to patients who present after 10 days if there are signs of persisting inflammation. Of note, IVIG resistance, however, occurs in up to 10–20% of cases
- Aspirin 30–50mg/kg/day in four divided doses. The dose of aspirin can be reduced to 2–5mg/kg/day when the fever settles and the child improves (disease defervescence). Aspirin at antiplatelet doses is continued for a minimum of 6 weeks
- Corticosteroids (IV methylprednisolone 0.8 mg/kg bd for 5–7 days until CRP normalizes, and then convert to prednisolone 2mg/kg/day PO, and wean off over the next 2–3 weeks; OR 10–30mg/kg for 3 days, followed by prednisolone 2mg/kg/day PO until CRP normalizes, and wean off over the next 2–3 weeks) should be considered for:
  1. Patients who have already declared themselves as IVIG-resistant
  2. Patients with features of the most severe disease (and therefore the greatest likelihood of developing CAA). In the absence of validated risk scores outside of Japan, we suggest that such patients include the very young; those with markers of severe inflammation, including persistently elevated CRP despite IVIG, liver dysfunction, hypoalbuminaemia, and anaemia; and the small group who develop features of HLH and/or shock
  3. Patients who already have evolving coronary and/or peripheral aneurysms with ongoing inflammation at presentation.
- In patients who have shown some, but not complete, response, we suggest that a second dose of IVIG is given at the same time as commencing steroids if they have not already been commenced for signs of severe disease.
- In refractory cases, infliximab, a human chimeric anti-TNF-α monoclonal antibody, given IV at a single dose of 6mg/kg, has been reported to be effective and is increasingly used for IVIG-resistant cases.
- Echocardiography should be repeated at 2 weeks and 6 weeks from initiation of treatment (refer to paediatric cardiology).
- If the repeat echocardiogram shows no CAAs at 6 weeks, aspirin can be discontinued, and lifelong follow-up at least every 2 years should be considered.
- In cases of confirmed CAA <8mm with no stenoses present, aspirin should be continued until aneurysms resolve.
- If giant aneurysms and/or stenoses are present, aspirin at a dose of 2–5mg/kg/day should be continued for life. The combination of aspirin and warfarin therapy in patients with giant aneurysms has been shown to decrease the risk of myocardial infarction.
- In patients who develop CAA, echocardiography and ECG should be repeated at 6-monthly intervals, and an exercise stress test considered.
- Other specific interventions, such as PET, addition of calcium channel blocker therapy, and coronary angioplasty, should be organized at the discretion of the paediatric cardiologist.

Fig. 82.1 summarizes the guidelines for the management of Kawasaki disease.

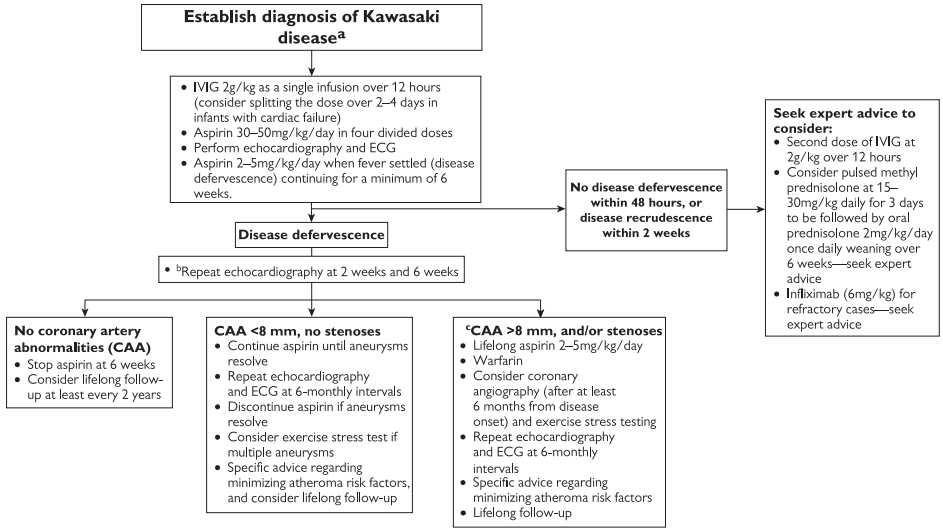

Fig. 82.1 Guideline for the management of Kawasaki disease.

[a] Treatment can be commenced before full 5 days of fever if sepsis excluded; treatment should also be given if the presentation is >10 days from fever onset.

[b] Refer to a paediatric cardiologist.

[c] Other specific interventions, such as PET, addition of calcium channel blocker therapy, and coronary angioplasty, at the discretion of the paediatric cardiologist.

Outcome

- Treatment with IVIG and aspirin reduces CAA from 25% for untreated cases to 4–9%.
- IVIG resistance occurs in up to 10–20% and is associated with higher risk of CAA.
- The overall outlook of children with Kawasaki disease is good, with the acute mortality rate due to myocardial infarction having been reduced to <1%, in part due to the alertness of clinicians to the diagnosis and prompt treatment.
- Nonetheless, the disease may contribute to the burden of adult cardiovascular disease and cause premature atherosclerosis, an area of active ongoing research.

Future research

- To further advance our understanding of the environmental triggers and host responses resulting in Kawasaki disease.
- Genetic studies of Kawasaki disease so far suggest a polygenic contribution, and ongoing international collaborative studies will hopefully provide a greater understanding of the genetic factors contributing to the pathogenesis.
- Peripheral blood biomarkers of vascular injury to allow reliable non-invasive monitoring of disease activity and guide therapeutic decisions.
- To optimize current treatment protocols for IVIG-resistant Kawasaki disease.
- To investigate the longer-term adult cardiovascular morbidity in children with Kawasaki disease with and without CAA.

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Chapter 83

Legionella

Name and nature of organism

- *Legionella* is a Gram-negative, rod-shaped bacterium with fastidious growth requirements, found primarily in aquatic environments as intracellular pathogens of protozoa. It is also found in biofilms in man-made water systems.
- Naturally occurring *Legionella* survive and multiply in water at temperatures between 25°C and 45°C, with an optimal temperature range of 32–42°C. Water temperature is a crucial factor in colonization of water distributions systems.
- The family *Legionellaceae* includes >70 serogroups. *Legionella pneumophila* serogroup 1 is responsible for 70–90% of cases in adults. In a paediatric series, *L. pneumophila* serogroup 1 accounted for 48% of cases, and serogroup 6 accounted for 33%. *Legionella micdadei* and *Legionella dumoffii* are the second and third commonest species to cause legionnaires' disease in children, respectively.
- *L. pneumophila* was named following a pneumonia outbreak at the American Legion Convention in 1976.

Epidemiology

- *Legionella* causes both sporadic and epidemic community-acquired (CAP) and nosocomial pneumonia. It causes 2–15% of all cases of CAP requiring hospitalization, and it is the second most frequent cause of severe pneumonia requiring ICU admission.
- Pontiac fever tends to occur in outbreaks, with high attack rates (>90%) and no mortality.
- *Legionella* infection is rarely diagnosed in children. In the US, only 1.7% of all cases of legionnaires' disease were reported in the paediatric age group, mostly in children 15–19 years old (44.3%), with 18.1% in infants. Most reported cases have involved children with an underlying respiratory disease and children who are immunocompromised.
- Legionnaires' disease tends to occur in neonates and children with acquired or congenital immunodeficiency (e.g. prematurity, malignancy, transplantation, corticosteroid use), as well as in children with pre-existing respiratory disease (e.g. asthma, acute and chronic lung disease, including bronchopulmonary dysplasia, tracheal stenosis, and tracheobronchomalacia).
- Serological surveys suggest that *Legionella* infection is common in school-aged children, but is usually asymptomatic, or mildly symptomatic or self-limiting in immunocompetent children.

Transmission and incubation period

- Water systems produce bacteria-containing aerosols that are dispersed into the atmosphere and can be inhaled. Infection may also be caused by aspiration of contaminated water. In the hospital, the sources of infection are drinking water, respiratory therapy, and medical equipment (incubators, humidifiers). Nosocomial legionellosis has been reported in a few neonates after water birth.
- The incubation period ranges from 2 to 10 days for legionnaires' disease, and from 12 to 48 hours for Pontiac fever.
- There is no evidence of person-to-person transmission of either legionnaires' disease or Pontiac fever.

Clinical features

Can present as a potentially fatal multisystem disease involving pneumonia (legionnaires' disease); a self-limited influenza-like infection (Pontiac fever); or a milder, non-pneumonic form of legionnaire's disease, distinct from Pontiac fever (extrapulmonary infection).

Legionnaires' disease

- Pneumonia is the predominant clinical manifestation of legionnaires' disease. A small proportion of mild CAP in older children is due to legionnaires' disease.
- Chest radiograph: unilateral changes (which may extend to bilateral involvement) with or without pleural effusion, pulmonary infiltrates, and cavitation. In adults, cavitation is commoner in immunocompromised patients but has been described in immunocompromised and immunocompetent children.
- Non-specific symptoms: fever, malaise, cough (often dry, it may become productive with purulent sputum and haemoptysis), chills, myalgias, dyspnoea, tachypnoea, hypoxia, chest pain, fatigue.
- Neurological manifestations: headache, agitation, stupor, cerebellar ataxia, lethargy, confusion. Neurologic examination occasionally shows hyperactive reflexes, tremor, and Guillain–Barré syndrome.
- GI manifestations: vomiting, nausea, and diarrhoea (watery and non-bloody).
- Neonatal legionellosis can manifest itself either as pneumonia or as non-specific sepsis.

Pontiac fever

- The symptoms mimic influenza with fever, headache, chills, myalgia, malaise, nausea, non-productive cough, abdominal pain, arthralgia, dry or sore throat, ear pain, and rash.
- Other symptoms: vomiting, diarrhoea, fatigue, dizziness, dyspnoea, low back pain, thoracic pains, poor concentration.
- The chest radiograph is normal.
- Recovery within 1 week is usual.

Extrapulmonary infection

- Extrapulmonary legionellosis is rare. Manifestations include pancreatitis, peritonitis, cellulitis, sinusitis, perirectal abscess, pericarditis, endocarditis, pyelonephritis, glomerulonephritis, and lymphadenopathy. In children, extrapulmonary sites may include the brain, lymph nodes, liver, and spleen.

Diagnosis

The key to the diagnosis of legionnaires' disease is to perform the appropriate microbiological tests. The following laboratory methods are used to diagnose *Legionella* infection:

- Isolation by culture (buffered charcoal yeast extract (BCYE) agar supplemented with antibiotics) of *Legionella* spp. from clinical specimens: sputum or BAL specimens, lung biopsy specimens, bronchial aspirates, and blood. Culture of *Legionella* spp., with a specificity of 100%, is the gold standard. The disadvantage is that the positive result is obtained only after 3 or more days of incubation; moreover, 25–78% of patients with legionnaires' disease have a non-productive cough, necessitating invasive specimen collection. The culture method allows recognition of co-infection with other pathogens.
- Urine ELISA using validated reagents: antigenuria is detectable very early and often provides the first evidence of *L. pneumophila* serogroup 1. The assay is highly specific (>99%), which is essential when testing for relatively rare diseases. The antigen test positivity rate varies with the severity of the disease, being positive in 40–53% of mild cases and in 88–100% of severe cases. It is an efficient, very rapid (15 minutes to 3 hours) test, often used in immunocompetent CAP patients. The results remain positive for weeks after administration of appropriate antibiotics. A serious drawback of the urinary antigen test is its low sensitivity in the detection of serogroups other than *L. pneumophila* serogroup 1.
- Serology: a 4-fold IgG or IgM rise between acute and convalescent titres by the indirect immunofluorescence antibody test (IFAT), using *L. pneumophila* serogroup 1 antigen. A single elevated titre >1:256 does not confirm a diagnosis of legionnaires' disease; titres of 1:256 or more are found in 1–16% of healthy children. The disadvantage of the method is possible cross-reaction with *Pseudomonas* spp., *C. burnetii, M. pneumoniae, F. tularensis, Haemophilus* spp., and others, and the inability to detect all *Legionella* spp. and serogroups accurately.
- Direct fluorescent antibody staining of *Legionella* in respiratory secretions or lung tissue, using evaluated monoclonal reagents: The test is rapid and highly specific but has low sensitivity because large numbers of organisms are required for microscopic visualization. Moreover, the test gives occasional false positive results with *S. aureus* (due to non-specific binding to protein A). There is also a possibility of cross-reaction with *Pseudomonas* spp. or *B. pertussis*.

- PCR test: diagnostic PCR assays have principally targeted specific regions within 16S rRNA genes, 23S–5S spacer region, 5S rDNA, or the macrophage inhibitor potentiator (*mip*) gene. Detection of *Legionella* DNA by PCR in serum, BAL fluid, or urine is potentially a rapid and specific alternative approach to the diagnosis of legionnaires' disease. PCR assays have a relatively good sensitivity (33–70%) and high specificity (98–100%).
- Non-specific laboratory findings commonly seen in legionnaires' disease in paediatric cases include:
  - Leucocytosis (>15 000 WBC/mL) or leucopenia (<5000 WBC/mL), thrombocytosis, thrombocytopenia, coagulopathy
  - Increased CRP or ESR
  - Elevated serum creatinine kinase
  - Elevated LFTs
  - Hyponatraemia.
- Histopathology of the lung: intense intra-alveolar inflammation (a large number of polymorphonuclear leucocytes, alveolar macrophages, necrotic debris).

Management and treatment

- Early initiation of appropriate treatment is crucial for a successful outcome of legionnaires' disease and significantly reduces the mortality rate. Only symptomatic treatment is recommended for Pontiac fever.
- Antibiotics which have good intracellular penetration into macrophages and achieve high intracellular concentrations should be used: macrolides, fluoroquinolones, tetracyclines, rifamycins, and ketolides.
- Macrolides, usually azithromycin, are an effective and well-tolerated first-line treatment for 5–10 days. In children, 10mg/kg/day of azithromycin is usually applied IV as a single daily dose for initial treatment, which can be followed by the same dose administered orally for 5–10 days when the clinical response is good. Rifampicin is recommended, in addition, in patients with severe acute disease or who are unresponsive to monotherapy.
- Doxycycline is not recommended in children ≤8 years old due to the possibility of permanent discoloration of the teeth.
- Fluoroquinolones are very effective in the treatment of legionnaires' disease in immunocompromised children. A 7- to 10-day course of treatment is usually sufficient. Ciprofloxacin and clarithromycin can be used in immunocompromised children.
- TMP-SMX can be used in children ≥2 months.
- A 7- to 10-day course of therapy is usually sufficient. Patients with empyema, endocarditis, lung abscesses, cavitating pneumonia, and extrapulmonary infection may require longer courses of therapy.
- Despite advances in the diagnosis and treatment of legionnaires' disease, the reported mortality rate is still high.

Prevention

- The disease is not passed from person to person, so isolation is not necessary.
- Legionnaires' disease is the result of inhalation of contaminated aerosol transmitted from the environment. Hence, environmental monitoring, especially of potable water, cooling towers, and related sources, as well as reducing bacteria in biofilms that are formed in these water systems, has become a major focus in efforts to control the spread of this disease. There are a number of disinfection methods that can be used for the control of *Legionella* in infrastructure building and hospital water systems that include thermal eradication (heat and flush), hyperchlorination, copper–silver ionization, point-of-use filters, and chlorine dioxide.
- For water births, installation of a filter system into the birthing tub hose is crucial.

Future research

- Thorough understanding of the ecology of *Legionella*, i.e. recognition of the factors that affect bacteria survival and growth in the natural environment.
- Improvement of diagnostic methods of identification of all *Legionella* spp. and serogroups.
- Further work on the importance of *Legionella* testing in children with pneumonia of unidentified aetiology.

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Chapter 84

Leishmaniasis

Name and nature of organism

- *Leishmania* is a group of intracellular protozoan parasites, belonging to the haemoflagellates.
- *Leishmania* has two subgenera: *Viannia* (endemic in the New World) and *Leishmania* (endemic throughout the Old World).
- There are multiple *Leishmania* spp., causing three major types of clinical syndromes in humans and vertebrate hosts: cutaneous leishmaniasis (CL), mucocutaneous leishmaniasis (MCL), and visceral leishmaniasis (VL).
- A single *Leishmania* sp. can produce >1 clinical syndrome, and each of the syndromes is caused by >1 species (Table 84.1).
- Sandflies *Phlebotomus* (worldwide) and *Lutzomyia* (in the Americas) are the vectors.
- Both human beings (anthroponoses) and several mammals (zoonoses) are hosts.

Table 84.1 *Leishmania* spp., origin, and clinical syndromes

Location	Cutaneous leishmaniasis (CL)	Mucocutaneous leishmaniasis (MLC)	Visceral leishmaniasis (VL)
Old World (Africa, Europe, and Asia)	*L. major, L. tropica, L. aethiopica*	–	*L. donovani, L. infantum, L. tropica* (rarely)
New World (the Americas)	*L. mexicana, L. amazonensis, L. pifanoi, L. garnhami, L. venezuelensis, L. (Viannia) braziliensis, L. panamensis, L. peruviana, L. amazonensis*	*L. braziliensis, L. panamensis, L. peruviana, L. amazonensis*	*L. chagazi, L. amazonensis* (rarely)

Epidemiology

- Leishmaniasis affects countries across the tropical, subtropical, and temperate regions in 88 countries.
- More than 350 million people are at risk.
- An estimated 12 million people suffer from leishmaniasis worldwide.
- A total of 1.5 million new cases of CL and 500 000 new cases of VL per year globally, with ~70 000 deaths/year globally (almost all from VL).
- CL is common throughout the world, including the Mediterranean, the Middle East, central and western Asia, Africa, India, and China.
- MCL is mainly found in Central and South America.
- VL is mainly found in India, Sudan, and Brazil.
- In Europe, VL has been reported from Greece, Spain and the Balearic Islands, Portugal, Turkey, and many other countries.
- In recent years, leishmaniasis outbreaks were reported in several European countries, including Spain (2009–2012) and the Netherlands (2005–2012).[1]

Transmission and incubation period

- *Leishmania* have a dimorphic life cycle. Amastigotes are the intracellular form (in macrophages). They multiply asexually in the host. Promastigotes are the extracellular form. They multiply in the vectors (i.e. sandflies).
- The life cycle begins when promastigotes are transmitted by a bite (during a blood meal) from the ♀ sandflies into the skin of a mammalian host.
- After inoculation, promastigotes lose their flagellum and are phagocytosed by macrophages in the dermis and transform into amastigotes.
- Amastigotes survive inside phagolysosomes by inhibiting lysosomal enzymes, nitric oxide, and other oxidative killing mechanisms.
- Amastigotes multiply inside phagolysosomes by binary division, eventually rupturing the cell. Released amastigotes go on to infect other mononuclear phagocytes.
- Amastigotes disseminate through regional lymphatics and the vascular system to infect mononuclear phagocytes throughout the reticuloendothelial system.
- ♀ sandflies ingest parasitized cells from human beings (anthroponoses) and several mammals (zoonoses).
- In the sandflies, parasites develop to become infectious metacyclic promastigotes.
- The cycle is completed when infective metacyclic promastigotes are injected at a subsequent blood meal into the skin of the new host (Fig. 84.1).
- Other modes of transmission include infections as a result of organ transplantation, transplacental spread, transfusion, and sharing needles.
- In CL, specific species of the parasite (e.g. *L. major*) are causing the disease by infecting skin macrophages.

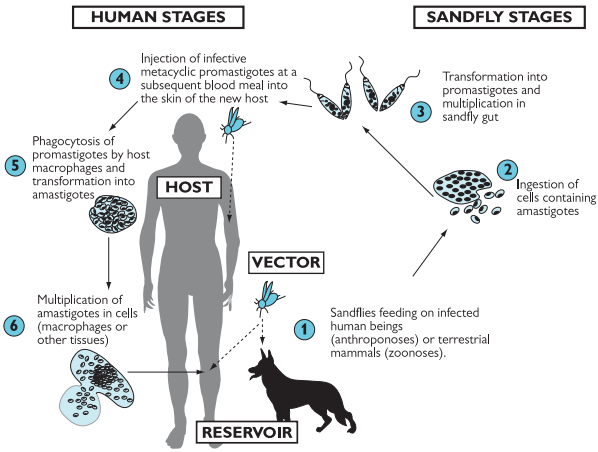

Fig. 84.1 Life cycle of *Leishmania* parasites.

(Reprinted from The Lancet Infectious Diseases, Vol. 7 No. 9, Richard Reithinger, Jean-Claude Dujardin, Hechmi Louzir, Claude Pirmez, Bruce Alexander, and Simon Brooker, Cutaneous leishmaniasis, 581-596, Copyright 2007,[2] with permission from Elsevier.)

- In MCL, other specific species (e.g. *L. braziliensis*) are causing the disease initially by infecting skin macrophages, and later parasites progress (in a course of several weeks to several months) to the mucosal tissue, especially the nasal mucosa.
- In VL, other specific species (e.g. *L. donovani*) initially do not cause skin disease usually, but, in a course of several months (can vary from 2 weeks up to several years), they progress to infect cells of the reticuloendothelial system (mainly the spleen, liver, lymph nodes, and bone marrow).

Clinical features and sequelae

Cutaneous leishmaniasis

- In CL, disease is limited to the skin.
- Skin lesions typically begin at or near a sandfly bite site, usually on exposed skin such as the face and/or extremities. The bite itself and the skin lesions/ulcers are usually painless.
- Affects individuals of any age, but frequently seen in children.
- It presents as a papule which enlarges to a nodule and ulcerates over weeks to months.
- Generally, it is not possible to differentiate CL from other skin infections, like impetigo, based on appearance.

- However, there are certain differences in the typical forms of presentation.
- In Old World CL, most lesions are papules, nodules, or nodule ulcers, while ulcerative lesions are commoner in New World CL.
- Lesions are usually unresponsive to topical or systemic antibiotics, although there are many exceptions (e.g. paromomycin ointment, azithromycin, or fluconazole systemically).
- In the absence of bacterial superinfection, the lesions usually heal after 3–6 months, leaving a depressed scar.

Mucocutaneous leishmaniasis

- Haematogenous spread from cutaneous lesions to the nasal or oropharyngeal mucosa with some types of *Leishmania*, such as *L. braziliensis*, results in this serious and life-threatening manifestation.
- Generally, patients have had active cutaneous lesions over the past 2 years.
- Nasal mucosa is involved in the majority of cases. Typical symptoms are nasal congestion, epistaxis, and discharge, and ulceration and destruction of the oronasal structures.

Visceral leishmaniasis (kala-azar)

- *L. infantum* or *L. chagasi* generally affects children <5 years of age in the Mediterranean region and the New World.
- *L. donovani* infects older children and young adults in Africa and Asia.
- Initial symptoms are non-specific, such as low-grade fever, weakness, malaise, weight loss, and progressive enlargement of the liver and spleen. Darkening of the skin, especially on the hands, feet, abdomen, and forehead, although typical for this disease (kala-azar means 'black fever' in Hindi), is actually infrequent.
- Pancytopenia is common and caused by hypersplenism, bone marrow infiltration, and autoimmune mechanisms. A Coombs' positive haemolytic anaemia is seen.
- VL is considered to be an opportunistic infection in HIV patients, who usually present with a more severe disease.
- Children may be misdiagnosed as having leukaemia or lymphoma.
- Without treatment, the prognosis is poor, with mortality rates being >90%. The main causes of death are complications of bacterial infections, haemorrhage, and progressive cachexia.

Diagnosis

Cutaneous and mucocutaneous leishmaniasis

- Presence of one or more nodular or ulcerative skin lesion, in combination with potential contact with the parasite or travel to endemic regions, makes the diagnostic of CL probable.
- Because of the toxicity of some of the drugs used to treat leishmaniasis and the prognostic importance of knowing the species causing CL or MCL, a confirmed parasitologic diagnosis is often desirable.

- Definitive diagnosis is mostly made by direct microscopic visualization of amastigotes or culture (visualization of promastigotes) in biopsies from the ulcer base of the lesion.
- PCR diagnosis allows species identification, and it is increasingly used. PCR diagnosis is important in certain settings (e.g. when a person from a CL-endemic region travels to an MCL-endemic region), in terms of the preferred treatment and prognosis.
- Serological antibody or antigen-searching tests are of less value.

Visceral leishmaniasis

- Diagnostic gold standard is by direct visualization of amastigotes in tissue (mainly bone marrow, spleen, and lymph nodes) or aspiration samples, or isolation of the organism by culture.
- Sensitivity for splenic biopsy is >95%, bone marrow 55–97%, and lymph node aspirate smears 60%.
- Measurement of antileishmanial IgG is diagnostic in high titre.
- New methods include freeze-dried antigen (no refrigeration needed), rapid detection of anti-K39 antibody with finger stick blood in an immunochromatographic strip test (sensitivity >90%), and urine testing for leishmanial antigen or antibody.
- Due to increasing numbers of immunocompromised hosts (HIV-infected patients and transplant recipients), testing of peripheral blood and bone marrow by PCR has become increasingly important.

Management and treatment

- Outcome of infection (including spontaneous healing and prevention of reactivation) is determined by the interaction of the host (innate and acquired immune responses) with the pathogen.
- Successful microbiologic treatment (eradication of the parasites) does not guarantee absence of scarring.
- Due to the potential for fatal outcome, systemic therapy with parenteral antimony or amphotericin is indicated in all cases of VL and MCL.

Localized cutaneous leishmaniasis

- It is important to distinguish between the different species. Lesions caused by the subgenus *Viannia* should be treated more aggressively because of its high risk of developing mucosal disease.
- Old World lesions self-cure within 2–4 months (*L. major*) or 6–15 months (*L. tropica*).
- New World lesions due to *L. mexicana* resolve spontaneously after 3 month in >75% of cases, but spontaneous resolution of *L. panamensis* and *L. braziliensis* infection is less common.
- Indications for systemic or topical treatment are not clearly defined.

Criteria for systemic treatment

- Lesions in cosmetically or functionally critical areas, such as the face, hands and feet, and/or near joints.
- Lesions with low tendency of self-healing for >6 months.

- More than five lesions or large lesions over 4cm.
- Suspicion of disseminated disease or mucocutaneous disease.

Local treatment

- Several local treatments are available; most of them are not very well established or have proven efficacy against specific species.[3] These include:
- Topical treatments with creams and ointments, like paromomycin ointments (highly efficacious against *L. major*, but not for other species), topical imidazole cream regimens, topical nitric oxide, and topical amphotericin B
- Thermotherapy
- Cryotheraphy with liquid nitrogen
- CO_2 laser
- Photodynamic treatment
- Intralesional antimony injection.

Systemic treatment for cutaneous leishmaniasis

- Several oral treatments are available; as is the case with local/topical treatment, most of them are not very well established. These include: fluconazole, ketoconazole, itraconazole, miltefosine, allopurinol, and azithromycin.
- Efficacious parenteral treatments are available. However, in this self-healing disease, treatment toxicity must be considered. These include:
  - Parenteral antimony remains the gold standard for CL
  - Pentamidine has high efficacy (60–95%; *L. braziliensis* <50%) in a short-course, low-dose regimen, particularly in South and Central America
  - Liposomal amphotericin (rarely used for CL)
  - Combination of cryotherapy and intralesional antimony has proved to be more effective than either therapy alone.

Systemic treatment for mucocutaneous leishmaniasis and visceral leishmaniasis

- A country's wealth affects the treatment choice (balance between drug efficacy, toxicity, and costs associated with patient care).
- Main treatment options are pentavalent antimony salts and amphotericin deoxycholate or lipid formulations of amphotericin.
- Dose and schedule of administration vary, according to the geographical region and patient profile.
- Currently, various combination therapies are being used, and the evidence base is too limited to be able to compare therapies.
- Cure rates are very high, >95% with nearly all standard therapies.
- Aim is to increase treatment efficacy, and minimize costs and risk of parasite resistance development. In Europe, probably the most commonly used regimen is Liposomal amphotericin on days 1, 2, 3, 4, 5, and 10.
- A randomized trial in 410 patients in India showed that one single infusion of Liposomal amphotericin was not inferior.[4]

Prevention

Protection against sandfly bites

- Use of insect repellents, appropriate clothes (cover arms and legs).
- In regions where sandflies are endophagic (mainly feeding indoors), bed nets reduce significantly the risk of infection.

Control of zoonotic infection

- In areas, such as Latin America, the Mediterranean basin, central and south-west Asia, the control of dogs, the 1° animal reservoir, is of great importance.
- In sites where leishmaniasis is a zoonosis involving sylvatic mammals, reservoir control is rarely possible.
- Rapid identification, sensitive and specific diagnostic tests, and effective culling are essential for an effective reservoir control.
- Deltamethrin-treated collars are one of the most effective strategies, reducing the number of infected dogs.

Insecticide spraying of houses

- House spraying with pyrethroid is the most widely used strategy for controlling endophilic (resting mostly indoors after feeding) sandflies.

Vaccines

- Vaccines based on killed parasites have been shown to be safe and immunogenetic; however, long-lasting protection could not be achieved.

Future research

- Standardized protocols of experimental, clinical, and epidemiological studies.
- Further understanding into the pathology and immunology of this disease.
- Expanding and improving treatment options, including the development of highly efficacious, non-toxic topical drugs for CL.
- To achieve long-lasting immunity, research is focused on the identification of novel antigens, live-attenuated vaccines, recombinant purified proteins, bacteria expressing *Leishmania* antigens, and targeting dendritic cells (specialized antigen-presenting cells, which play an important role in the clearance of *Leishmania*-infected cells).

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Chapter 85

Listeriosis

See also Chapters 10, 12, 14, 20, 21, 29, 30.

Name and nature of organism

- Listeriosis is a severe, but relatively rare, infection in the general population, and it affects primarily pregnant women, unborn and newly delivered infants, the immunocompromised, and the elderly.
- The genus *Listeria* are non-sporing, aerobic, motile, Gram-positive bacilli, ubiquitous in the environment.
- The genus contains seven species, but almost all cases of human listeriosis are due to *L. monocytogenes*.
- Almost all outbreaks of listeriosis have been caused predominantly by serovar 4b strains.
- In clinical specimens, the organisms may be Gram-variable and look like diphtheroids, cocci, or diplococci, and therefore can be mistaken for a contaminant. Beware the 'diphtheroid contaminant' in the CSF—could it be *Listeria*?—ask the microbiologist again!
- The bacilli exhibit characteristic 'tumbling' motility at 25°C.
- Its ability to survive and multiply under conditions used for food preservation makes *Listeria* problematic to the food industry.

Epidemiology

- *L. monocytogenes* is an important zoonosis in herd animals.
- It has also been recovered from a variety of raw foods, such as uncooked meats and vegetables, or food items that become contaminated during their processing such as soft cheeses. *L. monocytogenes* is killed by pasteurization and cooking. In ready-to-eat foods, contamination may occur after cooking, before packaging.
- The peak incidence of human disease occurs in summer.
- In 2006, listeriosis was the fifth commonest zoonotic infection in Europe, after *Campylobacter, Salmonella, Yersinia*, and VTEC.
- The infection rate in Europe varied between one and ten cases per million of the population, and ~20% were neonates.
- There has been a recent increase in pregnancy-related cases in the UK, linked to ethnic minority women.
- Listeriosis is very rare in children >3 months of age (100 cases per million), and pregnant women are 20 times more likely to develop the infection than the general population.

Transmission and incubation period

- Alimentary transmission is the commonest route of acquisition.
- Microbiological and epidemiological evidence supports an association with many food types (dairy, meat, vegetable, fish and shellfish, sandwiches) in both sporadic and epidemic listeriosis.
- Maternal infection is associated with abortion, preterm delivery, and fetal death.
- Late-onset neonatal infection can result from acquisition of the organism during birth or from environmental food sources.
- The incubation period is from 1 to 90 days, with an average for intrauterine infections of around 30 days.

Clinical features and sequelae

Infection in pregnancy

- Most maternal infections occur during the third trimester of pregnancy when T-cell immunity is most impaired.
- ~65% of infected women typically develop a non-specific 'flu-like' syndrome (fever, headache, myalgia), GI symptoms, or back pain but may remain asymptomatic.
- Twenty-two per cent of perinatal listeriosis results in stillbirth or neonatal death.

Neonatal infection

- Neonatal listeriosis is classified as early or late infection, depending on timing of the onset of symptoms. Infants are believed to be infected *in utero* because of the maternal bacteraemic phase.
- The mean onset of symptoms is 1.5 days after birth.
- Disease can be early-onset, with a sepsis-like picture in the first day or two of life, or late-onset, more commonly presenting with meningitis at around 1–2 weeks of age.
- A sepsis-like picture predominates, but other common manifestations are acute respiratory distress, pneumonia, meconium staining, fever, rash, jaundice, and more rarely meningitis or myocarditis.
- In both early- and late-onset neonatal listeriosis, the mortality rate ranges from 10% to 30%.
- Listeriosis in children older than 1 month is very rare, except in those with underlying disease.

Diagnosis

- The organisms can be recovered on blood agar media from cultures of blood, CSF, meconium, amniotic fluid, placenta, gastric washings, placental tissue, and other infected tissue specimens, including joint, pleural, or pericardial fluid.

- When the CNS is infected, polymorphonuclear leucocytes predominate in 70% of cases. Protein levels are usually elevated, and higher values are correlated with poor prognosis. In 60% of the cases, glucose levels in CSF are normal.
- The Gram stain of CSF is positive in <40% of patients; however, blood cultures are positive in 60–70%.

Management

- No controlled trials have established a drug of choice or duration of therapy for listeriosis.
- *L. monocytogenes* is susceptible to a wide range of antibiotics *in vitro*, including benzylpenicillin, ampicillin, erythromycin, vancomycin, sulfamethoxazole, trimethoprim, chloramphenicol, rifampicin, tetracyclines, and aminoglycosides.
- *Listeria* are always resistant to cephalosporins. This is a problem, because ceftriaxone and cefotaxime are the standard first-line drugs for meningitis in many countries. Neonatal sepsis empirical antibiotic regimens without penicillin/ampicillin or gentamicin do not treat listeriosis.
- IV ampicillin and amoxicillin, which are superior to penicillin, are the mainstay of treatment, although high drug concentrations are required for bactericidal effects.
- Gentamicin has had synergistic effects in some studies and should be added initially to the treatment.
- Gentamicin with ampicillin (amoxicillin) is recommended for *Listeria* meningitis to decrease the number of bacteria, because most bacteria are extracellular. Almost no resistance has developed to this treatment.
- No systematic study examined the duration of therapy, but the current recommendations are 10–14 days of treatment for invasive infection without meningitis, and 14–21 days for *L. monocytogenes* meningitis.
- Longer courses are needed for patients who are severely ill or who have endocarditis or thromboencephalitis.
- The prognosis for live-born children with sepsis is relatively good if they are promptly treated, but long-term neurological deficits are common after meningitis.

Prevention

- Although food-borne outbreaks of listeriosis are uncommon, they remain a major public health problem. Therefore, detecting an outbreak early and identifying its source are a priority.
- There is no vaccine to prevent *Listeria* infection.
- Recommendations for prevention of listeriosis from a food-borne source include washing of raw vegetables; avoidance of unpasteurized dairy products; thorough cooking of raw food; and washing of hands, knives, and cutting boards after exposure to uncooked foods.

- Pregnant women and immunocompromised patients should be advised to avoid unpasteurized soft cheeses, deli meat, shop-bought sandwiches, hot dogs, refrigerated pâtés, and smoked seafood, because they can harbour high levels of contamination.
- Cases of listeriosis should be reported to the local health authorities to facilitate early recognition of outbreaks.

Future research

- *L. monocytogenes* has been used as a model pathogen for >40 years; however, recent studies suggest there are still unidentified immunological aspects of *L. monocytogenes* infection and immunity.
- The epidemiological risk factors for pregnancy acquisition are still not fully understood.
- How *Listeria* precisely interacts with the intestinal barrier is an important issue for understanding later stages of infection.
- How *Listeria* precisely crosses the placenta and the blood–brain barrier is a question that requires an answer.
- At present, there is no satisfactory therapy for the treatment of *Listeria* infection. Thus, new drugs with a better activity against these bacteria need to be discovered.

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Chapter 86

Lyme disease

Name and nature of organism

- The spirochaete *B. burgdorferi* causes Lyme disease.
- *B. recurrentis* causes louse-borne relapsing fever, and *Borrelia turicatae, Borrelia hermsii, Borrelia parkeri*, and *Borrelia duttoni* cause tick-borne relapsing fever.

Epidemiology

- Lyme disease was first recognized in 1975 in Lyme, Connecticut, US.
- Lyme is the commonest vector-borne human infection in the UK. The infection is endemic in parts of the US, with around 15 000 cases reported/year. The infection is spread across all age groups. There were 998 laboratory-confirmed cases in the UK in 2012, of which 20% were contracted abroad. The incidence is commonest in summer and early autumn.
- The number of cases may be higher because of the significant false seronegative rate in patients tested early in the clinical course.

Transmission and incubation period

- From tick vectors (*Ixodes* spp. in northern Europe: *Ixodes ricinus* deer or sheep ticks), with a nymph and larval stage. The tick bite needs usually to be longer than 24 hours for human infection to occur.
- Usual reservoirs are small mammals in the UK.
- Feeding for several hours on the human being is a prerequisite for transmission.
- Person-to-person transmission does not occur.
- Incubation period is 3–20 days, with a median of 12 days.

Clinical features and complications

- Clinical disease can be divided into three stages, based on the timing after infection. The commonest first feature is the typical rash of erythema migrans, or erythema chronicum migrans, a raised circular lesion (average diameter of around 15cm) which spreads out from the site of the tick bite. This usually occurs around 3–30 days after the tick bite and lasts around 3 weeks.
- Non-specific flu-like symptoms, with fever, arthralgia, myalgia, headaches, and neck stiffness, may occur at the same time.

- Neurological disease then usually develops between 2 and 10 weeks after the tick bite. Aseptic meningitis, chorea, cerebellar ataxia, and cranial nerve palsies have been reported. Lyme meningitis has been associated with a long duration of headache, cranial neuritis, and CSF mononuclear cells.
- Facial palsy is usually unilateral; this occurs usually several weeks or months after infection.
- Arthritis also usually begins around 4 weeks after the tick bite and is most often of a single large joint (knee, shoulder, elbow). This is transient but may persist or recur for years. It is uncommon in the UK.
- Carditis can also very rarely occur (more in young men).
- The much later neuropsychiatric manifestations (after months or years) and chronic fatigue are extremely rare in children.

Diagnosis

- The skin lesion is pathognomonic. With a history of a tick bite, a clinical diagnosis can be made.
- Serological tests may not be positive in the early weeks of infection. These tests are not straightforward and require the expertise of specialist laboratories. In the UK, the PHE Rare and Imported Pathogens Laboratory (RIPL) uses a two-stage procedure. The first stage is an EIA screen—positive or indeterminate samples are then tested with an immunoblot or a Western blot test to confirm the presence of *B. burgdorferi* (Bb) antibodies. There are formal criteria to diagnose a positive Western blot, requiring multiple positive bands. Late-stage disease should virtually always have a strongly positive IgG. In the UK, positive serology is confirmed by RIPL at PHE, Porton Down.
- PCR testing of joint aspirates and skin samples is also useful.

Treatment

- For early, localized Lyme disease and disseminated disease, including isolated VIIth nerve palsy and arthritis, in a child of ≥12 years, use doxycycline or amoxicillin orally for 14–21 days.
- In the younger child, amoxicillin in three divided doses is preferred.
- Azithromycin can be used where there is a definite history of penicillin allergy.
- Use IV ceftriaxone for meningitis and all other neurological disease for between 2 and 4 weeks.
- The great majority of children make a full recovery with no long-term complications.

Prevention

- Wearing long trousers and shirts when walking in the woods, using insect repellents, checking children for ticks each day, and removing any ticks with tweezers.
- Use of routine prophylactic antibiotics after tick bites is not indicated.

Future research

- Vaccine development is under way for Lyme disease.
- Improved evidence base for different treatment strategies and long-term outcome.

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Chapter 87

Malaria

Name and nature of organism

- Vector-borne infection caused by protozoan parasites of the genus *Plasmodium*.
- Five species known to infect humans.
- *P. falciparum* causes the most severe disease and is responsible for most of the long-term complications and deaths related to malaria.
- *Plasmodium vivax, Plasmodium ovale*, and *Plasmodium malariae* usually cause milder disease and are not fatal, except in individuals with underlying co-morbidities.
- *P. knowlesi* usually causes malaria in primates and only infects humans opportunistically, but recent studies have suggested that *P. knowlesi* may contribute to a significant proportion of malaria cases in parts of South East Asia where such infections may be misdiagnosed as *P. malariae*.
- Unlike *P. malariae*, however, *P. knowlesi* has a higher rate of replication (every 24 hours), resulting in high level of parasitaemia, and may be associated with severe infection and death.

Epidemiology

- Malaria is one of the commonest infectious diseases globally.
- In 2014, 97 countries and territories had ongoing malaria transmission.
- An estimated 3.3 billion people are at risk of malaria, of whom 1.2 billion are at high risk. In high-risk areas, more than one malaria case occurs per 1000 population.
- In 2013, there were an estimated 198 million cases of malaria worldwide (range, 124–283 million) and 584 000 deaths (range, 367 000–755 000).
- Around 90% of all malaria deaths occur in Africa and, in 2013, 437 000 African children died before their fifth birthday due to malaria. Globally, the disease caused an estimated 453 000 under-5 deaths in 2013.
- In Europe, the confirmed case rate of malaria reported by EU/EEA countries remains stable, fluctuating around one per 100 000 population; 99% of cases are imported, with the exception of Greece where 41% of cases are locally acquired.
- In 2011, 5482 confirmed cases of malaria were reported by 25 EU member states and one EEA country in continental Europe; 83% of cases were reported by four countries: France, the UK, Germany, and Spain.
- The UK has one of the highest burdens of imported malaria, with 1300 and 1800 cases diagnosed annually over the past decade. In 2013, there were 1501 cases of imported malaria, mainly due to *P. falciparum* (1192

cases, 79%), and seven deaths. Most cases were acquired in Western Africa (n = 906, 60%), followed by Central Africa (n = 117, 8%) and Eastern Africa (n = 150, 10%); only 140 cases (9%) were acquired in Southern Asia.

- Children consistently account for 15–20% of all reported cases.
- Children have different risk factors for developing malaria compared with adults and have a higher risk of severe disease, as they are more likely to be non-immune to the infection.
- A recent BPSU study estimated the burden of imported malaria in the UK to be 2.8/100 000 children; *P. falciparum* accounted for 85% of childhood cases; 90% of all malaria cases occurred among black African children, who mainly acquired the infection in Africa (particularly Nigeria, 55%).
- Two-thirds of children who developed malaria lived in the UK and had travelled to a malaria-endemic country, mainly during school holidays (July to October and January to February) visiting friends and relatives (VFR), and only 8% had taken appropriate antimalarial prophylaxis.
- Families on VFR are less likely to seek pre-travel advice or take antimalarial prophylaxis or bite prevention measures, and are more likely to travel to rural malaria-endemic areas for longer periods; they are also more likely to delay seeking medical help when returning to their country of residence, often because of cultural and language barriers.
- Imported childhood malaria is generally associated with a low case fatality of ~1% in Europe; in the UK, two of 1456 children (0.14%) died between 1999 and 2003—both had been seen by a healthcare professional at least once, and malaria had not been suspected.

Transmission

- Malaria is transmitted by the ♀ *Anopheles* mosquito.
- Chronically infected humans are the major reservoir of malaria.
- The *Anopheles* mosquito acquires the parasite during a blood meal from an infected person and transfers it to another person during the next blood meal.
- Rare cases have been reported following blood transfusion or a needle-stick injury from infected donors.
- Airport malaria occurs in or around international airports when a parasitized mosquito that survived a long-distance air flight from an endemic country infects a person.

Incubation period

- The duration between infection and the development of symptoms varies with the species responsible.
- *P. falciparum* infections usually present (85% of cases) within a month, with <1% of cases presenting after 6 months.

- In contrast, only 25% of non-falciparum malaria cases present within 1 month, while 60% present within 6 months, and 90% within a year.
- In addition, the life cycles of *P. vivax* and *P. ovale* have a hypnozoite form, during which the parasite can persist in the liver for months before emerging and inducing recurrence after the initial infection.

Clinical features

- Symptoms are varied and often mimic other common childhood illnesses.
- Fever is invariably present, but the characteristic regular tertian and quartan patterns are seen in <25% of children; however, children are more likely to have high fever >40°C, which may lead to febrile convulsions.
- Nausea and vomiting are also common and should be taken into consideration if intending to treat the infection with oral antimalarials.
- Compared with adults, children are less likely to complain of chills, arthralgia/myalgia, or headache but are more likely to have hepatomegaly, splenomegaly, and jaundice.
- *P. malariae* infections are also associated with the development of nephrotic syndrome.
- **Severe malaria** occurs almost exclusively with *P. falciparum* infections.
- Five to 15% of children with imported malaria present with features of severe malaria, as defined by WHO; these criteria, however, were developed for endemic countries and may not necessarily be appropriate for imported malaria.
- In imported cases, severe malaria is associated with young age (<5years), delayed diagnosis, and non-immunity to malaria.
- Immunocompromised children, asplenics, and those with homozygous sickle-cell disease are more likely to develop severe malaria. The vast majority of children with imported malaria, however, are healthy.
- Features of severe or complicated malaria include impaired consciousness, coma, seizures, respiratory distress, acidosis (pH <7.3), hypoglycaemia (<2.2mmol/L), severe anaemia (<8g/dL), prostration (the inability to stand or sit), and parasitaemia >2% of red blood cells.
- Children with severe malaria may also develop focal neurological signs, decerebrate or decorticate posturing, spontaneous bleeding, DIC, hypotension, cardiovascular shock, pulmonary oedema, haemoglobinuria, acute renal failure, and multi-organ failure.
- Concurrent bacterial septicaemia is rare (<5%) but should be considered in children presenting with severe symptoms.
- Children who have taken any antimalarial prophylaxis and those who have been partially treated for malaria may present with minimal symptoms or signs.
- Tropical splenomegaly syndrome, also known as hyperreactive malarial syndrome (HMS) is a rare complication that occurs after repeat exposure to malaria. It is characterized by gross splenomegaly, high antibody levels against *Plasmodium* spp., hypergammaglobulinaemia (mainly IgM), clinical and immunological response to antimalarial therapy, and regression of splenomegaly over several months after antimalarial therapy.

Diagnosis

- Malaria remains a relatively rare cause of fever in non-endemic areas and requires a high index of suspicion; obtaining a history of foreign travel or of immigration from a malaria-endemic area is vital.
- Delays in diagnosis are associated with an increased risk of severe malaria, requirement for intensive care, and death.
- The presence of thrombocytopenia in children with fever following travel to a malaria-endemic area is highly predictive of malaria.
- Diagnosis is usually confirmed by microscopic examination of thick and thin blood films (preferably at the height of fever), which should be requested in any unwell child who has travelled to a malaria-endemic area in the preceding 12 months, irrespective of any chemoprophylaxis taken.
- Thick blood smears are more sensitive in detecting malaria parasites, because the blood is more concentrated, allowing for a greater volume of blood to be examined.
- Diagnosis may be missed because of a lack of experienced laboratory support or because the initial blood film may be negative (up to 7% of cases); therefore, three negative blood films should be obtained before malaria can be safely excluded.
- In falciparum malaria, the proportion of parasitized red blood cells, the presence of *P. falciparum* schizonts, and pigment deposits in peripheral polymorphonuclear leucocytes may indicate the severity of infection.
- Rapid antigen detection tests by means of a 'dipstick' format can distinguish between the four common species, and its use in routine diagnosis has increased.
- PCR and serological tests may also be used to confirm the diagnosis but are usually preformed in reference laboratories and reserved for retrospective diagnosis and epidemiological research.
- *P. knowlesi* infection should be considered in patients with malaria who have a history of travel to forested areas in South East Asia (Borneo, Malaysia, the Philippines, Thailand, and Singapore), especially if *P. malariae* malaria is diagnosed or atypical plasmodia are seen on microscopy—specialist opinion should be sought if *P. knowlesi* malaria is suspected.

Management and treatment

- Management varies according to the *Plasmodium* spp. responsible, national guidelines, antimalarial availability, and individual patient factors.
- Treatment does not usually differ between non-immune travellers and immigrants.
- All children suspected of, or diagnosed with, *P. falciparum* malaria should be admitted to hospital for at least 24 hours, because of the possibility of rapid progression in severity of malaria and poor tolerance of oral therapies.
- A thick and thin blood smear, FBC, electrolytes, blood glucose, and renal and liver function tests should be performed on all patients, as well as testing for glucose-6-phosphate dehydrogenase (G6PD) deficiency.

- Haematological and biochemical parameters are often abnormal.
- Anaemia occurs in 31–100% of cases, although the need for transfusion is rare (<2%).
- Thrombocytopenia (platelet counts $<150 \times 10^9$/L) is characteristic of malaria and occurs in 50–70% but, unlike adults, is not associated with bleeding, even at very low counts.
- Leucocytosis and leucopenia (19–30%) may occur but are usually not associated with the severity of imported malaria or concurrent bacterial infections in imported cases.
- Jaundice (30–50%) and raised liver enzymes (25–40%) are also relatively common but not usually associated with an adverse outcome in imported malaria.
- Children with uncomplicated malaria, low parasitaemia, and no vomiting may be treated with oral antimalarials.
- The combination of oral quinine (10mg/kg of quinine salt 8-hourly for 7 days) with a single dose of sulfadoxine–pyrimethamine (Fansidar®) (up to 4 years (>5kg), 1/2 tablet; 5–6 years, one tablet; 7–9 years, 1.5 tablets; 10–13 years, two tablets; 14–18 years, three tablets) remains highly effective in the UK, with very low relapse rates.
- If Fansidar® is contraindicated (e.g. in children with G6PD deficiency) or is not available, alternatives include: (i) clindamycin (7–13mg/kg/dose 8-hourly for 7 days), although liquid preparations are not readily available, thus limiting its use to children who can swallow capsules; (ii) doxycycline (200mg once daily for 7 days) may also be given, but only in children >12 years because of risk of dental hypoplasia and permanent teeth discoloration.
- Alternative oral antimalarial combinations are increasingly being used in non-endemic paediatric settings:[1] (i) arthemeter–lumefantrine, (artemether 20mg/lumefantrine 120mg; five doses to be taken at diagnosis, and 8, 24, 36, 48, and 60 hours: 5–<15kg, one tablet; 15–<25kg, two tablets, 25–<35kg, three tablets and 35kg and over, four tablets) and is currently licensed for patients of 5kg bodyweight and above; (ii) atovaquone–proguanil (>40kg, four 'standard' tablets daily for 3 days; 31–40kg, three 'standard' tablets daily for 3 days; 21–30kg, two 'standard' tablets daily for 3 days; 11–20kg one 'standard' tablet daily for 3 days; 9–10kg, three 'paediatric' tablets daily for 3 days; 5–8kg, two 'paediatric' tablets daily for 3 days) is expensive but is increasingly gaining popularity for both prophylaxis and treatment of malaria, but vomiting is a common side effect.
- Mefloquine is also effective but is not recommended in the UK because of its side effects and high rate of non-completion of treatment courses.
- Halofantrine has also been used in other countries to treat acute, uncomplicated malaria but is associated with potentially fatal cardiac arrhythmias, particularly in individuals receiving drugs that may prolong the QT interval.
- Children infected with unknown or mixed *Plasmodium* species should be treated for falciparum malaria and also receive primaquine (see treatment for non-falciparum malaria below).

Severe malaria

- Guidelines for the management of severe imported childhood malaria in the UK have been proposed recently (see Further reading, p. 670).
- Children with severe or complicated malaria should be managed in a paediatric ICU or HDU, together with support/advice from a paediatric ID/tropical medicine specialist who has experience in managing malaria.
- Judicious and slow administration of volume resuscitation is important in those children presenting with shock, following the results of the FEAST trial that showed a detrimental effect of fluid bolus administration (see Further reading, p. 670).
- Children with features of severe or complicated malaria should also have a blood gas, blood culture, lactate, clotting profile, as well as a urine dipstick and culture, on admission.
- Children with respiratory distress should have a CXR.
- Febrile patients with impaired consciousness or repeated seizures should have an LP to exclude meningitis, once the patient's condition is stable.
- Aggressive management is recommended for those with: depressed conscious level, active seizure activity, irregular breathing, hypoxia, shock, dehydration, hypoglycaemia, metabolic acidosis, and hyperkalaemia.
- Children with anaemia associated with severe malaria may require blood transfusion, although the haemoglobin level at which transfusion should be given remains uncertain.
- Exchange transfusion for hyperparasitaemia >20% (or >10% in the presence of severe symptoms) has been used in adults, but there is little evidence that it improves overall outcome.
- Concurrent bacterial infections (meningitis or septicaemia) are rare in children with imported malaria, even in severe cases, but most clinicians would advocate empiric broad-spectrum antibiotics, such as a third-generation cephalosporin, until they can be safely excluded through appropriate blood, urine, and CSF cultures.
- Platelet transfusions for thrombocytopenia, even at platelet levels $<20 \times 10^9$/L, are generally not recommended, because thrombocytopenia is not associated with bleeding problems in children.
- Serious complications, such as renal or liver impairment or raised ICP, may warrant early transfer to an ICU for careful assessment, close monitoring, and specialist management.
- Clear evidence from a large randomized trial (artesunate versus quinine in the treatment of severe falciparum malaria in African children or AQUAMAT) now shows that, although quinine remains effective, artesunate is associated with a survival advantage (relative risk reduction of 22.5%) and a significant reduction in clinical complications (development of coma, convulsions, and deterioration of coma score). This and other clinical trials have led to a change in the WHO guidelines, such that IV artesunate should be used preferentially over quinine as the drug of choice for treatment of severe falciparum malaria in children.
- IV (or alternatively IM) artesunate at a dose of 2.4mg/kg should be given at diagnosis, 12 hours later, and then 24 hours after the first dose.

If the child cannot tolerate oral medication, then a once-daily dose should be continued for a maximum of 7 days, until oral medication can be given.

- If artesunate is not immediately available, then IV quinine is still indicated—treatment should not be delayed while waiting for artesunate to become available.
- Current guidelines recommend a loading dose of 20mg/kg of quinine dihydrochloride in 5% glucose (INN) or glucose (INN) saline as a slow infusion over 4 hours, followed by 10mg/kg ((maximum 600mg) every 8 hours for the first 48 hours or until the patient can swallow.
- The frequency of dosing should subsequently be reduced to 12-hourly if IV quinine continues for >48 hours.
- Close monitoring is required for hypoglycaemia, hypoxia, and seizures.
- IV treatment should be changed to oral medication, once the patient's condition improves and parasite levels fall.

Non-falciparum malaria

- Uncomplicated non-falciparum malaria does not usually require hospital admission.
- Antimalarial therapy should target both the asexual erythrocytic forms that cause symptoms and, for *P. ovale* and *P. vivax* infections, the liver hypnozoites to prevent relapse.
- Chloroquine (initial dose 10mg/kg/base (max 600mg), then 5mg/kg/base (max 300mg) 6–8 hours later and on days 2 and 3) remains the treatment of choice for eliminating the erythrocytic forms of non-falciparum malaria.
- In cases of treatment failure (persistent symptoms and/or parasitaemia) or mixed infection with *P. falciparum*, any of the antimalarial combinations recommended for treating *P. falciparum* malaria would be effective in treating the erythrocytic forms of non-falciparum malaria.
- In children without G6PD deficiency, primaquine is recommended for eliminating liver hypnozoites and preventing relapse in *P. ovale* or *P. vivax* malaria, which may occur in up to 25% of cases treated with chloroquine alone.
- In *P. ovale* malaria, a single daily dose of 0.25mg/kg (maximum dose 15mg) should be given for 14 days.
- For *P. vivax* malaria, however, because of increasing resistance to primaquine, particularly in South East Asia where most UK cases are acquired, a higher single daily dose of 0.5mg/kg (maximum dose 30mg) for 14 days is recommended.
- *P. knowlesi* infections respond adequately to chloroquine and primaquine.
- Children with G6PD deficiency who develop malaria should be referred to specialists in paediatric ID for further management; treatment options include giving primaquine 0.5–0.75mg/kg (max 30mg) as a single weekly dose for 8 weeks in children with mild G6PD deficiency or withholding primaquine and treating any relapse promptly.

Prevention

- Families wishing to travel to a malaria-endemic country should be encouraged to visit their GP or practice nurse, or visit a travel clinic for specific advice, travel vaccinations, and antimalarial prophylaxis for the country they are visiting.
- Unfortunately, those at highest risk of developing malaria—the VFR group—are the least likely to seek pre-travel advice or take antimalarial prophylaxis.
- The recent BPSU study also identified that up to a quarter of children who had travelled to a malaria-endemic country had previously been diagnosed with malaria, reflecting missed opportunities to educate families on malaria prevention when they are admitted to hospital.
- Health-care professionals providing travel advice should emphasize the ABCD of malaria prevention, which includes Awareness of risk, Bite prevention, Chemoprophylaxis, and prompt Diagnosis and treatment.
- Bite prevention measures include regular use of appropriate insect repellents when outdoors, avoiding areas of stagnant water which may be breeding grounds for mosquitoes, wearing long-sleeved, loose clothing when going outdoors at dawn or dusk, closing doors and windows in sleeping accommodations, and using insecticide-containing sprays or mosquito coils, as well as using bed nets (preferably treated with insecticide) and air conditioning where possible. The following websites provide useful information for the prevention and treatment of malaria among travellers and provide up-to-date guidance on the risk of malaria in different parts of the world, the most appropriate antimalarial prophylaxis and indications, contraindications, doses by age/weight, and duration for the different antimalarials:
  - ECDC (🔗 <http://www.ecdc.europa.eu/en/healthtopics/malaria/pages/index.aspx>)
  - PHE (🔗 <https://www.gov.uk/search?q=malaria>)
  - UK National Travel Health Network and Centre (NaTHNaC) (🔗 <http://www.nathnac.org>).

What's new?

- IV artesunate is now the treatment of choice for severe imported malaria; quinine, however, is a suitable alternative, and treatment should not be delayed if artesunate is not readily available.
- A recent literature review identified the following as the main risk factors for malaria deaths in travellers: non-use or inappropriate use of chemoprophylaxis, age, delay in seeking care, incorrect treatment, delay in diagnosis, infection with *P. falciparum*, non-immunity, travelling as a tourist, and sex. The case fatality rate, however, is low (0.2–3%)
- The recent FEAST trial found that fluid boluses significantly increased the 48-hour mortality in critically ill children with malaria and impaired perfusion in resource-limited African settings, and has raised questions about the optimal fluid management for such children.

What's next?

- The epidemiology of imported childhood malaria in Europe is now clearly defined; most cases are acquired in children of black African families who are settled in Europe and travel to their country of origin during school holidays, without receiving appropriate travel advice or taking antimalarial prophylaxis.
- Future studies should focus on interventions aimed at encouraging antimalarial prophylaxis uptake in this high-risk group.
- With increasing availability of newer antimalarial combinations, there is also a need to standardize recommendations for the prevention and treatment of imported childhood malaria in Europe.
- While recent progress has been made in reducing malaria mortality with other interventions, prevention through vaccination remains the 1° goal; the most clinically advanced candidate RTS,S is presently undergoing phase 3 evaluation in young African children. In the 12-month period following vaccination, RTS,S conferred ~50% protection from falciparum malaria in children aged 5–17 months, and ~30% protection in children aged 6–12 weeks. Several second-generation malaria vaccines with novel candidate antigens are currently undergoing early clinical trials.

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Chapter 88

Measles

See also Chapters 11, 21, 27, 34, 44.

Name and nature of organism

- Measles (also known as rubeola) virus causes an acute illness, characterized by rash, fever, and respiratory symptoms.
- Caused by *Paramyxoviridaevirus* of the genus *Morbillivirus*.
- An enveloped single-stranded RNA virus. The genome encodes eight proteins, including haemagglutinin (H) and fusion (F) proteins.
- The complete measles genome has been sequenced, allowing the differentiation of various wild (24 so far, though not all in circulation this century) and vaccine genotypes.

Epidemiology

- Only found in humans.
- Highly infectious. In the pre-vaccination era, >90% of individuals had a symptomatic infection by the age of 10 years.
- In temperate areas, it is commonest in late winter and early spring, whereas, in the tropics, it is commonest in the dry season.
- Where infection is common, epidemics occur every 2 years.
- WHO estimates that worldwide deaths fell from 562 000 in 2000 to 122 000 in 2012.
- In the EU and EEA/European Parliamentary Technology Assessment (EPTA) in 2006, there were 2723 reported cases and six deaths. This rose to 10 271 cases and three deaths in 2013, with eight cases of measles encephalitis. Five countries (the Netherlands, Italy, the UK, Germany, and Romania) accounted for 91% of cases. The majority of affected children were unimmunized, with only 20% of the 1–4 year olds immunized. The highest notification rate was in those under 1 year old.
- In England and Wales, confirmed cases increased from a low of 56 in 1998 to over 2000 cases in 2013, with one death in each of 2006, 2008, and 2013.
- In the first 5 months of 2014, there were 334 cases, more than in any complete year since measles was eliminated from the US in 2000.
- Immunity after natural infection is usually lifelong, due to both neutralizing antibody to the H protein and cell-mediated immunity.

Transmission and incubation period

- Highly infectious, up to 90% of susceptible contacts are infected.
- Spread from person to person via respiratory droplets, which may persist in the air for several hours.
- Can survive on surfaces for up to 2 hours, but its lipid envelope is destroyed by ethanol-based handscrubs.
- Incubation period is from 6 to 19 days (median 13 days). There is a short 1° viraemia from the pharynx to local nodes, with a main 2° viraemia around a week after infection, leading to URTI symptoms, then a rash.
- Virus is shed from 2 days before to 3 days after symptoms appear.
- The period of infectiousness is not known but is thought to be 1–2 days prior to the appearance of the rash to 4–5 days after.

Clinical features and sequelae

- Prodrome of high fever, cough, coryza, and conjunctivitis.
- Maculopapular rash appears next around 2–4 days later, first behind the ears, then spreads down the body; generally the more rash, the more unwell the child is—the rash can look almost haemorrhagic.
- Koplik spots (small 1mm bluish white spots on the buccal mucosa) are present about 1–3 days before the onset of the rash and are characteristic of measles, though not found in all cases.
- Three days after the rash appears, children improve and are usually fully recovered 7–10 days after the onset of illness.
- Complications occur in 6–7% of otherwise healthy individuals in developed countries.
- Complications include otitis media, measles pneumonitis, or 2° bacterial pneumonia—difficult to distinguish clinically (38/1000), convulsions (5/1000), encephalitis (1.2/1000), idiopathic thrombocytopenic purpura (1 in 2000–3000), and diarrhoea.
- Acute encephalitis occurs around 2–5 days after the onset of rash; CSF shows lymphocytosis with elevated protein—may be PCR-positive. Most children recover. A severe fulminant encephalitis has been reported.
- SSPE occurs in 4/100 000 overall, but 18/100 000 in children infected with measles under a year old. SSPE presents with gradual neurological deterioration around 5–10 years after measles; proceeds to myoclonic epilepsy, coma, and death. Diagnosis is based on classic EEG pattern of bilateral, high-amplitude, periodic complexes and monoclonal measles antibody titres in the CSF.
- In those malnourished, especially if vitamin A-deficient, or immunocompromised, there is a higher morbidity and mortality. There may be no rash in the immunocompromised who present with unexplained pneumonia or encephalitis.
- Mortality is greatest in infants and adults. Overall, it is about 1 in 1000–3000 in industrialized nations.
- Globally, up to 5% of deaths in the <5 year olds are still due to measles.

Diagnosis

- As the disease has become less common, the accuracy of clinical diagnosis, especially of sporadic cases, has become poor, with as few as 1–2% of suspected cases being confirmed. The differential diagnosis includes adenovirus, rubella, enterovirus or EBV infection, streptococcal disease, and Kawasaki disease.
- Laboratory diagnosis used to depend on the finding of measles-specific IgM or a 4-fold rise in IgG in blood.
- Diagnosis is now possible by salivary measles-specific IgM.
- Using RT-PCR, viral RNA can also be found in saliva, allowing genotyping and epidemiological mapping. Oral fluid is the best sample—ideally collected using special kits.

Management and treatment

- Treatment of individual cases is symptomatic, with complications being managed individually as they arise. Antibiotics are only needed for 2° bacterial pneumonia.
- WHO recommends that all cases should be treated with vitamin A and that, even in countries where measles is not usually severe, a dose of vitamin A at diagnosis, and another a day later, should be given to all severe cases. There is little evidence that this is efficacious in patients not deficient in vitamin A.
- The daily dose of vitamin A is 50 000IU for infants <6 months old, 100 000IU for infants aged 6–11 months, and 200 000IU for those ≥12 months. A recent Cochrane analysis reported a fall of over 60% in pneumonia mortality associated with high-dose vitamin A use.
- Patients should be isolated until 4 days after the onset of rash.
- Contacts should be traced, and consideration given to vaccination or administration of immunoglobulin, depending on their age and immunization status and the interval elapsed after contact with the index case (see Prevention, p. 673–4 for more details).

Prevention

- Measles vaccines have been available for almost 50 years.
- Initially, both live and killed vaccines were used. The latter caused many cases of a severe atypical infection and rapidly gave way to the live attenuated vaccines, which are the only ones now available.
- The measles virus strains in commonest use are derived from the Edmonston strain (named after the boy from whom the measles virus strain was isolated). There is little to choose between them.
- A single dose of a measles-containing vaccine protects 90–95% of recipients, if given to children ≥12 months old.
- To attain herd immunity, it is necessary to give two doses.
- When given to children <12 months old, the efficacy is less, in large part due to the presence of maternal antibodies.

- In countries where measles is a major problem in infants, measles vaccine may be given to individuals as young as 9 months. In outbreak situations, the vaccines may be used in children as young as 6 months.
- High-titre vaccines were produced in an attempt to protect infants, but they are not in use due to evidence of higher non-measles death rates in recipients.
- Most affluent countries give measles vaccine as part of the combined MMR vaccine. Two doses are given: one at 12–15 months, and the other at anything between 2 and 10 years later, with a few countries giving it earlier.
- Side effects of the vaccine usually occur in the second week after vaccination and include a transient rash (2%), fever and other symptoms of measles (5–10%), febrile convulsions (1 in 3000), and idiopathic thrombocytopenia (1 in 30 000). These reactions are much less common after the second dose.
- The relative incidence of febrile seizures following MMR is higher in children vaccinated between 16 and 23 months, compared with 12 and 15 months.[1]
- Anaphylaxis after the vaccine occurs in 1 in 100 000 or fewer recipients.
- The vaccine is contraindicated in pregnancy and in individuals who are significantly immunocompromised (HIV is an exception where it may sometimes be given).
- In the UK, after spurious reports of an association of MMR with autism, immunization rates fell markedly. Following clear evidence of absolutely no link between MMR and autism, national immunization rates rose again and now exceed pre-scare levels among 2-year-old children.[2] Of UK children reaching 2 years old at the end of 2013, 93.3% have received one dose of MMR, and 89.6% of 5 year olds have received two doses. Uptake in the rest of Europe and across the US varies.
- It may be possible to prevent disease in susceptible contacts:
  - Immunosuppressed individuals, whose last contact was within 6 days, should have an urgent assessment of antibody levels and given human normal immunoglobulin (HNIG) if negative or equivocal. If urgent testing is not possible, immunoglobulin as HNIG should be given. The dose recommended is 0.6mL/kg subcutaneously or 0.15g/kg IV. Infants <1 year should be given 0.6mL/kg IM, up to a maximum of 5mL.[3]
  - As the incubation period of the vaccine virus is shorter than that of wild measles virus (7, as opposed to 10, days), if given within 3 days of exposure, MMR or measles vaccination reduces the risk of development of measles.
- A combined MMRV (measles, mumps, rubella, and varicella) vaccine is available in some countries. When the first dose is given at or below 47 months of age, there is an increased risk of fever, febrile convulsions, and rash, when compared with MMR and varicella vaccines given separately, but on the same occasion. For this reason, in the US, it is advised that, when the first dose of MMR is given at or below 47 months, it should not be given as part of MMRV.

Future research

- Why does a small proportion of the population not become immune after a single dose of measles vaccine?
- Should the age for vaccination be reduced in countries where maternal immunity is vaccine-based?

Key references

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Chapter 89

Meningococcal disease

See also Chapters 6, 26, 31.

Name and nature of organism

- *N. meningitidis* is a Gram-negative diplococcus.
- Thirteen serogroups, based on the polysaccharide capsule characteristics, are recognized, but meningococci are also classified by the typing of surface proteins and oligosaccharides found beneath the capsule in the outer membrane (using serology or genetic sequencing).
- The outer membrane contains LPS (endotoxin), which is responsible for the inflammatory response. Live meningococci continuously shed membrane vesicle-like structures (blebs), causing extremely high endotoxin exposure in invasive meningococcal disease.
- Meningococci are commonly isolated from the nasopharynx of healthy individuals; humans are the only natural hosts.

Epidemiology

- Rates of disease vary over time and between regions. Annual incidence rates have decreased from the year 2000 onwards for unknown reasons. The confirmed case rate of invasive meningococcal disease across Europe is ~0.73/100 000 population. During epidemics, in the meningitis belt of sub-Saharan Africa, the incidence can be as high as >100/100 000 population.
- Most disease is caused by serogroups A, B, C, Y, and W135.
- The case fatality rate is ~10%.
- Different epidemiological patterns are recognized: epidemics, clusters, hyperendemic disease, and sporadic disease.
- Most endemic disease occurs in young children and teenagers.
- Cycles of *epidemic disease* occur in the sub-Saharan African meningitis belt. Most of these cases are caused by serogroup A, though W135 and X have been recognized in the past decade.
- *Clusters* of cases occur in closed communities such as schools and colleges. Meningococcal disease rates are increased in individuals with complement deficiency (especially terminal components, C5–9, also properdin or factor D) and anatomic or functional asplenia.

Transmission and incubation period

- *N. meningitidis* asymptomatic carriage in children is low at ~1.5%, with a peak incidence in the second year of life (4%) and in adolescence (up to 25%) to decrease in adulthood to ~7% in 50 year olds.
- Transmission is via respiratory secretions and requires close contact with a carrier (hence greatest risk of 2° disease for household and kissing contacts).
- Following acquisition, most infections result in harmless colonization which has a duration from days to months before clearance.
- Susceptible individuals develop invasive disease usually within 4 days of acquisition.

Clinical features and sequelae

Rash

The rash in meningococcal disease is typically a non-blanching petechial or purpuric rash (80% of cases), which evolves from an initial blanching maculopapular rash in 38% of cases. The rash may be absent, especially in early disease. In severe cases, large ecchymotic areas develop (*purpura fulminans*) which involve haemorrhage and necrosis in the skin. The differential diagnosis of petechial rashes also includes:

- Viral infections (enterovirus, influenza, measles, EBV, CMV, parvovirus)
- Other bacterial infections (Gram-positive and negative infections, and especially pneumococcal disease)
- Vomiting or coughing (petechiae on the face and upper chest)
- Accidental and non-accidental injury
- Henoch–Schönlein purpura
- Idiopathic thrombocytopenic purpura
- Leukaemia
- Drug reactions
- Protein C or S deficiency
- Vasculitis.

Meningitis

- The presentation of meningococcal meningitis includes:
  - Non-specific symptoms (vomiting and irritability, especially in young children)
  - Headache, fever or a history of fever, photophobia
  - Neck stiffness, bulging fontanelle in infants
  - Decreased level of consciousness
  - Seizures or convulsive status epilepticus
  - Focal neurological signs
  - Petechial or purpuric rash.
- Up to 40% of children with meningitis also have features of sepsis.
- Signs of raised ICP should be carefully evaluated , as this is the commonest cause of death in cases of meningitis:
  - Reduced level of consciousness
  - Relative bradycardia and hypertension

- Focal neurological signs
- Abnormal posturing
- Unequal, dilated, or poorly responsive pupils
- Papilloedema.

Laboratory tests are similar to those in other types of bacterial meningitis and include raised WBC and inflammatory markers (CRP, ESR, PCT). Some cases will have normal laboratory values. If an LP is performed, the CSF WCC and protein are raised, and glucose is decreased.

Sepsis

Features of meningococcal sepsis include:

- Initial influenza-like symptoms (fever, headache, myalgia, vomiting, abdominal pain)
- Maculopapular rash evolving to a petechial/purpuric rash or purpura fulminans—a complex coagulation disorder with a combination of intravascular thrombosis and a bleeding diathesis
- Limb pain, cold hands and feet
- Pallor (including a mottled appearance and cyanosis)
- And later confusion, agitation, and finally coma.

Evaluation for signs of shock (seen in one-third of cases of septicaemia) should be a priority, as this is the commonest cause of death:

- Tachycardia
- Poor peripheral perfusion (prolonged capillary refill time and cold peripheries)
- Tachypnoea
- Oliguria
- Signs of decreased cerebral perfusion (confusion, agitation, or decreasing consciousness)
- Multi-organ failure
- Hypotension (late sign in children).

Poor outcome is associated with young age, coma, low temperature, and decreased WCC and platelet counts.

Laboratory features in meningococcal septicaemia include raised WBC count and inflammatory markers (CRP, ESR, PCT). Some cases will have normal laboratory values, despite severe disease, and those who are most seriously ill and have a rapid onset of disease may have a depressed WCC. Other common laboratory findings in meningococcal sepsis are:

- Anaemia, coagulopathy
- Hypoglycaemia, acidosis
- Hypokalaemia, hypocalcaemia, hypomagnesaemia
- Hypophosphataemia
- Raised creatinine.

Chronic meningococcaemia

- Recurrent episodes of non-blanching rash, with fever, arthralgia, and splenomegaly.
- Untreated cases may develop meningococcal septicaemia.
- Indistinguishable from other causes of petechial rash and fever.
- Check for complement deficiency.

Meningococcal post-infectious inflammatory syndrome

- Relatively common immune complex disease, which causes diagnostic confusion.
- Up to 10% of cases have some features.
- Onset from as early as 4 days after presentation with meningococcal infection, but often in the second week.
- Features include:
  - Fever
  - Maculopapular or vasculitis rash (2%)
  - Arthritis (8%), iritis (1%), pericarditis, polyserositis.

Other syndromes

These include pneumonia, conjunctivitis, endophthalmitis, pericarditis, OM, arthritis, peritonitis, and urethritis.

Sequelae of invasive meningococcal disease

Mortality is around 10%. Ten per cent of survivors suffer from major disabling deficits (hearing loss, digit or limb amputations, skin scarring, neurological disability), and 30% of survivors suffer from physical, cognitive, psychological functioning, memory deficit, or executive function problems.

Diagnosis

A clinical diagnosis should be suspected on the presence of red flags or worrisome signs, including neck stiffness, rash, photophobia, confusion, leg pain, or cold hands and feet, in a child with an unexplained acute febrile illness.

In all suspected cases, urgent and appropriate management should be assured. Blood must be taken for culture and PCR (whole blood EDTA sample).

A microbiological diagnosis of meningococcal disease is made by identification of the organism in specimens from normally sterile sites, e.g. blood (up to 50% of cases are culture-positive, but only 5% if obtained after antibiotics), CSF (Gram stain-positive in 65% of cases, and >70% are culture-positive). PCR is highly sensitive in both blood and CSF and increases the diagnostic rate by as much as 40%.

If there are temporary contraindications to LP, the test should be performed as soon as the contraindication has resolved.

Management and treatment

Current immediate management

The priority in emergency medical care in children with suspected meningococcal disease follows the approach to sepsis/meningitis, as propagated by the Advanced Paediatric Life Support protocols. Recognition and

management of hypovolaemic shock and raised ICP are crucial. A step-wise approach to initial management is:

1. Involve an experienced clinician and anaesthetist immediately
2. Control the airway, particularly if depressed conscious level (poor cerebral perfusion in shock or raised ICP in meningitis)
3. Give oxygen therapy in case of pulmonary oedema or oligaemia
4. Intubate and ventilate if respiratory failure present as a result of shock or impaired conscious level
5. Give fluid resuscitation (IV or intraosseous) if signs of shock, using boluses of 20mL/kg of 0.9% saline over 5–10min.
6. If signs of raised ICP present, correct the coexistent shock
7. If still shocked after 40mL/kg of fluid resuscitation, contact the regional PICU
8. If still shocked after 40mL/kg of fluid resuscitation, continue fluids (and inotropes), and electively intubate and ventilate
9. Catheterize to monitor urinary output
10. Correct metabolic derangements (hypoglycaemia, acidosis, hypokalaemia, hypocalcaemia, hypomagnesaemia, hypophosphataemia, anaemia, coagulopathy)
11. Use manoeuvres to improve cerebral perfusion if raised ICP present (mannitol/furosemide; maintain carbon dioxide in the normal range; use sedation, minimal handling; avoid neck lines; maintain head raised at 30°).

(See also <http://www.meningitis.org>.)

If meningococcal disease is suspected, antibiotic therapy should be:

- IV ceftriaxone or cefotaxime for 7 days
- Cefotaxime is preferred in neonates because of hepatic immaturity, but ceftriaxone is easier and more cost-effective to administer in other age groups. Importantly, third-generation cephalosporins provide cover for other organisms, which may present with similar features (e.g. *S. pneumoniae*). Ceftriaxone should not be administered at the same time as calcium-containing infusions
- Adjunctive steroids are beneficial in bacterial meningitis, but there is no specific evidence for meningococcal meningitis. Steroids should be given within 4 hours of the first dose of antibiotics when there is a high chance of bacterial meningitis (positive CSF Gram-stain, CSF WCC >1000 cells/mL, or CSF pleocytosis with CSF protein >1g/L).
- Treatment doses of steroids should not be used in shock.

Management after initial/emergency treatment

- Many children with meningococcal disease can be safely managed on a paediatric ward.
- Because of the risk of deterioration, especially in the first 6 hours after initial management has been instituted, patients with suspected meningococcal disease should be reviewed and reassessed repeatedly after hospital admission.
- Those who do not stabilize after initial intervention should be transferred to a PICU by a specialist paediatric intensive care transfer team.

- After transfer, children should be treated in a paediatric intensive care setting and managed according to intensive care protocols.
- Renal failure may complicate meningococcal shock.
- Experimental therapies should not be used in meningococcal disease outside of a clinical trial.
- Skin scarring occurs in about 10% of cases and may be severe enough to require skin grafting.
- Limb ischaemia due to *purpura fulminans* should be managed in conjunction with plastic and orthopaedic surgeons. Severe limb ischaemia may present early and should be left to demarcate (in the absence of infection), but about 2% of patients will require a delayed amputation.
- Meningococcal post-infectious inflammatory syndrome should be treated with NSAIDs and will usually resolve spontaneously.

Reporting

All confirmed, presumptive, and probable cases of invasive meningococcal disease should be reported to the appropriate public health department.

Follow-up

- Patients who have had meningococcal disease should be reviewed in convalescence (4–6 weeks after discharge).
- All patients should have an audiological assessment (4% hearing loss).
- Screening for developmental or cognitive deficits and behavioural or psychological disorders is advised.
- Chronic renal failure is a rare complication of hypovolaemic shock.
- Orthopaedic and plastic surgical follow-up may be required for some patients.
- Patients who have recurrent meningococcal infection or infection with unusual serogroups of meningococcus should be assessed for complement deficiency. Some experts recommend all endemic meningococcal disease patients should receive immunological evaluation (complement deficiencies, hypogammaglobulinaemia, asplenia).

Prevention

Isolation

Droplet precautions are recommended for the first 24 hours of treatment.

Management of contacts: chemoprophylaxis and vaccination

- When a case of meningococcal disease is suspected, the local public health team should be involved as early as possible to plan the prevention of 2° cases.
- Household and kissing contacts of a case of meningococcal disease have up to 1000 times the population risk of disease (1–3% of household contacts).
- Health-care workers are only at risk if directly exposed to secretions in the first 24 hours after antibiotic therapy.

- Those at risk should be offered chemoprophylaxis with:
  - Rifampicin—orally twice daily for 2 days
  - Ciprofloxacin—one oral dose
  - Ceftriaxone—one IM dose.
- ECDC guidelines also recommend that vaccination should be offered to those at risk, following contact with a vaccine-preventable serogroup case.

Vaccines

Plain polysaccharide vaccines

- Plain polysaccharide vaccines have been superseded by the conjugate vaccines and no longer have a place in countries where the conjugate vaccines are available.

Protein–polysaccharide conjugate vaccines

- Contain meningococcal polysaccharides conjugated to a carrier protein (tetanus toxoid, diphtheria toxoid, or CRM197).
- Induce immunological memory (booster responses are seen with additional doses).
- Appear to induce herd immunity.
- Antibody levels wane if given in early childhood, and therefore booster doses may be required.
- MenC is recommended for routine childhood immunization in many European countries.
- Booster doses for teenagers may be required and are now recommended in the UK. Meningococcal conjugate vaccines with several (combinations of) serogroups are available in Europe (e.g. C, ACWY, CY)
- MenC has successfully controlled disease caused by serogroup C meningococci in countries where it has been introduced routinely.
- Massive population vaccination campaigns to eliminate meningococcal serogroup A epidemics are carried out in sub-Saharan Africa.

Group B meningococcal vaccines

- The group B polysaccharide is not immunogenic, as it shares chemical identity with human antigens, and subcapsular antigens have been considered as vaccine candidates.
- Outer membrane vesicle (OMV) vaccines containing surface proteins in a lipid membrane have been developed to control clonal outbreaks (hyperendemic) of meningococcal disease in Cuba, Norway, New Zealand, and Normandy.
- Many different clones of meningococci cause disease in Europe, and a single OMV vaccine is not suitable.
- An effective serogroup B meningococcal vaccine has been licensed for Europe in 2013. The vaccine consists of three recombinant proteins and OMVs of meningococcus serogroup B and aluminium hydroxide.
- The UK has been the first country where the government advisory body recommended MenB vaccination to be taken up in the routine childhood vaccination programme.
- More vaccines containing multiple OMVs and/or relatively conserved surface proteins are at an advanced stage of development.

Vaccination of special risk groups

- Children at increased risk are advised to be vaccinated.
- Functional or anatomical asplenia.
- Complement deficiency.
- Travellers to endemic regions:
  - Sub-Saharan Africa (December to June)
  - Mecca, Saudi Arabia (during annual Hajj).
- Meningococcal vaccine should be offered to household contacts of a case of vaccine-preventable serogroups, as appropriate.

Future research

- Identification of differences in genetic make-up and regulation that determine susceptibility and severity of infection and vaccine effectiveness and failure.
- Further development of improved broad-coverage, cost-effective vaccines and vaccination strategies.
- Development of protective treatments for all-cause sepsis/purpura fulminans-associated organ damage and vascular dysfunction. Adjuvant treatments to prevent cerebral damage.

Further reading

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Chapter 90

Mumps

See also Chapters 14, 15, 29, 44.

Name and nature of organism

- An acute illness with swelling of the parotid glands.
- Mumps virus is a paramyxovirus containing negative-strand RNA. Two proteins (haemagglutinin–neuraminidase and fusion) are on the surface and carry neutralizing epitopes.

Epidemiology

- Epidemics of infectious parotitis have been known since ancient times.
- Ubiquitous in temperate climates before the introduction of vaccines, with epidemics occurring every few years—usually in spring. The peak age group affected was children aged 5–9 years.
- Infection is less ubiquitous in the tropics.
- Serological surveys suggest that eventually 70–90% of individuals are infected, but about one-third are asymptomatic or do not have salivary gland swelling.
- In the UK, high coverage of MMR after 1988 resulted in a substantial reduction in mumps incidence, including those too old to have been immunized. In October 1996, a two-dose MMR schedule was introduced.
- In 2004–2005, a large outbreak of mumps occurred in the UK, mainly affecting individuals aged between 18 and 24 years who were too old to be eligible for routine MMR vaccination, but who had minimal exposure to mumps during childhood because of the MMR vaccine programme. There were 43 378 confirmed mumps cases in England and Wales in 2005; from 2007 onwards, numbers fell, but smaller increases occurred in 2009/2010 and 2013/2014.
- In the US also, mumps outbreaks began in 2009, primarily in universities or other institutions for young adult populations.
- Vaccination has shifted the incidence to higher age groups, thought to be the result of waning immunity. Immunity after natural infection is permanent, but, even before vaccination, the accumulation of susceptibles, as in military populations, resulted in outbreaks.
- Many cases are now reported in college and boarding school settings, despite most of the population being fully vaccinated; this suggests that waning immunity can contribute to transmission in settings with very close contact.

Transmission and incubation period

- The virus is excreted in the saliva and urine.
- Transmission is only from human to human, probably in large droplets by the respiratory route, as suggested by recent outbreaks in colleges among students not necessarily having intimate contact.
- Less contagious than measles or varicella.
- Incubation period of mumps ranges from 12 to 25 days, with 16–18 days being the commonest.
- The virus is often present in the saliva from 2 to 4 days before symptoms up to 4–5 days afterwards.
- A case is considered infectious for 5 days after the onset of symptoms.
- Isolation of cases may have little effect on an outbreak, as infectiousness may precede symptoms.
- Virus can also be isolated from urine, blood, and CSF (with or without meningitis), but these are not thought to play a role in transmission, although viruria may persist for 2 weeks.

Clinical features and sequelae

- Non-specific febrile prodrome of several days, which may include pain in the ears.
- Characteristic symptom is swelling of the parotid glands in about 70% of patients. Parotitis increases for several days and then begins to resolve.
- Involvement may be unilateral.
- The submandibular glands may also be involved.
- Examination of the parotid duct is likely to show erythema and oedema.
- To test for parotitis, give the patient a citrus drink, which causes pain in the gland.
- Inapparent mumps, or mumps presenting with respiratory symptoms, is common in young children.
- Mumps involves many different organs, but the principal complications occur in the CNS, cochlea, pancreas, and the testis and ovaries.
- CNS invasion occurs commonly, with lymphocytic pleocytosis seen in about 50% of infections and positive RT-PCR in virtually all patients. Nevertheless, meningismus will be present only in about 10%.
- CNS disease is usually benign in outcome, but symptoms are likely for a week, including signs of general or local neural inflammation.
- True encephalitis occurs only rarely—around a week after clinical infection—is serious, but usually has a good outcome.
- Mumps affects hearing in about 4% of cases and is rarely a cause of permanent acquired deafness.
- Pancreatic glands are involved in about 5% of cases, causing abdominal pain and GI symptoms. Serum amylase will be elevated but is not diagnostic, as parotitis can also increase the amylase. Determination of pancreatic lipase can make the distinction. The relationship of mumps pancreatitis to subsequent diabetes mellitus is controversial.
- Orchitis is seen in up to a third of post-pubertal men (rare in younger children), most often unilateral, and usually starting 4–10 days after the

appearance of parotitis. Although testicular atrophy is a common result, sterility follows in only 3% of cases.
- Oophoritis also occurs in about 5% of post-pubertal women, manifesting as pain.
- Myocardial involvement occurs frequently but is usually asymptomatic. Migratory arthritis, myocarditis, hepatitis, and nephritis are other complications that may arise after mumps.
- Mumps virus can pass from pregnant women infected in the first trimester to their fetuses and cause spontaneous abortion. No congenital malformation has been definitely associated with it, although endocardial fibroelastosis is strongly suspected to be a result of intrauterine mumps.

Diagnosis

- During an epidemic, the presence of parotitis has a high specificity for the diagnosis of mumps.
- Many other viruses can cause parotitis, notably Coxsackie and influenza viruses. Bacterial parotitis must always be suspected if there is pus coming from the parotid duct.
- HIV, autoimmune disease, cancer, and other non-infectious diseases are considerations if the parotid enlargement is chronic.
- Persistent bilateral parotid enlargement for >3 months is a good sign of paediatric HIV infection.
- Virus isolation in monkey or human cells can be performed using saliva, urine, or spinal fluid.
- RT-PCR to detect mumps RNA is the most sensitive test, but positivity decreases after the second day of symptoms.
- Serologic diagnosis is generally accomplished by ELISA. Mumps-specific IgM detected by ELISA is a useful test, but maximum positivity is only reached 5 days after the onset of symptoms.
- Oral fluid is an acceptable alternative to serum for IgM testing and can also be used for RT-PCR in the early stages of the illness. Notified cases of mumps in the UK are routinely offered oral fluid testing for confirmation.
- Although the presence of ELISA antibodies indicates prior infection, only neutralizing antibodies are considered to be protective.
- 2° infection in vaccinated individuals is associated with high IgG levels in the first 7 days of illness and can be confirmed by testing for high avidity. 2° infection may be associated with classic mumps, although the rate of complications is reduced.

Management and treatment

- Ribavirin has been used, with possible anecdotal success in very severe disease, but there is no accepted antiviral or immunoglobulin treatment of mumps.

- Symptomatic treatment is important to mitigate the painful swelling of salivary glands and gonads.
- Meningitis and encephalitis are treated conservatively with bed rest and relief of increased CSF pressure.

Prevention

- At least 13 attenuated strains of mumps virus have been produced, but, outside Japan, generally only three are used: Jeryl Lynn, Urabe, and Leningrad.
- Many of those strains have caused cases of aseptic meningitis. However, the Jeryl Lynn strain and its derivatives have not been isolated from CSF and is not associated with meningitis.
- Mumps vaccine is used almost entirely as a component of the MMR vaccine. The first dose of MMR is routinely recommended to be given between 12 and 15 months of age, with a second dose later in life, often recommended at age 4–6 years. Jeryl Lynn is manufactured in chick embryo cell culture, but allergic reactions have been very rare, and allergy to eggs is not a contraindication to vaccinate.
- Although no congenital abnormalities have been associated with mumps vaccines, vaccinated women should avoid pregnancy for 1 month following vaccination.
- Despite the limitations of the vaccine strains, routine use has had marked effects. In the UK, routine vaccination was started in 1988 and, by 1994, had profoundly reduced the incidence of mumps. However, the drop in MMR vaccine coverage, caused by the autism scare, allowed the reappearance of mumps outbreaks.
- In the US, mumps incidence decreased from the introduction of vaccination in 1967 to reach an all-time low in 2003. However, numerous outbreaks have occurred recently throughout the world in adolescents and young adults, many of whom have been previously vaccinated. Although vaccine effectiveness has been moderately high, waning of immunity after one or two doses has been implicated in these outbreaks. There is also some evidence that vaccine-induced antibodies inhibit newer strains to a lesser degree than the vaccine strain. Measures to deal with these phenomena, including third doses, are being investigated.

Future research

An effective antiviral agent would be a useful treatment option for severe disease due to mumps.

Further reading

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Chapter 91

Non-tuberculous mycobacterial infection

See also Chapters 1, 9, 15, 17, 22, 33, 38.

Name and nature of organism

- NTM are environmental mycobacteria found throughout the world in soil, dust, water, food, and animals. More than 50 species have been implicated in human disease.
- NTM are acid- and alcohol-fast, Gram-positive organisms.
- Classification was traditionally based on pigment production and rate of growth. Further differentiation of species by morphology, physiology, biochemistry, and antibiotic sensitivity is routine. Molecular typing has increased NTM species to >125.
- Rapid identification is by microscopy and staining with fluorochrome. Ziehl-Neelsen staining is less sensitive. Culture may take <2 weeks on rapid broth media for rapid-growing NTM or >2 months for slower-growing on solid media.
- NTM can cause invasive or disseminated disease, or local infection.

Epidemiology and aetiology

- Geographical distribution is similar when the environment is sampled, but isolates found in lymphadenopathy vary, with, for example, *Mycobacterium avium* complex (MAC) found worldwide, *Mycobacterium malmoense* in northern areas, *Mycobacterium haemophilum* in Israel.
- NTM lymphadenopathy typically affects young children between 1 and 5 years; increased incidence has been reported in association with stopping neonatal BCG vaccination.
- Outbreaks of cutaneous NTM infection in older children and adults have been linked to whirlpool baths. *M. marinum* is associated with 'fish tank' granulomas on the hands or other water-borne lesions.
- Respiratory infection is associated with underlying chronic respiratory disease, in particular cystic fibrosis. Fast-growing NTM species, such as *M. abscessus, M. chelonae*, and *M. kansasii*, are frequently implicated, with *M. abscessus* responsible for >80% of pulmonary infection in the US.
- Disseminated disease occurs with 1° or 2° immunodeficiency, in particular affecting T-cell function, and IL-12 and IFN-γ signalling.

Transmission and incubation period

- Infection results from environmental acquisition by inhalation, ingestion, or direct contact with a contaminated source. NTM submandibular or cervical lymphadenopathy suggests that the oral mucosa is a portal of mycobacterial entry.
- Unlike TB, NTM infection is not transmitted from person to person. Contact tracing or isolation of an infected child are unnecessary.

Clinical features and sequelae

Non-tuberculous mycobacterial lymphadenopathy

- Local lymph node infection, typically in 1- and 5-year-old children (exceptionally at older age).
- Any node may be involved—submandibular, cervical, or preauricular are most frequently, and axillary and inguinal nodes occasionally involved.
- Sudden or gradual onset of firm, painless, usually unilateral lymphadenopathy; characteristic reddish pink colour over the indurated skin, which deepens to purple blue, typically, but not always, develops over time.
- Typically >2 cm in size but may become very large and disfiguring.
- Eventually, node may soften, rupture, and discharge, with sinus formation, and, if not removed, can continue to do so for months to years before gradual spontaneous healing.
- General condition is good; no evidence of dissemination; no hepatosplenomegaly; fever is reported in some children.
- Most commonly caused by MAC.

Other infections

- NTM can infect any organ, e.g. bones.
- Sporadic cases and outbreaks of cellulitis, soft tissue abscesses, and extracutaneous disease associated with rapidly growing NTM have been documented in healthy individuals.
- NTM can cause papules and nodules, which may be linear.
- *M. marinum* follows trauma in water and leads to clusters of nodules that may ulcerate on the hands and feet.
- *Mycobacterium ulcerans* is seen in Australia and Central Africa, causing Buruli ulcer, a single large, painless ulcer usually on the extensor surface of the leg, with local necrosis. Infection may resolve without intervention but may also be severe, protracted, and cause potentially scarring lesions.

Respiratory infections

- NTM are isolated regularly in cystic fibrosis, with incidences between 6% and 16% in most studies.
- The main problem is discriminating colonization from disease; the pathogenic role is difficult to be established in the individual case.

- NTM are implicated as occasional pathogens in chronic lung disease other than cystic fibrosis.
- Risk factors include allergic bronchopulmonary aspergillosis and treatment with steroids, aerosolized medications, and bronchoscopes (contamination).
- Infection is more often associated with severe underlying disease.
- Disseminated fatal infection has occurred after lung transplantation.

Central venous catheter-associated NTM infections

- May occur together with leukaemia, lymphoma, and solid tumours.
- Usually infections are due to rapidly growing NTM, but *M. avium* and *M. intracellulare* have also been reported.
- Occasionally, NTM in blood cultures is mistaken for *Corynebacterium* or *Nocardia* spp., which leads to inappropriate therapy.
- Affected patients may be neutropenic or, more frequently, lymphopenic ($<1000/mm^3$) and may also have lung involvement.
- NTM infection should be considered in all persistently febrile children with cancer or leukaemia, particularly those who do not respond to conventional antibiotics or antifungals. Blood cultures in special mycobacterial bottles are indicated.

Disseminated disease

- Found in 1° and 2° immune deficiency.
- Predisposition for dissemination is seen where the T-cell count or function is very low (SCID, HIV, malignancy with chemotherapy), where monocytes and/or dendritic cells are missing (IRF-8 and GATA-2 deficiency), and with CGD. Mendelian susceptibility to mycobacterial disease (MSMD) describes a range of autosomal and X-linked single gene defects in families with an increased predisposition to invasive or recurrent NTM disease (e.g. IFN-γ receptors 1 and 2, IL-12β receptor, STAT-1, ISG15, nuclear factor κB essential modifier—NEMO). NTM and BCG infections appear to predominate, but infections with *M. tuberculosis*, non-typhoidal salmonellae, and several herpesviruses have also been problematic. Finally, autoantibodies to IFN-γ can cause disseminated NTM infections.
- Systemic symptoms include fever, weight loss, sweats, diarrhoea, cough, and focal lesions such as bone or joint involvement.
- Infection may be found in blood, bone marrow, lung, bones, joints, GI tract, and rarely CNS, as well as local skin and soft tissue.

Diagnosis

Lymphadenopathy

- Differential diagnosis includes pyogenic lymph node abscess, TB, cat scratch disease, toxoplasmosis, mumps, salivary stone, cervical cyst, EBV, tularaemia, malignancy, and CGD.
- Relative risk of NTM and MTB infection depends on the local incidence rates.

- May be distinguished from bacterial abscesses by lack of systemic or local temperature, no systemic upset, persistent duration, and non-response to oral or IV antibiotics.
- Clinical diagnosis can usually be made, based on classic features alone.
- Diagnosis is often made post-surgical exploration for incision and drainage when histology subsequently indicates caseating granulomata and/or acid-fast bacilli are seen.
- Initial microscopy of acid-fast bacilli does not distinguish MTB from NTM. Subsequent culture can take from 3 weeks to 2 months. PCR can distinguish MTB from NTM and should be performed on tissue samples.
- Investigations should include detailed history, including family history of infection, travel, and contact with MTB, CXR, FBC, including leucocyte differential, CRP, ESR, LFTs, and serology—*Bartonella, Toxoplasma*, EBV.
- A positive Mantoux (induration >5mm), in the presence of a 3-week history of localized lymphadenitis (>2cm in diameter), in the absence of contact history with MTB (and a negative IGRA or T SPOT TB), has a sensitivity of 80% for NTM lymphadenitis.
- Fine needle aspirations are of limited use because of potential sampling errors and the increased risk of fistulation.
- The decision for LN excision should be made early, since (a) the diagnosis can be established in most cases and (b) the disease resolves faster with fewer problems than with conservative treatment.
- MRI of the affected region may help to guide the surgical intervention (in particular in advanced disease).

Central venous catheter infection

- Conventional blood cultures will detect rapidly growing NTM, but they are unlikely to detect *M. avium* or other slow-growing mycobacteria. Specific mycobacterial blood culture bottles are required for this purpose.

Respiratory infection

- In the case of deteriorating lung function in the face of NTM isolate warranting a trial of treatment, consider NTM respiratory disease and drug treatment.

Disseminated disease

- High index of suspicion in the immunocompromised. Investigation should include mycobacterial blood cultures, imaging, and guided biopsy for histology and mycobacterial culture.
- In disseminated NTM infection, the possibility of an underlying specific immune deficiency should always be explored.

Management and treatment

Lymphadenopathy

The three options are surgical, medical, and observation.

- Parents should be counselled about the chronicity of the condition, the lack of infectivity, and eventual resolution. Considerable upset can occur due to the cosmetic appearance, and this can lead to social isolation in a child.
- Surgical excision, where possible, is often curative—although new lesions may appear locally or on the other side. The extent of excision (complete versus 'almost complete') should always be weighed against potential complications (bleeding, nerve damage). Wound healing is often complicated by granulation.
- The great majority of lesions will also resolve spontaneously over a 1- to 2-year period. A waxing and waning course with flare-ups is common. In open lesions, 2° infection due to staphylococcal or streptococcal infection may also occur (which is why lesions sometimes seem to partially respond to conventional antibiotics).
- Large lesions, such as those involving significant areas of the skin, deep infection, or those close to the facial nerve, may not be possible to safely excise without morbidity or extensive scarring.
- Antimicrobial treatment may be helpful, if excision is not possible, or incision and drainage has produced an active discharging lesion. Efficacy appears variable and may depend on underlying mycobacterial sensitivities.
- There are limited data on which to base treatment decisions. One randomized trial in 100 children with proven cervical NTM compared surgical excision to 3 months of clarithromycin and rifabutin. Although cure rates were significantly better with surgery (96% versus 66%), substantial rates of complications were also seen with both therapies (28% versus 78%).[1] If the family is in agreement, masterly inactivity (doing nothing) is a reasonable option.
- In a controlled study, 1° antibiotic therapy without surgery has not been shown to be advantageous, as compared to simple watch-and-wait in uncomplicated cases.

Central venous catheter infection

- Some children have been effectively treated with CVC removal alone. However, standard treatment includes line removal, treatment with at least two antimycobacterial drugs for 2–12 weeks for localized disease, and 6 months or longer for widespread disease.

Drug treatment

- As a general rule, mycobacterial infections should be treated with a combination of antimicrobial agents to avoid resistance development. Treatment is required for several months.
- In NTM infections, resistance testing is of limited value, however, should be performed by experienced laboratories. Choice of antibiotics is largely guided by clinical experience and should—at least in difficult cases—be discussed with expert microbiologists and ID specialists. Some guidance is provided by the American Thoracic Society (ATS)/IDSA guidelines. Examples for resistance testing and antibiotic choice are:

- MAC isolates should be routinely tested for susceptibility to macrolides, which are the treatment backbone for these organisms.
- In infections with slow-growing NTM including lymphadenopathy, combinations of a macrolide *with* rifabutin or rifampicin and ethambutol are a commonly used combination. A non-controlled study on NTM pulmonary disease employing this combination over 24 months suggests efficacy. The inclusion of ethambutol is based on its antimicrobial synergism with rifampicin against the majority of *M. avium*, *M. intracellulare*, and *M. malmoense* spp. Yet this synergism is of questionable advantage *in vivo* and has not been established in controlled clinical studies.
- If rapidly growing mycobacteria are found, resistance testing for amikacin, imipenem (*Mycobacterium fortuitum* only), doxycycline, quinolones, sulfonamides, cefoxitin, clarithromycin, linezolid, and tobramycin (*M. chelonae* only) should be performed. *M. abscessus* pulmonary disease is treated by multidrug clarithromycin-based therapy, if necessary, together with surgical resection of localized disease.
- Routine susceptibility testing of *M. kansasii* isolates is recommended for rifampin only. *M. kansasii* pulmonary disease is usually treated with isoniazid, rifampin, and ethambutol (until sputum is culture-negative for 1 year).
- Combinations of at least three, and up to five, drugs are favoured for disseminated disease in immunodeficiency. These can include a macrolide, rifabutin or rifampicin, ethambutol, quinolones, amikacin, and newer drugs such as moxifloxacin, or linezolid.
- Surveillance for side effects of vision, including visual acuity or colour discrimination (ethambutol), the presence of eye pain or uveitis (rifabutin), hepatitis (isoniazid, rifampin, ethionamide, clarithromycin, rifabutin), renal impairment or auditory dysfunction (streptomycin, amikacin), CNS dysfunction (cycloserine, ethionamide), and haematological abnormalities (sulfonamides, cefoxitin, rifabutin), is very important.
- Interferon alfa and interferon gamma have been used in single cases with (suspected) MSMD.

Prevention

- Antimycobacterial prophylaxis is unnecessary for localized disease.
- In HIV, low, age-related $CD4^+$ cell count levels are considered as high-risk for MAC, warranting consideration of macrolide prophylaxis (available at: <http://www.chiva.org.uk>).
- In other immune deficiencies with a specific predisposition to NTM infection, macrolide 1° and 2° prophylaxis should be considered.

What's new?

- Autoantibodies against cytokines underlying mycobacterial disease may be underestimated.

What's next?

- Controlled clinical trials establishing the role of specific drug combinations in pulmonary NTM infections, which are an emerging entity, are urgently needed.

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Chapter 92

Mycoplasma infections

Name and nature of the organism

Mycoplasmas are prokaryotes that lack a cell wall. They are the smallest free-living forms and are ubiquitous pathogens. They can grow in cell-free media and contain both RNA and DNA, clearly separating them from viruses.

- The family *Mycoplasmataceae* is composed of two genera responsible for human infection—*Mycoplasma* and *Ureaplasma*.
- In 1945, Eaton identified an organism which passed through viral filters and could cause focal areas of pneumonia in rodents. This was initially called the Eaton agent and was subsequently classified as *Mycoplasma pneumoniae*.

Mycoplasma pneumoniae

Epidemiology

- *M. pneumoniae* is endemic worldwide, and there is no significant seasonality.
- Epidemics are common and occur in 4- to 7-year cycles. They are believed to be due to decreasing herd immunity and different *M. pneumoniae* genotypes circulating in the human population. Few *M. pneumoniae* infections are seen between outbreaks.
- *M. pneumoniae* outbreaks have been reported to occur within families, schools, institutions, camps, and military bases.
- Manifest *M. pneumoniae* infections occur in all ages but are predominant in school-aged children and young adults. Following infection, *M. pneumoniae* may remain in the respiratory tract for weeks to months.
- Asymptomatic carriage of *M. pneumoniae* in the upper respiratory tract is frequent (up to 50%).

Transmission and incubation period

- *M. pneumoniae* is transmitted by respiratory droplets through close contact.
- The incubation period is 1–3 weeks.

Clinical features and sequelae

Respiratory tract infection

- *M. pneumoniae* infections are generally mild and self-limiting.
- The commonest clinical syndromes are URTIs (including pharyngitis), otitis media, and acute bronchitis.

- Most *M. pneumoniae* infections are clinically apparent with slow onset of fever, cough, malaise, and headache, and continue for 2–3 weeks with an usually subacute course.
- In about 5–10% of cases, the infection progresses to pneumonia. *M. pneumoniae* is thought to be responsible for more than one-third of CAP cases requiring hospitalization.
- Compared with other children with CAP, patients with *M. pneumoniae* infection may be older (>3 years of age) and have a longer duration of fever (>2 days). The CXR appearance can vary but most commonly shows bilateral interstitial infiltrates (the abnormalities are often more extensive than would be expected from the clinical examination).
- The role of *M. pneumoniae* in asthma is still controversial. Although *M. pneumoniae* has been found more frequently in association with chronic asthma than acute exacerbations, it may not have a direct effect in most asthmatic children.
- While the infection is generally mild and self-limiting, patients of any age can develop severe and fulminant disease (both normal and immunocompromised children).

Extrapulmonary manifestations

- *M. pneumoniae* is often associated with extrapulmonary disease involving almost any organ system, especially the skin and nervous system, but also the haematologic (e.g. haemolytic anaemia), cardiovascular (e.g. pericarditis, myocarditis), urogenital (e.g. glomerulonephritis), and musculoskeletal systems (e.g. polyarthralgia, arthritis).
- These manifestations may be due to either a direct infection (dissemination) or an immune-mediated process (autoimmunity), and do mostly, but not necessarily, come along with a respiratory prodrome.

Dermatological involvement

- Skin manifestations occur in ~25% of all *M. pneumoniae* infections, including mostly non-specific exanthems, erythema nodosum, and urticaria.
- These lesions usually clear within 1–2 weeks without scarring.
- More severe manifestations can also occur, e.g. erythema multiforme, Stevens–Johnson syndrome, and an isolated mucous membrane involvement (*M. pneumoniae*-associated mucositis).

Neurological disease

- Encephalitis, aseptic meningitis, transverse myelitis, brainstem dysfunction, Guillain–Barré syndrome, and peripheral neuropathies have all been reported.
- Encephalitis and Guillain–Barré syndrome constitute the commonest neurological manifestations, in which *M. pneumoniae* infection is established in up to 10% and 15% of the cases, respectively.
- The CSF cellular response is usually minimal, with slightly elevated protein and normal glucose.
- Because the detection rate of *M. pneumoniae* by PCR or culture in CSF is relatively low, an immune-mediated neurological damage has been postulated.

- The prognosis for children with *M. pneumoniae* neurological disease varies; both benign courses and neurologic sequelae have been reported.

Increased susceptibility to M. pneumoniae infections

- Patients with sickle-cell disease or sickle-related haemoglobinopathies infected with *M. pneumoniae* may develop serious respiratory disease.
- In patients with functional asplenia, with associated opsonization deficiency, overwhelming pneumonia may occur during *M. pneumoniae* infection.

Diagnosis

Respiratory tract infection

- *M. pneumoniae* respiratory tract infections in children cannot be reliably diagnosed by clinical signs and symptoms or radiographic findings.
- The routine laboratory diagnosis of *M. pneumoniae* infection depends on the detection of specific antibodies or antigens (Table 92.1).
- However, recent studies have shown that *M. pneumoniae* serology based on single samples and on PCR in the respiratory tract cannot discern between colonization and infection in a clinically relevant time frame. The main reason for this is the high prevalence of *M. pneumoniae* in the upper respiratory tract of healthy children. The demonstrated positive serological results (IgM, IgG, and IgA) in such asymptomatic PCR-positive children may simply reflect one or more previous encounters with *M. pneumoniae* and are not necessarily related to the presence of *M. pneumoniae* in the respiratory tract. This may give rise to an overestimation of the *M. pneumoniae*-related disease burden.
- A more reliable diagnosis of *M. pneumoniae* infection may be achieved by using paired sera in order to detect seroconversion and/or a 4-fold increase in antibody titres, in addition to PCR.

Neurological disease

- The diagnosis of *M. pneumoniae* CNS disease is made after exclusion of other causes.
- The routine diagnostic work-up of *M. pneumoniae* CNS disease should aim for the detection of *M. pneumoniae* antibodies in both CSF and serum, in addition to *M. pneumoniae* PCR in CSF. It has been demonstrated that intrathecal antibodies and intrathecal antibody synthesis (as a marker for infection of the CNS), but not bacterial DNA, can be present at the onset of clinical CNS disease.
- Intrathecal antibodies can be detected by widely accessible EIAs or immunoblotting (Table 92.1).
- Intrathecal antibody synthesis can be established either by calculation of an antibody index or through parallel immunoblotting of simultaneously collected CSF and serum samples.

Table 92.1 Overview of diagnostic tests for *M. pneumoniae*

Method	Test	Target/antigen	Antibodies	Specimen(s)	Performance	Value	Comments
Direct identification of *M. pneumoniae*	PCR	Different target genes (e.g. P1 gene, 16S rDNA, 16S rRNA, RepMP elements, etc.)	–	Respiratory specimen (other bodily fluids or tissues)	High sensitivity, high specificity	RD	• Nucleic acid amplification tests provide fast results (in less than a day) and may be earlier than serology (because antibody production requires several days) • Validation and standardization required for routine diagnostics
	Culture	–	–	Respiratory specimen	Low sensitivity, high specificity	AD	• Special enriched broth or agar media • Isolation takes up to 21 days
Non-specific serological tests for *M. pneumoniae*	Cold agglutinin test ('bedside test')	Erythrocytes (I antigen)	Cold agglutinins (IgM)	Serum	Low sensitivity, low specificity	[1]	• Positive in only about 50% and in the first week of symptoms • Less well studied in children • Cross-reactivity with other pathogens and non-infectious diseases

Specific serological tests for *M. pneumoniae*	Complement fixation test	Crude antigen extract with glycolipids and/or proteins	Igs (no discrimination between isotypes)	Serum	Sensitivity and specificity comparable to EIA	[1]	• Positive criteria: 4-fold titre increase between acute and convalescent sera or single titre ≥1:32
	Particle agglutination assay		IgM and IgG simultaneously			[1]	• Cross-reactivity with other pathogens and non-infectious diseases
	EIA	Proteins (e.g. adhesin protein P1) and/or glycolipids	IgM, IgG, IgA[2]	Serum (other bodily fluids)	Moderate to high sensitivity, moderate to high specificity	RD	• Sensitivity depends on the time point of the first serum and on the availability of paired sera (for seroconversion and/or rise in titre) • 'Gold standard': 4-fold titre increase, as measured in paired sera
	Immunoblotting				High sensitivity, high specificity	AD	• Confirmatory assay
	IFA				Less sensitive and less specific than EIA	AD	• Subjective interpretation

[1] Largely replaced by EIA.

[2] Kinetics of antibody responses in blood: *IgM*: onset: within 1 week after the onset of symptoms; peak: 3–6 weeks; persistence: months (to years). *IgG*: onset and peak: 2 weeks after IgM; persistence: years (to lifelong); reinfection in adults may lead directly to an IgG response in the absence of an IgM response. *IgA*: onset, peak, and decrease earlier than IgM.

AD, advanced diagnostic test; EIA, enzyme immunoassay; IFA, immunofluorescence assay; PCR, polymerase chain reaction; RD, routine diagnostic test; RepMP, repeated *M. pneumoniae* DNA.
Source data from Meyer Sauteur *et al*. *PLoS Pathog* 2014;**10**:e1003983.

Management and treatment

Respiratory tract infection

- Surprisingly, there is no clear evidence that antibiotic treatment of *M. pneumoniae* respiratory tract infection is actually effective.
- Because *M. pneumoniae* lacks a cell wall, it is naturally resistant to cell wall synthesis inhibitors such as β-lactam antibiotics.
- The first-line antibiotics for *M. pneumoniae* infections in children are macrolides, including clarithromycin and erythromycin.
- Treatment alternatives are tetracyclines (>8 years of age) and fluoroquinolones (after adolescence). They should not be used in young children because of deposits in growing bones and teeth. However, the occurrence of arthropathy due to fluoroquinolones is uncertain, and all musculoskeletal adverse effects reported in the literature have been reversible following withdrawal of treatment.
- Current guidelines for the management of CAP in children suggest empiric macrolides against *M. pneumoniae* at any age if there is no response to first-line β-lactams or in the case of very severe disease.
- Treatment can shorten the duration of illness and may reduce the spread of infection (by reducing cough and bacterial load).

Neurological disease

- No data exist that treatment of extrapulmonary manifestations with antibiotics alters the course of disease, as this is the case for immunomodulatory treatment (corticosteroids and immunoglobulins).
- Macrolides, in general, do not traverse the blood–brain barrier, whereas tetracyclines can achieve therapeutic levels in the CNS.

Antibiotic resistance

- Extensive use of macrolides has led to rapid worldwide emergence of macrolide-resistant *M. pneumoniae* (MRMP). In Asia, resistance rates exceeding 90% have been reported, and increased spread of MRMP strains is observed in Europe and North America.
- MRMP can have important clinical consequences for the treatment and progression of *M. pneumoniae* infections, i.e. longer duration of symptoms and hospitalization, and more severe CAP and increased extrapulmonary manifestations.

Prevention

- Hand hygiene (in general) and droplet precautions (for hospitalized patients) are recommended for the duration of symptomatic illness.

Future research

- Future research may involve the development of vaccines or the development of more effective antimicrobial agents for children. There is also a need for improved diagnostic methods for *M. pneumoniae.*

Genital mycoplasmas: *Ureaplasma urealyticum, Mycoplasma hominis,* and *Mycoplasma genitalium*

Epidemiology, clinical features, and sequelae

Ureaplasma urealyticum

- *U. urealyticum* is highly prevalent in the genital tracts of healthy, sexually active women at rates of 60–70%. The prevalence in the ♂ urethra is lower at 10–20%. During pregnancy, both cervicovaginal colonization and/or amniotic fluid infection may induce an inflammatory response, resulting in chorioamnionitis, preterm onset of labour, or premature rupture of membranes, all leading to potential adverse neonatal outcomes. In immunocompromised individuals, *U. urealyticum* can disseminate and cause disease.
- Infants can be vertically infected *in utero* or during delivery, and *U. urealyticum* has been associated with preterm birth.
- Full-term newborns: *U. urealyticum* can rarely cause a diffuse interstitial neonatal pneumonia and neonatal meningitis.
- Premature newborns: the rate of respiratory tract colonization with *U. urealyticum* is relatively high (up to 45%, especially in VLBW infants), and a significant association between respiratory tract colonization and bronchopulmonary dysplasia has been observed. The detection of *U. urealyticum* in cord blood, venous blood, and/or CSF (up to 20%) and in gastric aspirates and rectal cultures has been associated with intraventricular haemorrhage and necrotizing enterocolitis, respectively. Inflammatory cytokines, antenatally induced by *U. urealyticum*, are hypothesized to be the causative link between intrauterine infection and organ damage. However, the exact role of *U. urealyticum* in these morbidities of prematurity remains unclear.

Mycoplasma hominis

- *M. hominis* is less prevalent and has been recovered from a variety of extragenital sites, including the kidneys, joints, and surgical wounds. It can cause disease in immunocompromised individuals.
- In neonates, *M. hominis* is a rare cause of neonatal meningitis and has been recovered from the blood of newborns with signs of sepsis. It has also been isolated from the upper respiratory tract and is thought to be a cause of neonatal pneumonia. It has been associated with stillbirths and recovered from fetal lung and liver tissue.

Mycoplasma genitalium

- Although genital mycoplasmas are generally commensals in the normal flora, *M. genitalium* is associated with about 20% of non-gonococcal urethritis in ♂, and it may have a role in cervicitis and endometriosis.

Diagnosis

- The gold standard for the identification of genital mycoplasmas is culture.
- PCR-based identification is also available, and it is more sensitive, less time-consuming, and allows for differentiation between genera and species.

Management and treatment

- Genital mycoplasmas are generally susceptible to tetracyclines and fluoroquinolones but have different susceptibilities to macrolides; *U. urealyticum* has limited susceptibility to macrolides (in which azithromycin and clarithromycin are *in vitro* significantly more active than erythromycin); *M. hominis* is naturally resistant to macrolides, and *M. genitalium* is susceptible to macrolides.
- Tetracyclines are not recommended for children <8 years of age, and fluoroquinolones before adolescence, because of deposits in growing bones and teeth.
- Detection of *U. urealyticum* or *M. hominis* from a sterile site (in the absence of other organisms) may warrant antimicrobial treatment if there is evidence of inflammation. Without inflammation, treatment decisions are challenging, because these organisms can be isolated from the blood and CSF of newborns with no adverse outcomes and with spontaneous clearance.
- The treatment of choice for *U. urealyticum* neonatal infections (except CNS infections) is erythromycin (although there are no trials and no comparisons with other antimicrobials). Erythromycin in preterm infants colonized with *U. urealyticum* cannot prevent bronchopulmonary dysplasia or eradicate respiratory tract colonization. Treatment of CNS infections remains difficult; fluoroquinolones and chloramphenicol may be possible agents.
- Treatment of *M. hominis* neonatal infections is problematic, as tetracyclines should be avoided in young children. There is evidence of *in vitro* sensitivity of *M. hominis* to linezolid, an antibiotic that penetrates the CNS and can be given to neonates and children.

Prevention

- There is no mechanism to prevent the transmission of genital mycoplasmas either horizontally or vertically, and no vaccine is available.

Future research

- Future research may involve the role of *U. urealyticum* in preterm infants, especially those with morbidities of prematurity, and the development of a vaccine or more effective antimicrobial agents against genital mycoplasmas.

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Chapter 93

Head lice (pediculosis)

See also Chapters 3, 21.

Name and nature of organism

- Head lice (*Pediculus humanus capitis*) are arthropods.
- Humans are the only known host. The lice almost exclusively live on the scalp and attach to the hair shafts by means of specialized claws.
- The parasites feed on scalp blood, accessed by piercing the skin. Without a blood meal (i.e. after leaving the host), head lice usually die within 2–3 days but can rarely survive a few days longer.
- The adult head louse has a lifespan of ~1 month.
- During adult life, the ♀ lays between 5 and 10 eggs each day, which are attached to the hair shafts.
- Nymphs emerge from the eggs after 6–10 days, develop through several nymphal stages, and become adults after about 10 days.
- Adult lice are ~1–3mm in size. Eggs measure ~0.8–1mm but are still visible to the naked eye.
- Technically, 'nits' are empty egg cases (not unhatched eggs).

Epidemiology

- Recent large-scale epidemiological data are scarce.
- The most recent regional studies in the UK have reported a prevalence of between 2% and 10% among school-aged children. The prevalence is highest in preschool and early 1° school children.
- Infestation of family members (most frequently siblings) of the index case is common.

Transmission

- Head lice are wingless insects and cannot fly or jump.
- Transmission predominantly occurs via close physical contact (head to head).
- There is limited evidence that transmission can also occur via fomites (e.g. combs, hair accessories, hats, and clothing).

Clinical features and sequelae

- Many infestations are asymptomatic.
- Pruritus affecting the scalp is the commonest, and frequently the only, symptom reported. Pruritus tends to occur within 2–6 weeks during the first infestation, but considerably earlier during subsequent infestations (often within 1–2 days). It is thought that this phenomenon is based on a delayed-type hypersensitivity reaction.
- Other potential signs include localized erythema and urticaria, as well as post-auricular and cervical lymphadenopathy.
- 2° bacterial infection (most commonly with *S. aureus*) may occur.
- Head lice infestation can cause considerable distress to affected children and their families. Related bullying, social stigmatization, and exclusion from school can have a significant impact on the child's emotional and psychological well-being.

Diagnosis

- The diagnosis of active head lice infestation is based on the detection of live lice.
- The entire scalp should be combed thoroughly with a detection comb (finer-toothed than a conventional comb); wetting of the hair or use of hair conditioner can facilitate this process. The comb should be inspected for the presence of live lice after each pass, which may be aided by the use of a magnifying glass.
- Eggs should also be searched for, although their presence does not confirm active infestation. Viable eggs are tan- or brown-coloured, while hatched eggs are white or opaque. Eggs further than a few inches away from the scalp are unlikely to be viable, as new eggs are laid close to the scalp.
- Eggs should not be confused with dandruff; the latter is easily removed with a comb, whereas eggs stick firmly to the hair shafts.

Management and treatment

General principles

- Treatment should only be initiated when live lice are identified.
- The entire family of an index case should be screened; all affected individuals need to be treated to break the cycle of re-infestation within the household.
- General household 'decontamination' measures (e.g. furniture and carpets) are unnecessary, as lice cannot survive for long periods without host contact. However, lice have been reported to migrate onto bed linen, towels, and clothes. Although potential re-infestation from these sources continues to be debated, it may be advisable to change and wash these items regularly during the treatment phase. Machine laundering at 50°C or above is effective for decontaminating fabrics.

Topical pediculocidal treatment

- Four 'conventional' pediculocidal agents (which are essentially neurotoxic insecticides) are licensed for the treatment of head lice in the UK: malathion, permethrin, phenothrin, and carbaryl. However, the production of the latter two agents has been discontinued in the UK. There are no reports of neurotoxic side effects in patients when treatment is applied correctly. All preparations are available over the counter. Various formulations are available; lotions and liquid formulations are more effective than shampoos.
- Before the mid 1990s, all 'conventional' pediculocides showed efficacies in excess of 80% in clinical trials. In the past decade, several studies have reported a significant decline in the efficacy of these agents. Subsequently, *in vitro* studies have documented the emergence of resistance in the parasite population (based on genetic changes). Although a considerable proportion of 'treatment failures' are thought to be due to incorrect use of treatment and re-infestation, rather than resistance, it is recommended to use a different class of pediculocide for re-treatment (note: permethrin and phenothrin both belong to the class of pyrethroids).
- Relatively recently, two new topical preparations for the treatment of head lice have been licensed—a dimeticone-based solution and a solution containing isopropyl myristate/cyclomethicone. More recently, a further dimeticone-based product has become available in the UK. Unlike 'conventional' pediculocides, their pediculocidal action is not based on neurotoxic effects but is thought be due to disruption of the water balance in lice. Early trials assessing these preparations reported cure rates of between 70% and 82%.
- Pediculocidal treatment has to be applied on two occasions, 7 days apart, as all agents primarily kill nymphs and adult lice, while their ovicidal activity is relatively poor. This time gap allows surviving eggs to hatch; new nymphs are then killed by the second application.
- The hair should be re-examined 2–3 days after the second application to detect any remaining lice (note: treatment will not remove eggs). If live lice are detected, treatment should be repeated with another class of pediculocidal agents.

Ivermectin

- In recent years, ivermectin has received considerable attention following the publication of a cluster RCT in a high-profile journal that compared the efficacy of oral ivermectin with malathion in children who previously failed topical head lice treatment. However, the available data regarding the safety of oral ivermectin in children are limited, and it therefore appears difficult to justify the systemic use of this drug for the treatment of head lice, considering that there are several alternative treatment options with no or only minor safety concerns.
- A recent randomized, double-blind, placebo-controlled trial reported that topical ivermectin lotion (0.5%) achieved a cure rate of 74%. The frequency and severity of side effects were similar to those observed in

the placebo group. Subsequent safety studies of topical ivermectin have also not identified any major concerns. However, clinical experience with topical ivermectin remains limited to date, and currently there are no commercial topical preparations of ivermectin available in the UK.

Alternative forms of treatment

- Wet combing, based purely on the mechanical removal of lice, is a potential alternative to treatment with pediculocides. Most studies reported cure rates ranging between 50% and 75% with this approach. A number of different louse and nit combs, as well as combined kits, are commercially available (e.g. the Bug Buster Kit—available on NHS prescription). Combs used for wet combing are even finer-toothed than regular combs and detection combs. Any shampoo or conditioner can be used for this process, as these merely act as lubricants. Wet combing sessions (lasting for >30min) should be carried out every 3 days for 14 days (i.e. five sessions in total). Although labour-intensive, compared to pediculocidal treatment, there are no potential side effects, and there are some data to suggest that many parents favour this approach over pediculocidal treatment, when offered the choice.
- There is no convincing evidence that 'natural treatments' traditionally used in some cultures (e.g. herbal remedies, vinegar, alcohol, mayonnaise) are effective; some of these 'treatments' are potentially dangerous (e.g. petroleum, kerosene).

Prevention

- There are no effective strategies to prevent head lice infestation. Head lice have no preference for 'clean' or 'dirty', or 'short' or 'long' hair. Also, contrary to common belief, the risk of head lice infestation is not related to social status.
- Although there is little evidence for this route of transmission—sharing of combs, brushes, and hair accessories with individuals known to have head lice should be avoided.
- Exclusion from school is not justified; however, prompt treatment should be encouraged.

Future research

- Knowledge about local resistance patterns within the parasite population may aid in improving treatment success rates.
- Although the mode of action of dimeticone- and isopropyl myristate/cyclomethicone-based preparations makes the development of resistance relatively unlikely, this aspect requires close monitoring.
- All currently available treatment options are associated with considerable failure rates. Outside study conditions, treatment success rates are likely to be even lower. Therefore, novel agents and treatment methods should be actively investigated.

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Chapter 94

Norovirus

Name and nature of organism

- Noroviruses were first identified in 1972 as a cause of the illness commonly known as the 'winter vomiting disease', characterized by the sudden onset of self-limiting vomiting and diarrhoea that typically peaked during the colder months. The virus was visualized by immune EM examination of stools of volunteers challenged with faecal filtrates from students affected by an outbreak of gastroenteritis in 1969 in Norwalk Ohio, as well as in stools from individuals affected in this school outbreak. The Norwalk virus, the prototype agent of the genus *Norovirus* (previously denoted as 'Norwalk-like viruses'), belongs to the *Caliciviridae* family.
- Four other genera are now described in the *Caliciviridae* family: *Sapovirus* (previously called 'Sapporo-like viruses'), *Lagovirus, Vesivirus*, and *Nebovirus*. Of these, norovirus and sapovirus infect humans and are thus also referred to as 'human caliciviruses'; the other genera infect animals. Norovirus have been associated with near 90%, and sapovirus 10%, of human calicivirus infections.
- Noroviruses are subdivided into five genogroups, based upon sequence homology. Genogroups GI, GII, and GIV include human pathogens, and multiple genotypes are recognized within each genogroup.
- Noroviruses are positive, single-stranded RNA viruses, with no lipid envelope, of ~40nm in diameter. They are therefore not so easily inactivated by alcohol-based gels but are inactivated by chlorine-based detergents.

Epidemiology

- Noroviruses infect people of all ages, from infants to the elderly. Most infected individuals will have an asymptomatic infection or mild disease, although moderate to severe disease requiring oral and/or IV rehydration is not uncommon. Children <5 years, immunocompromised persons, and elderly patients are at a greater risk for severe norovirus disease.
- Two clinical scenarios have been documented for norovirus-associated infections: epidemic gastroenteritis associated with a common source exposure implicating individuals of all ages, and childhood endemic gastroenteritis implicating mostly children bellow 5 years of age.

- Noroviruses are the leading cause of epidemic gastroenteritis, causing >90% of non-bacterial, and >50% of all-cause, gastroenteritis outbreaks in many settings worldwide. Disease outbreaks are reported year-round, with peaks during months with cold weather in industrialized regions with temperate climates. Shellfish have been a commonly implicated source of outbreaks, although several other food products and contaminated water sources can cause small group to very large community outbreaks.
- Outbreaks have been reported in hospitals, cruise and battleships, schools, nursing homes, restaurants, summer camps, resorts, and other environments which combine gathering of people and a common food and/or water source. Large outbreaks, including hundreds, and even thousands, of affected individuals associated with water and/or food contamination have been reported in different regions throughout the past decades.
- Norovirus is second to rotavirus as a cause of acute endemic gastroenteritis in children in middle- and middle to high-income countries and is becoming the first cause in countries that have incorporated rotavirus vaccines such as the US and Finland. The role of norovirus in low-resource countries is less clear at the moment.
- Since the mid 1990s, most epidemics and endemic cases of norovirus infection globally have been caused by genotype II.4 strains. These strains have been associated with higher hospitalization and death rates than other genotypes. The proportion of outbreaks attributed to the New Orleans GII.4 strain increased from 19% to 58% between September and December in 2012.

Transmission, incubation period, and immunity

- Faecal–oral spread is the most important mode of transmission. In outbreak situations, a food or water source contaminated with norovirus explosively initiates the outbreak which continues for several days to weeks due to person-to-person transmission.
- Transmission from infectious vomit, both by mechanical transmission from environmental surfaces (e.g. hand/mouth contact) and aerosolization, are likely to propagate spread.
- Common sources of food-borne outbreaks are contaminated shellfish and salads, and water-borne outbreaks such as contamination of water treatment plants with sewage water or stools of an infected individual.
- Person-to-person spread among contacts of 1° cases further propagates and prolongs epidemic outbreaks. Several characteristics of noroviruses facilitates spread:
  - Low infectious dose (<10 particles)
  - Prolonged shedding (2–4 weeks), even after symptom resolution
  - Viral stability in the environment.

- Repeat infections are common, possibly due to wide strain diversity, with incomplete cross-protection and likely short-lived immunity against repeated asymptomatic mild infections.
- Incubation period is typically 24–48 hours (range 18–72 hours).
- The difficulty in diagnosing norovirus infection and the lack of correlates of protection have made it challenging to assess immunity after norovirus infection. Early volunteer studies suggest that protective immunity after norovirus exposure could be short-lived (i.e. 6–14 weeks), although more recent studies suggest that protective immunity could actually last several years. The decreasing duration of symptoms with increasing age in one community cohort study and the fact that repeated symptomatic infections with the same genogroup did not occur in another child cohort study suggest the possibility of protection against symptomatic disease after natural norovirus infection against strains of the same genogroup.
- Interestingly, in volunteer studies, ~13–40% of exposed persons never became infected, and only 50% developed illness. Recent research suggests that host genotype is a prominent factor in the development of norovirus infection—norovirus infection depends on the presence of specific human histo-blood group antigen receptors in the gut of susceptible hosts.

Clinical features and sequelae

- Disease is characterized by acute onset of nausea, vomiting, abdominal cramps, and non-bloody diarrhoea. Fever is reported in nearly half of all patients and typically subsides within 24 hours. Generalized myalgias, malaise, and headache can be prominent.
- Sudden onset of continuous, severe profuse vomiting is often the first sign of disease. Some studies suggest that vomiting is relatively commoner in children >1 year, whereas diarrhoea is commoner in infants. Importantly, vomiting or diarrhoea can be the only symptom of norovirus infection. Stools are characteristically non-bloody, lack mucus, and may be loose to watery.
- Symptoms in less severe cases typically resolve in 2–3 days but may persist for 4–6 days. In children requiring emergency room care or hospitalization, vomiting and fever last 1–4 days, and diarrhoea 4–7 days, with a lower severity score, compared to rotavirus infections, but with nearly 60% of cases within the moderate to severe category, according to the Vesikari score.
- Disease can be more severe in children <12 months, elderly adults, and patients with underlying disease who acquire infection during nosocomial outbreaks. Norovirus has been associated with necrotizing enterocolitis and post-infectious irritable bowel syndrome, which resolves after 3 months, although this requires more study. Benign infantile seizures have also been associated with norovirus infections. Prolonged viral shedding with vomiting for over a year has been reported in paediatric oncology patients.

Diagnosis

- Norovirus gastroenteritis may be suspected, based on clinical manifestations alone; studies have identified and validated four epidemiological features of norovirus disease that can be useful in determining if norovirus is the causative agent in an outbreak, in the absence of access to diagnostic testing:
  - Vomiting in more than half of affected persons
  - Mean (or median) incubation period of 24–48 hours
  - Mean (or median) duration of illness of 12–60 hours
  - Absence of bacterial pathogen in stool culture.
- Identification of the viral aetiology is not generally required for management. In an outbreak situation, aetiologic diagnosis can be important for monitoring success of interventions to interrupt transmission and for prevention of future outbreaks.
- Aetiologic diagnosis rests on finding noroviruses in a faecal or vomitus specimen of patients with suspected gastroenteritis or, less commonly, in detecting a significant rise in antibody titres in the sera of an infected patient.
- Genomic amplification by RT-PCR or other nucleic acid-based testing in stool samples is currently the most widely used diagnostic test. Antibody-based testing methods to detect norovirus in stools have been developed, based on the use of virus-like particles (VLPs) to generate hyperimmune reagents or monoclonal antibodies. Immunoassays have lower sensitivity and specificity than RT-PCR. In any case, diagnostic tests must be interpreted with caution and together with epidemiologic and clinical factors, as well as negative results for other tests such as rotavirus. Asymptomatic shedding is common, and detection alone does not necessarily establish norovirus as the aetiology of acute illness, especially for the interpretation of RT-PCR, which can detect a low stool viral load (<100 particles/g).
- PCR techniques are also used widely for viral detection in food and environmental samples.
- Noroviruses were first identified by EM, aided by the addition of convalescent sera which causes clumping of virus particles. However, EM is relatively insensitive for the aetiologic diagnosis of norovirus and is not routinely used outside research laboratories.

Management and treatment

- First-line therapy for uncomplicated norovirus gastroenteritis should be ORS that provide essential electrolyte replacement plus sugar (glucose or sucrose).
- Significant dehydration or the inability to tolerate oral hydration may warrant early parenteral fluid plus electrolyte replacement.
- As tolerated, initiating oral caloric intake as early as possible in the illness favours a more rapid patient recovery.
- Antibiotic therapy is not indicated for norovirus gastroenteritis.

- Studies have demonstrated that antimotility agents, such as diphenoxylate or loperamide, do not reduce intestinal fluid losses. Antimotility agents should be avoided in children <3 years, as they are associated with complications (ileus, lethargy, or even death).
- Ward outbreaks in paediatric units need prompt recognition and action to close the ward and stop transfer of children to other wards.

Prevention

- Prevention of norovirus outbreaks and reduction of ongoing outbreaks rely on identifying the mode of transmission and interrupting it by controlling contamination and reducing spread. This is especially important if contamination of water treatment plants is suspected.
  - Disinfection of environmental surfaces contaminated with vomitus and faeces with appropriate solutions is crucial. Depending on the extent of contamination, the facility or institution may have to be closed to interrupt transmission.
  - Molecular assays have been developed to detect noroviruses directly from contaminated products/water and could supplement prevention efforts. Identification of contaminated sources, together with intense outbreak investigation, in order to determine the origin of the potential contamination, is critical to appropriately control community outbreaks.
  - Strict personal hygiene is critical for the prevention of person-to-person transmission such as through food handler-associated transmission.
  - Food handlers should be excused from work during illness to prevent virus transmission.
- No licensed vaccines are currently available for the prevention of norovirus disease. One vaccine candidate, based on VLPs against GI and GII strains, is in advanced stage of development, moving into phase 2/3 trials in infants during 2015.

Future research

- Noroviruses cannot be cultivated at the moment, and animal models to investigate the pathogenesis and immunity are limited. The development of an animal model and/or cell culture system for cultivating noroviruses will be an important future step toward improving diagnosis and developing a safe and effective norovirus vaccine.
- Studies on immune correlates of protection from natural infection, duration of protection, and cross-protection could improve the prospects of vaccine development, although, as for rotavirus, it is probable that a vaccine will see the light in the absence of a reliable immunologic correlate of protection.
- Better information is needed to identify populations susceptible to infection, for whom the impact of short-term morbidity from gastroenteritis is great (e.g. military troops, travellers), and those at

highest risk of severe disease from norovirus infection (e.g. the elderly, infants).

- Systematic surveillance, using broadly reactive, state-of-the-art diagnostic assays, is needed to fully understand the true burden of noroviruses in the aetiology of severe gastroenteritis, particularly among high-risk populations such as children <5 years and older people. These evaluations are especially necessary in resource-poor countries where diarrhoea remains a leading cause of childhood death, causing 700 000 annual deaths in children below 5 years of age.
- Hospital control measures need further investigation, e.g. duration of ward closure.
- Efficacy and safety of vaccine candidates, as sole antigen or in combination with rotavirus antigens, are in the horizon.

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Chapter 95

Other fungal infections

Introduction

Fungal pathogens cause a wide spectrum of disease, ranging from mild superficial skin infections to life-threatening invasive infections in immunocompromised hosts. Recurrent or persistent superficial fungal infections (SFIs), as well as IFIs, in an otherwise healthy host should be considered as a potential presenting symptom of an underlying 1° immunodeficiency. Defects in the Th17 pathway are associated with recurrent and persistent mucocutaneous mycoses, while underlying defects in the IFN-γ/IL-12 pathway are increasingly detected in patients with endemic mycoses. Fungal infections include infections caused by either yeasts or moulds. This chapter will focus on endemic mycoses and dermatomycoses. Specific information about infections caused by *Candida, Aspergillus, Scedosporium, Fusarium, Cryptococcus* spp., and *Zygomycetes* can be found in the related Chapters 35, 47, 51.

Endemic mycoses

Epidemiology

The endemic mycoses are caused by fungal organisms restricted to specific geographical areas of the world, with the exception of *Sporotrix schenckii* (Table 95.1). Blastomycosis, (para)coccidioidomycosis, and histoplasmosis are the commonest. Infection mainly follows inhalation of the organism, and cutaneous manifestations develop 2° to lymphatic and haematogenous dissemination. The group of fungi causing endemic mycoses are commonly found in soil and characterized by their ability to grow in both a yeast form (at 37°C) and a mycelial form (25°C) and are therefore called 'dimorphic' fungi. Although these mycoses are rare in Europe, returning travellers and immigrants might present with them. In the last years, several cases have been described in patients originating from European countries without any travel history.

Causative organisms and clinical disease

Blastomyces dermatitidis

- *B. dermatitidis* infections are mainly localized to the lungs but can disseminate to multiple organs, including the skin.
- Infection is acquired by inhalation of conidia, and the incubation period is 30–45 days.
- Pulmonary blastomycosis may be an acute self-limited, and often unrecognized, infection but may progress to chronic and progressive infection.

Table 95.1 Dimorphic fungi causing endemic mycoses

Fungal organism	Geographic area
Blastomyces dermatitidis	• Zones with temperate climates in North America (Canada and the region between Ohio and Mississippi River valleys) • Central and East Africa

Coccidioides spp.	• Semi-desert areas on the American continent:
	  • *C. immitis*, mainly in California, US
	  • *C. posadasii*, mainly along the Mexican border and in Middle and South America
	• Tropical regions around the world

Histoplasma capsulatum	• Semi-desert areas on the American continent:
	  • *H. capsulatum* var. capsulatum in North America (Ohio and Mississippi River valleys), Middle and South America, southern Mexico
	  • *H. capsulatum* var. duboisii in tropical areas of Africa

Paracoccidioides brasiliensis	• Tropical regions in Central and South America, mainly Brazil, Columbia, Venezuela, Paraguay
Penicillium marneffei	• South East Asia
Sporothrix spp.	• All over the world (most cases reported from Japan, North and South America)

- Skin lesions are the commonest presentation of extrapulmonary disease, even in the absence of pulmonary involvement. Papules or papulopustules, verruciform plaques, single or multiple, with a tendency to ulceration, appear mostly on exposed surfaces and spread slowly.
- In immunocompromised patients, the severity of disease may be increased, but it is a less common opportunistic pathogen than *H. capsulatum* or *Coccidioides* spp.

Coccidioides species

- *Coccidioides* spp. *C. immitis* and *C. posadasii* mainly cause pulmonary infections (1° infection), often asymptomatic and self-limiting (75%), sometimes with dissemination to the skin and lymph nodes.
- Symptomatic disease typically presents with a flu-like illness or pneumonia 10–16 days after inhalation of conidia.
- Skin involvement (erythematous maculopapular rash, erythema multiforme, erythema nodosum) can be the only disease manifestation in some children.
- 1° infection in immunocompromised patients (HIV patients, compromised T-cell immunity, young infants) may result in severe fungal pneumonia and/or disseminated disease (bone, meninges).
- Progressive coccidioidomycosis develops months after 1° infection, with non-specific symptoms, including low-grade fever, anorexia, and weight loss.

Histoplasma capsulatum

- The mould form is found in moist soil, and its growth is enhanced by bat, bird, and chicken droppings.
- Most *H. capsulatum* infections are asymptomatic and have usually an incubation period of 1–3 weeks.
- Histoplasmosis presents in three ways: (1) acute 1° histoplasmosis with signs and symptoms of a flu-like illness; (2) progressive disseminated histoplasmosis, involving the reticuloendothelial system, with a subacute course and non-specific symptoms such as fever, weight loss, and fatigue, typically in infants <2 years of age; and (3) chronic cavitary histoplasmosis, characterized by progressive cough and dyspnoea.
- Progressive histoplasmosis is an AIDS-defining illness.
- Severe disease is commoner in infants and those with compromised T-cell immunity.
- Skin lesions are often molluscum contagiosum-like papules with a tendency to ulcerations and might resemble those seen in cutaneous cryptococcosis.

Paracoccidioides brasiliensis

- Paracoccidioidomycoses is also known as South American blastomycoses.
- Skin, mucous membranes, lymph nodes, and internal organs are mostly affected. Pneumonia is less common than in blastomycosis, coccidioidomycosis, and histoplasmosis.
- Clinical disease occurs months to years after infection and is rare in children.
- In the (sub)acute form, symptoms are related to the extensive involvement of the reticuloendothelial system (e.g. widespread enlarged lymph nodes, involvement of the spleen, liver, and bone marrow), while, in the chronic form, disease is either localized to the lungs or disseminated.

Penicillium marneffei

- Bamboo rats in South East Asia are the reservoir for *P.marneffei*.
- Inhalation (or by direct contact with rats) of conidia leads to chronic, disseminated disease most commonly observed in immunocompromised hosts (HIV patients, compromised T-cell immunity).
- Incubation period is up to 3 weeks.
- The development of molluscum contagiosum-like lesions on the face and trunk are quite characteristic, in addition to fever, bone marrow failure, generalized lymphadenopathy and hepatosplenomegaly, anorexia, and pulmonary infiltrates.

Sporothrix species

- Pathogenic species causing infections include, next to *S. schenckii, S. brasiliensis, S. globosa*, and *S. luriei*.
- Sporotrichosis is the result of direct inoculation of the skin.
- After an incubation period of 1–10 weeks (sometimes even longer), red, necrotic, and nodular lesions develop with a lymphangitic spread and tendency to ulceration.
- Disseminated disease is rarely observed and is associated with underlying conditions such as diabetes mellitus and HIV infection.

Differential diagnosis

Pulmonary infections caused by the dimorphic fungi need to be differentiated from each other, as well as from CAP, pulmonary TB, sarcoidosis, and malignant neoplasms localized in the lung. In immunocompromised patients, lung infections caused by filamentous fungi might present with similar non-specific signs and symptoms. If skin lesions are the main manifestation of an endemic mycosis, the differential diagnosis includes mycobacterial infections, CL, molluscum contagiosum, and syphilis. If lymphadenopathy, hepatosplenomegaly, and/or bone marrow failure are the dominant signs and symptoms, VL, leukaemia, lymphoma, and disseminated mycobacterial infections should be considered in the differential diagnosis. A detailed travel history, including outdoor activities undertaken, is crucial to guide investigations and will make particular diseases more or less likely.

Investigations

A definite diagnosis of a specific endemic mycosis requires microscopic demonstration of the fungus (with specific staining) in a clinical specimen and confirmation by culture (using specific media for fungi). Abnormalities on the CXR (focal or diffuse infiltrates, nodular or granulomatous lesions, cysts, and cavity formation in later stages of the disease) will not distinguish between the causative organisms. Current serodiagnostic tests have low sensitivity and specificity, and cross-reactivity. A significant decrease in the amount of specific antigens (histoplasmosis) or antibodies (paracoccidioidomycosis) has been associated with a successful response to treatment and can be used for monitoring disease activity. Eosinophilia may be an important clue in patients with coccidioidomycosis.

Treatment

Mild and moderate manifestations of endemic mycoses (not including penicilliosis) are treated with oral itraconazole. Both voriconazole and posaconazole show comparable, or even lower, MICs *in vitro*, when compared with itraconazole, and may be an alternative in selected cases. Coccidioidal meningitis is treated with fluconazole in a high dose (800–1200mg/day). Fluconazole and voriconazole are, in general, preferred for CNS disease due to their enhanced penetration of the brain and CSF. More severe and disseminated disease requires treatment with amphotericin. Duration of treatment varies between 3 and 6 months (histoplasmosis, paracoccidioidomycosis, sporotrichosis) up to 12 months (coccidioidomycosis). For chronic disease and/or infections in immunocompromised patients, even longer treatment periods may be necessary. *Sporothrix* spp. show, in general, higher MICs to the azoles and amphotericin, compared with the other dimorphic fungi. Penicilliosis is treated with 2 weeks of amphotericin, followed by 10 weeks of oral itraconazole.

Outcome

Morbidity from dimorphic fungal infection is not well documented. Delayed diagnosis, poorly targeted treatment, the severity and extent of dissemination, and underlying immunodeficiency adversely affect the outcome. A retrospective cohort study, based on a US database of hospital inpatients stays, showed a crude mortality rate of 5% and 7% among children and adults,

respectively. Pulmonary infections can lead to the development of cysts and cavities and progressive lung disease, while skin manifestations often lead to severe and retracting scarring.

Mucocutaneous mycoses

Epidemiology

Superficial fungal infections of the skin and nails are listed by WHO as the third commonest ailments after headache and backache. Probably over 1.5 billion people suffer from fungal infections comprising mainly mucocutaneous mycoses. Most affected children are healthy, although recurrent and more severe infections are associated with acquired immunosuppressive conditions (e.g. HIV) or are a presenting symptom of an underlying 1° immunodeficiency characterized by impaired T-cell function (SCID) or IL-17 immunity (CMC, APECED syndrome, hyper-IgE syndrome).

Causative organisms and clinical disease

All fungi, yeast, and moulds are able to cause 1° mucocutaneous disease, although most fungal organisms will only cause infections in immunocompromised patients or when the integrity of the skin is disturbed. The dermatophytes are a group of three genera belonging to the group of filamentous fungi (moulds) and responsible for the majority of SFIs in otherwise healthy children. The dermatophytes are unique in their ability to utilize keratin as a nutrient source, i.e. they have a unique enzymatic capacity (keratinase). A common aetiological classification for superficial (mucocutaneous) fungal infections is those caused by dermatophytes as opposed to those caused by non-dermatophytes, e.g. yeasts (e.g. *Candida* spp.) and other moulds (e.g. *Madurella* spp.).

Dermatophytes

Causative organisms typically are members of the *Trichophyton, Microsporum*, and *Epidermophyton* genera (the dermatophytes) and are acquired from infected humans, animals, or soil. These fungi are keratinophilic and infect the superficial keratinized tissues (skin, nails, hair). Infections caused by those dermatophytes are called tinea (ringworm) and are mostly restricted to a specific area of the skin (e.g. tinea capitis = scalp ringworm). Onychomycosis, an infection of one or several nails by dermatophytes (tinea unguium), accounts for one-third of all dermatomycoses. Specific causative agents affect different parts of the body and different geographic areas. *Trichophyton* spp. are the commonest cause of tinea capitis in the US and UK, while, in Europe, tinea capitis is mainly caused by *Microsporon* spp. Onychomycosis of the toenails is, in 80%, caused by *T. rubrum*. In contrast, fungal infections of the fingernails are, only in 20%, caused by *T. rubrum*; most infections are caused by *Candida* spp.

Kerion celsi

A kerion celsi is an aberrant inflammation of the subcutaneous tissues, surrounded by follicular pustules, and is thought to be a hypersensitivity

reaction to the causative dermatophyte. The painful local inflammation may be accompanied by regional lymphadenopathy and fever.

Majocchi's granuloma

A Majocchi's granuloma is a nodular granulomatous perifolliculitis, primarily caused by *T. rubrum*, although other dermatophytes and fungi, like *Aspergillus* and *Phoma* spp., may be involved. The disease is characterized by inflammatory papular, pustular, or nodular lesions in a circumscribed area on one of the lower or upper extremities. In an immunocompromised host, the inflammation easily extends into the deeper subcutaneous tissues.

Infections by Candida and Malassezia species

Non-dermatophyte infections include mucocutaneous candidiasis (*Candida* spp.) and pityriasis versicolor caused by *Malassezia* spp. Mucocutaneous infections by *Candida* spp. range from relatively mild diaper dermatitis and oral thrush in the newborn to recurrent dermatitis, persistent oral thrush, and oesophagitis in immunocompromised patients (HIV, impaired T-cell immunity, CMC) and recurrent vulvovaginal candidiasis being associated with specific mucosal immune defects (e.g. dectin-1 deficiency). Persistent and/or recurrent onychomycosis, as observed in patients with CMC, is not necessarily caused by *Candida* spp., and quite often common dermatophytes are the causative organisms, despite the name of this syndrome.

Malassezia spp. are a group of lipid-dependent yeasts and commonly colonize the skin. Skin infections are characterized by multiple scaling, and oval and macular lesions in a patch distribution over the upper portions of the trunk and proximal areas of the arms and neck. In children, facial involvement is quite common. Lesions are relatively darker in winter (brownish; hyperpigmented) and fail to tan during summer (fawn-coloured; hypopigmented).

Mycetoma

Mycetoma, mainly caused by *Madurella* spp., is a painless chronic granulomatous infection, characterized by extensive subcutaneous masses, usually with draining sinuses. Untreated, the disease will extend to deeper tissues and bones and leads to massive lesions and distant lymphatic metastases. Mycetoma can affect all parts of the body but are mostly localized on the feet (70%). The disease is endemic in tropical and subtropical regions, and the highest prevalences are found on the African continent.

Differential diagnosis

Lesions caused by dermatophytes (tinea corporis, tinea capitis, tinea cruris) are easily mistaken for atopic, seborrhoeic, or contact dermatitis and inflammatory skin disorders like erythema annulare and psoriasis. *Malassezia* spp. may complicate seborrhoeic and atopic dermatitis, making a clear differentiation difficult.

A kerion celsi is easily misdiagnosed as a bacterial abscess or cellulitis.

The differential diagnosis of Majocchi's granuloma is wide and depends on the characteristic features in an individual patient. CL, furunculosis, and folliculitis should always be differentiated from Majocchi's granuloma.

A fungal mycetoma (eumycetoma) should be differentiated from an actinomycetoma caused by *Actinomyces* and *Nocardia* spp. Actinomycetoma

presents as a more rapid infection, lesions being more diffuse, without a clear margin, and displaying numerous draining sinuses.

Investigations

Identification of the causative organism is important to target treatment. Direct microscopy of a KOH preparation (skin or nail scrapings, hairs) should be used to confirm the diagnosis of a dermatophyte infection. Culture on specific fungal media is indicated to specifically identify the dermatophyte and to be able to perform susceptibility testing in selected cases.

Skin scrapings or swabs can be used to detect *Candida* and *Malassezia* spp. by streaking them on Sabouraud agar or Sabouraud agar covered with lipids (e.g. sterile olive oil) to facilitate growth, respectively. Highly selective and specific media are available as well (CHROMagar for *Candida*; CHROMagar for *Malassezia*).

Suspicion of a Majocchi's granuloma should lead to direct microscopical examination of the extracted hairs where the fungal hyphae can be observed by using KOH and is positive in over 75% of the patients. If negative, a calcofluor white stain or an FNA might be used for cytological examination. The causative fungus needs to be identified by culture.

Examination of the grains (sclerotia = aggregates of fungal hyphae) seen in mycetoma should be performed to obtain a definitive diagnosis. KOH examination of a grain will reveal a diagnosis in most of the cases. Ideally, a surgical biopsy of the affected subcutaneous tissue, including the characteristic grains, should be used for histology and culture.

Molecular identification methods for both dermatophytes and fungi causing mucocutaneous infections are in development but not yet commonly used in clinical practice.

Besides investigations done to identify and treat the fungal infection, additional examinations need to be performed to exclude an underlying immune disorder (e.g. neutropenia, lymphocytopenia, impaired IL-17 response, mutations in STAT-1/STAT-3/CARD-9) in an otherwise healthy patient suffering from persistent or recurrent mucocutaneous fungal infections outside the neonatal period. The presence of obvious risk factors, like chronic use of oral or inhalation steroids and diabetes mellitus, need to be considered. If autoimmune endocrinopathies are present, a diagnosis of APECED syndrome should be suspected.

Treatment and outcome

Tinea corporis/cruris is primarily treated with topical formulation of terbinafine and has a cure rate of around 80%. Uncomplicated dermatomycosis caused by *Candida* spp. can be treated with topical miconazole. Tinea capitis is unlikely to respond to topical treatment and needs systemic treatment. Terbinafine is the first-choice oral treatment for infections caused by *Trichophyton* spp., while itraconazole is preferably used for *Microsporon* infections. Griseofulvin can be used as well but is less efficacious for *Trichophyton* spp., compared to terbinafine.

A kerion celsi and Majocchi's granuloma are treated as well with an oral antifungal agent with activity against the causative dermatophyte. Addition of a glucocorticoid to the treatment of a kerion celsi did not show any difference in cure rates and should therefore be discouraged.

Topical antifungal therapy (ciclopirox, amorolfine) is only used for superficial onychomycosis affecting up to one-third of the nail plate and <3 out of ten nails. Oral treatment with itraconazole, terbinafine, and, in selected cases, fluconazole (if susceptible *Candida* spp. are identified, only minority of cases) is the treatment of choice for more extensive disease. Prolonged treatment duration is necessary, e.g. a minimum of 6 and 12 weeks for fingernails and toenails, respectively. Relapse of infections remains a problem in many patients.

Mucosal candidiasis is treated with an oral azole, either fluconazole or itraconazole, although the need for repeated or prolonged treatment may result in azole resistance. In patients with an underlying immunodeficiency, azole prophylaxis or intermittent treatment may be indicated. Oral thrush in neonates and infants can be treated with topical miconazole. Superficial infections caused by *Malessezia* spp. are treated with oral fluconazole or itraconazole.

Eumycetoma should be treated with a combination of medical and surgical treatment. Itraconazole is, generally speaking, the drug of choice, but susceptibility testing of the causative fungus needs to be performed. Successful outcome depends on an early diagnosis.

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Chapter 96

Human papillomavirus

See also Chapters 19, 20, 34, 37.

Name and nature of organism

- HPV are small, non-enveloped, double-stranded, epitheliotropic DNA viruses. Sequencing of the capsid gene has identified >100 different types.[1]
- HPV are divided into cutaneous and mucosal types, depending on the epithelium they infect. Approximately half are mucosal HPVs belonging to the α-papillomavirus (α-PV) genus. Mucosal HPV are split into high-risk (oncogenic) and low-risk groups (non-oncogenic) types. The remainder are cutaneous HPVs, including the β-, γ-, μ-, ν-PV genera, and α-PV species 2, 4, and 8.
- The low-risk HPV types 6 and 11 are found in the vast majority (>90%) of anogenital warts.
- High-risk (oncogenic) HPV are involved in 100% of cervical cancers and 90% of anal cancers (HPV-16, 18). The association is less for other cancers, as around 40% of vulvar and vaginal cancers (HPV-16, 31, 33), 12% of oropharyngeal, and 3% of oral cancers are due to oncogenic HPV.
- Types 16 and 18 cause about 50% and 20% of cervical cancers, respectively.
- Cutaneous HPV types of α-PV species 2, 4, and 8, μ-, ν-, and γ-PV are those primarily responsible for cutaneous warts.
- The HPV life cycle is only completed in fully differentiated squamous epithelia, with infection of the basal cell layer occurring following minor trauma. Viral gene expression influences the proliferation and maturation of keratinocytes and results in growth of a benign tumour. Virus assembly does not lyse keratinocytes; the infectious virus is shed with desquamating cornified cells.

Epidemiology

Non-genital cutaneous warts

- Cutaneous warts are uncommon in infancy, increase in frequency in childhood, and reach a peak in the teenage years, occurring with equal frequency in both sexes. They are seen worldwide and in all age groups, with an overall prevalence of ~7–12%; most people will have had warts at some time.
- They are commonest, with a prevalence of up to 20% in school-aged children.
- Warts usually regress spontaneously; ~23% resolve within 2 months, and 65–78% within 2 years; in a UK study, 90% of children with warts at age 11 had cleared them by age 16 years.[2]

- Cell-mediated immune responses are important for host control of infections; impaired cell-mediated immunity is associated with markedly increased incidence and extensive spread of viral warts, e.g. after organ transplantation, HIV infection, chronic lymphatic leukaemia, and lymphoma.
- Immunosuppressed individuals often have multiple HPV types, notably cutaneous β-PV types. These HPVs were previously thought to occur only in the context of the rare genodermatosis epidermodysplasia verruciformis but now appear to be widespread in normal skin and hair follicles of the general population from early childhood, and they are more prevalent in immunosuppressed individuals.

Anogenital warts

- Genital warts are a very common STI.
- Anogenital HPV prevalence peaks in young women and declines toward middle age. In the UK, seroprevalence data show that 10.7% of 10- to 29-year-old women are seropositive. Overall, about 25% of women between 14 and 59 years have HPV. ♂ seroprevalence has been found to be 1.2–73% overall, depending on the population, with more than half of the studies showing a prevalence ≥20%.
- For the sexually active population, the overall lifetime risk of acquiring HPV is about 75%.
- Risk factors for infection with HPV are the numbers of sexual partners, sexual debut at a younger age, oral contraceptive use, and smoking. Risk factors for persistent HPV infection, cytological abnormality, and invasive cancer are HPV type, increasing age, smoking, and immune deficiency.
- Only around 10% of all HPV-positive individuals have clinically evident lesions.
- Most genital HPV infections are transient and are cleared within 2 years, with 70% clearance by 12 months and 90% by 2 years.
- High-risk HPV prevalence varies worldwide, with higher prevalence in Eastern Europe (21%) and sub-Saharan Africa (24%) in young women.

Aerodigestive warts

- Oral warts are rare in children, with an overall prevalence estimated at 0.03%. Warts in the upper airway, predominantly the larynx, are seen in the rare condition recurrent respiratory papillomatosis (RRP), which has a bimodal distribution, occurring in children under 5 years (mother-to-child transmission) or adults through STI.

Transmission

Cutaneous warts

- HPV transmission occurs by direct skin-to-skin contact with individuals with clinical or subclinical HPV-associated lesions, or indirectly via contaminated surfaces and objects, e.g. in swimming pools and bathrooms. Although the risk of transmission is considered to be low, HPV can resist desiccation, freezing, and prolonged periods outside host cells.

- Auto-inoculation from the lesion to surrounding skin is frequent.
- Productive infection and induction of hyperproliferation are initiated when the virus enters proliferating basal epithelial cells, and this requires abrasion or other minor trauma to the epithelium.
- The incubation period ranges from 1 to 6 months; however, latency periods of ≥3 years may occur.

Anogenital warts

- Transmission usually occurs by direct contact, which can be with clinical lesions, inapparent lesions or genital fluid containing infectious virus, and auto-inoculation (including digital–genital transmission).
- Once believed to be low, studies of HPV vertical transmission rates have shown inconsistent results, probably due to the heterogeneous nature of the clinical trials. A systematic review of vertical HPV transmission showed a pooled mother-to-child HPV transmission of 6.5%, higher after vaginal delivery than Caesarean section (18.0% versus 8.0%). Perinatally acquired lesions may not become clinically apparent for up to 2 years.
- The exact incubation period is unknown. Estimates are between 1 and 9 months, with a median of 3 months, but can be as long as years.
- Persistent HPV infection is a risk factor for neoplasia. Cytological abnormalities can be detected around 7 years after infection; invasive cancer may then follow another decade or two later.
- In prepubertal children, HPV can be acquired through non-sexual contact; however, studies have shown that a significant proportion of children with anogenital warts have been sexually abused.

Aerodigestive warts

- Because the skin of the hand is a common site of infection, most oral warts in children develop from orocutaneous transmission; as in adults, orogenital transmission is also possible.
- Respiratory papillomatosis is probably transmitted during vaginal birth.

Clinical features and sequelae

Clinical manifestations depend on the HPV type involved, the anatomical location, and the immune status of the host (Table 96.1).

Cutaneous warts

- Traditionally classified as: common warts (verruca vulgaris); palmoplantar warts (verruca plantaris), including superficial (mosaic) and deep (myrmecia) types; and plane/flat warts (verruca plana).
- In children, the majority (70%) have common warts, and one-quarter have plantar warts; plane warts are less common.
- Persistent wart infections are common, as HPV has evolved mechanisms to evade immune surveillance. However, a successful immune response is eventually generated in most cases; two-thirds of cutaneous warts regress spontaneously within 2 years, and multifocal lesions often regress simultaneously. The rate of clearance is influenced by viral type, age of the patient, and extent and duration of the warts and, in particular, the host immune status.

Table 96.1 Clinical and virological features of warts in childhood

Name	HPV types*	Common sites of infection	Clinical features
Common warts (verrucae vulgaris)	2, 4 (1, 7, 26, 27, 29, 41, 57)	Usually extremities, especially dorsa of hands/fingers, but may occur anywhere (rarely, oral)	Well-defined papule with irregular, 'cauliflower' surface. Size varies from 1mm to >2cm. Skin-coloured to brown to grey. Single or multiple. Clustering and satellite lesions may develop, and koebnerization (extension of lesions through trauma) is seen
Plane or flat warts (verrucae plana)	3, 10 (28, 29)	Dorsa of hands, face (cheek, chin, forehead)	Flat-topped, round/polygonal, smooth or slightly hyperkeratotic. Often multiple, forming confluent plaques. May koebnerize. Facial lesions often flatter and pigmented, and hand lesions more elevated and hyperkeratotic
Deep palmoplantar warts (verruca plantaris; myrmecia)	1 (2, 60, 63, 65)	Usually occur on pressure points of feet	Single, painful, endophytic, deep nodules with hyperkeratotic surface overlying soft keratinous debris and circumscribed by hyperkeratotic ring. Punctate bleeding or 'black dots' when pared (thrombosed dermal capillaries)
Superficial palmoplantar (mosaic) warts	2	Usually plantar	Painless, superficial, often recur, difficult to eradicate, may coexist with myrmecia
Epider-modysplasia verruciformis	5, 8 (β types)	Any site	Highly polymorphic; red macules and plaques; plane wart-like lesions; pityriasis versicolor-like lesions, papillomas and seborrhoeic keratosis-like lesions. Malignant conversion to squamous cell carcinoma occurs preferentially in sun-exposed sites in the third to fourth decades
Genital warts (condyloma acuminata)	6, 11 (16, 18, 2, 27, 57)	On or around the vagina, penis, anus (rarely oral)	May present as small verrucous papules; discrete, flat, smooth-topped papules or plaques, and as large exophytic/hypertrophic masses. Often asymptomatic, but may cause pruritus and bleeding
Recurrent respiratory papillomatosis (juvenile onset)	6, 11 (16, 18)	~95% involve the larynx, but may occur anywhere in the respiratory tract from the node to the lung	Recurrent growth of benign papillomas in the respiratory tract. Single or multiple. Multinodular and exophytic. Frequently causes hoarseness, poor cry, progressive dyspnoea, or stridor, and may present as an acute respiratory emergency

* Commonest HPV types involved are presented first, followed by other less frequently involved types in brackets.

Mucosal human papillomavirus-associated disease

- HPV infection in the oral mucosa is characterized by focal epithelial hyperplasia of 1–5mm size.
- Respiratory papillomatosis is a rare growth of benign papillomas in the respiratory tract, which may be single or multiple, multinodular, and exophytic, mainly on the vocal cords and larynx, presenting as a voice change, an abnormal cry, and stridor, and may present as an acute respiratory emergency. HPV-11-associated disease is more severe than HPV-6.
- Anogenital warts (condylomata acuminata) may present as small verrucous papules, discrete, flat, smooth-topped papules or plaques, and as large exophytic/hypertrophic masses. They are often asymptomatic, but may cause pruritus and bleeding, have a cauliflower-type shape, and are mostly multiple, with size varying from mm to several cm. They occur in ♀ on the vulva or perianal area, the cervix, or vagina. In ♂, the penis, scrotum, anus, and perianal area may be affected.

Human papillomavirus in the immunocompromised

- Warts occur more frequently in the immunocompromised child, and an unusually severe infection with warts should alert the clinician to investigate for an immune deficiency, either acquired or congenital.
- HIV-infected adolescents, even those with normal CD4 counts, tend to have a prolonged persistence of HPV.
- A rare HPV-associated disease in the immunocompromised is the genodermatosis epidermodysplasia verruciformis. Skin lesions may be highly polymorphic; red macules and plaques; plane wart-like lesions; pityriasis versicolor-like lesions, papillomas, and seborrhoeic keratosis-like lesions. Malignant conversion to squamous cell carcinoma occurs preferentially in sun-exposed sites in the third to fourth decades.

Diagnosis

- Visual inspection of warts can require internal examination, depending on the site (speculum, proctoscopy, or urethral meatoscopy).
- Histological and other laboratory tests, including HPV DNA detection and serology, are usually unnecessary and unhelpful in the diagnosis of most cases. In certain cases, diagnostic failures can lead to significant morbidity.
- The differential diagnosis of lesions may be wide, from syphilis to cancer.
- Knowledge of the precise infecting HPV type does not necessarily assist in identifying the likely nature of infection. For example, the presence of DNA from high-risk mucosal types in a genital wart is not an unequivocal indication of a sexual mode of transmission, and the presence of β-PV types does not occur exclusively in epidermodysplasia verruciformis or other immunosuppressed states.

Management and treatment

- There is no curative treatment for HPV, and many warts disappear spontaneously. Recurrence of warts after treatment is common.
- Indications for treatment are pain, interference with function, and psychological morbidity.
- No treatment may be a reasonable option, as ~23% of warts resolve spontaneously within 2 months, and 65–78% within 2 years. A wide range of treatments is currently available; none is 100% effective, and treatments may be needed for different types of warts and those at different anatomical sites.
- There is a lack of evidence regarding the efficacy of treatments for non-genital warts. A Cochrane systematic review recommended topical salicylic acid formulations as first-line treatment, since they are effective and safe, with clearance rates of 73% in 6–12 weeks.[3] One RCT has shown cryotherapy was superior for common warts. Planar warts showed no difference between cryotherapy, salicylic acid, or a wait-and-see approach. Although other treatments (e.g. topical dinitrochlorobenzene, fluorouracil, intralesional bleomycin and IFNs, photodynamic therapy) may have a therapeutic effect, none have significant advantages over simpler, safer topical salicylic acid preparations or cryotherapy, and their suitability/safety for children has not been clearly determined.
- There is similarly insufficient evidence to direct first- and second-line treatments for genital warts. Topical podophyllotoxin, imiquimod, trichloroacetic acid, cryotherapy, and electrosurgery/laser are all used. However, their suitability/safety for children has not been clearly evaluated.
- Immunomodulators: imiquimod 5% cream (apply once, three times a week, for up to 16 weeks; wash off with soap and water after 6–10 hours). This immune enhancer stimulates the production of IFN and other cytokines but may cause depigmentation.
- Warts in respiratory papillomatosis may require repeated surgical debulking, usually by microdebridement and laser procedures. Agents, such as topical cidofovir, may increase the interval between the need for these procedures.
- For detecting cellular abnormalities associated with malignancy in women later in life, screening by regular Papanicolaou smears is performed.

Prevention

- Patient education: avoid direct contact with warts from other people or other parts of the body; avoid sharing socks, shoes, and towels; wear flip-flops when using communal showers. Warts should be covered with waterproof tape in wet environments such as showers and swimming pools.
- Exclusion of children with warts from day-care facilities, school, or sports activities is not necessary.

- Condom use reduces the risk of acquiring HPV by 70% if condoms are reportedly used 100% of times. As transmission occurs via skin-to-skin contact, condoms do not completely prevent infection.
- Currently, there are two HPV vaccines used globally on the market: a quadrivalent HPV vaccine and a bivalent HPV vaccine. The former covers HPV types 6, 11, 16, and 18 and uses aluminum hydroxyphosphate sulfate as an adjuvant. Bivalent HPV vaccine covers types 16 and 18 and uses an adjuvant called AS04, which is a combination of aluminum hydroxide and monophosphoryl lipid A.
- In clinical trials, the vaccine efficacy for both vaccines was very high (≥90%), with the prevention of precancerous lesions associated with HPV-16 or 18 in those without evidence of prior infection. The first head-to-head trials showed similar results regarding virological and precancerous lesion endpoints for HPV-16/18. The immune response (neutralizing antibody titres in blood and cervical–vaginal secretions) appears better, and data suggest that more cross-protection also occurs with the bivalent vaccine. However, it is not clear whether this translates into differences in clinical outcome. Long-term studies are required to assess the later efficacy of both vaccines; persistence of protection has been shown for 8 years so far.
- Two-dose schedules appear adequate.
- Routine HPV vaccination of teenage girls (and, in some programmes, boys) is therefore recommended, and at least 40 countries have implemented HPV vaccination in their national immunization programmes (NIPs) by the beginning of 2012.

Future research

- There is a lack of evidence to guide treatment for cutaneous warts.
- No effective antiviral agents have yet been identified for HPV.
- Therapeutic vaccines for non-genital HPV conditions such as RRP.
- Cost-effectiveness of vaccinating ♂.

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Chapter 97

Parvovirus

Name and nature of organism

- Parvovirus B19 is a member of the *Erythrovirus* group of parvoviruses—small, non-enveloped, single-stranded DNA viruses.
- It binds specifically to P antigen or globoside that is present on erythrocytes, erythroblasts, megakarocytes, endothelial cells, and fetal liver and cardiac cells, explaining the clinical specificity.
- Parvovirus B19 tropism for proerythrocytes causes lysis of erythrocyte precursors, resulting in haemolysis and erythroid aplasia.
- Fifth disease (or erythema infectiosum) gets its name, because it was the fifth described classical childhood exanthem (just for interest, the others are: 1, measles; 2, scarlet fever; 3, rubella; 4, Duke's disease (which was probably never a separate entity), and 5, roseola.
- Slapped cheek syndrome refers to the characteristic pattern of the facial rash.
- Humans are the only known hosts of parvovirus B19.
- A novel parvovirus human parvovirus 4 has recently been identified. It is associated with the transmission of other blood-borne viruses, such as HIV and hepatitis C, but its clinical correlates remain uncertain.

Epidemiology

- Erythema infectiosum is a common disease worldwide.
- It is usually a benign infection of early childhood, although complications may arise in individuals with haemolytic disease, immunocompromised patients, and pregnant women.
- It affects children of all ages. In Europe, up to 10% of children are seropositive by 5 years, 50% by 10 years, and 75% by 30 years of age.[1]
- It is highly infectious, and a child with erythema infectiosum may infect up to 50% of susceptible household contacts.
- Outbreaks are common in childcare facilities and schools, with 10–60% of children being infected during an outbreak.
- Outbreaks occur most commonly in late winter and spring and have a 3- to 4-year cycle.
- Infection with parvovirus confers lifelong immunity.

Transmission and incubation period

- The incubation period of erythema infectiosum is 4–14 days but can be as long as 21 days.
- Children are infectious before the facial rash develops (Table 97.1). Parvovirus B19 can be detected in respiratory secretions and saliva during the prodromal period, which is usually 3–6 days before the rash. This partially explains why outbreaks occur, because it is hard to diagnose the disease during the most infectious period.
- The appearance of parvovirus B19 IgG and IgM coincides with the onset of the rash—when the rash appears, infectiousness goes down!
- It is generally spread via respiratory droplets.
- Vertical transmission from mother to fetus can occur.
- It can also be transmitted via blood and blood products, including packed cells, platelets, and clotting factors.
- Those with haemolytic disease or immune compromise have high viral titres in respiratory secretions and blood, and are infectious.

Table 97.1 Duration of infectivity by manifestations of parvovirus B19

Clinical condition	Duration of infectivity
Slapped cheek syndrome	Until rash appears
Polyarthropathy syndrome	Until joint symptoms occur
Papular purpuric gloves and socks syndrome	While symptoms are present
Transient aplastic crisis	For at least 7 days after symptoms start
Chronic persistent anaemia	Indefinitely in the immunocompromised host

Clinical features and sequelae

- In previously healthy children, erythema infectiosum is a benign, self-limiting illness with no long-term sequelae (Table 97.2).
- In 20–50% of children, the infection is asymptomatic.
- There is a prodromal period of mild flu-like symptoms: fever (30% of children), headache (20%), sore throat (15%), and myalgia. There may also be abdominal pain, nausea, fatigue, and rhinorrhoea. This usually lasts 3–6 days before the onset of the rash.
- Adults are more likely to develop arthralgias in the prodromal period than children.
- The characteristic rash of erythema infectiosum is an erythematous rash on both cheeks, with sparing of the nose, nasolabial folds, as well as circumoral and periorbital regions, giving the appearance that the cheeks have been slapped (Fig. 97.1). This rash is commonest in younger children. It usually lasts 1–4 days.

Table 97.2 Clinical associations of parvovirus B19 infection

Clinical condition	Typical host
Slapped cheek syndrome	Healthy child
Asymptomatic infection	Healthy child or adult
Respiratory illness with no rash	Healthy child or adult
Papular purpuric gloves and socks	Healthy child or adult syndrome
Polyarthropathy syndrome	Healthy adult ♀
Chronic persistent anaemia	Immunocompromised child or adult
Transient aplastic crisis	Individual with haemolytic disease
Fetal hydrops/congenital anaemia	Fetus (first 20 weeks' gestation)

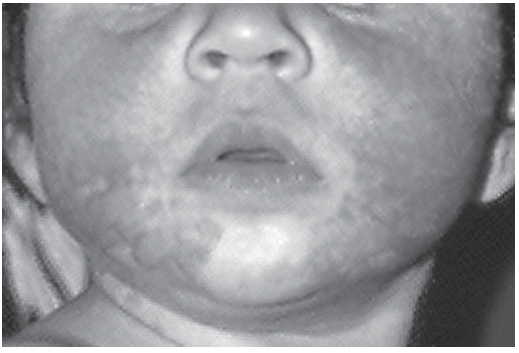

Fig. 97.1 The characteristic 'slapped cheek' appearance of parvovirus infection.

- A rash subsequently develops on the trunk, spreading to the arms and legs. This is an erythematous rash that clears from the centre outwards, giving a characteristic reticular or 'lacy' morphology (Fig. 97.2). The rash may be itchy. It usually fades after a couple of weeks but may recur for months after recovery with stimuli such as exercise or sunlight.
- There is occasionally an associated oral enanthem, with erythema of the tongue and pharynx, and red macules on the palate and buccal mucosa.
- Associated symptoms are rare in childhood, although about 10% of children develop arthralgia or occasionally arthritis. This predominantly affects large joints such as the knee. Adults, especially ♀, with parvovirus B19 infection are more prone to a polyarthropathy affecting the knees and small joints such as the digits. The arthritis may occur without a rash.

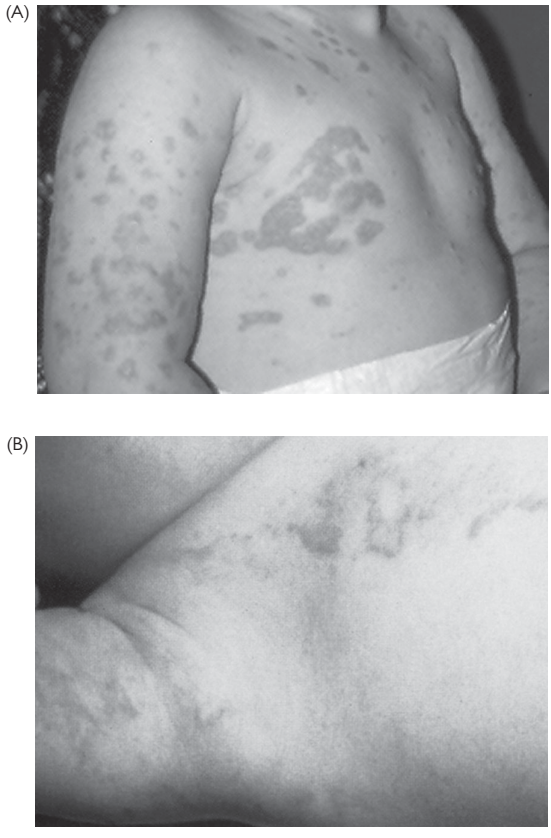

Fig. 97.2 The 'lacy' reticular rash of parvovirus infection (A) early and (B) late.

- A separate exanthem caused by parvovirus B19 is *papular purpuric gloves and socks* (*PPGS*) *syndrome*. This starts as erythema and oedema of the hands and feet, associated with mild fever. Purpuric papules develop on the palms and soles, extending as far as the wrists and ankles. The rash is itchy, and treatment is symptomatic with antihistamines. It usually resolves in 1–2 weeks, without sequelae. Other viruses, including HHV-6, HHV-7, CMV, and measles, have been associated with the syndrome.

- *Unilateral laterothoracic exanthem* (*ULE*) is marked by unilateral coalescing erythematous papules on one side of the chest. It is most often seen in children, is benign, but lasts around a month. It has been associated with various viral infections—most commonly, parvovirus B19.
- In healthy children, complications of parvovirus B19 infection are rare and include transient bone marrow suppression (anaemia, leucopenia, and thrombocytopenia), vasculitis, myocarditis, encephalitis, and glomerulonephritis.
- In haemolytic disease: patients with high red cell turnover, such as sickle-cell disease and haemolytic anaemia, are at risk of an aplastic crisis if infected with parvovirus B19. This is usually transient but may be profound and long-lasting.
- In immunocompromise: in patients with either 1° immunodeficiency or those who are immunocompromised 2° to chemotherapy or bone marrow or other organ transplantation, or in individuals with HIV, infection with parvovirus B19 may persist and lead to severe relapsing–remitting anaemia.
- In pregnant women: parvovirus B19 infection in non-immune pregnant women (around 50% in Europe) can cause IUGR, pleural and pericardial effusions, hydrops fetalis, and fetal death. It is the most frequent cause of non-immune fetal hydrops. The transmission risk is around 30%; the risk of fetal loss is 2–6% and is greatest in the first 20 weeks of pregnancy.

Diagnosis

- Diagnosis in healthy children is usually made clinically, because the rash is so characteristic. The differential diagnosis includes rubella, in which a maculopapular rash also starts on the face.
- PCR is the mainstay of laboratory diagnosis of parvovirus B19 infection, as it is rapid and accurate. PCR can be undertaken on blood, respiratory secretions, or CSF.
- Diagnosis can be made serologically with IgM and paired IgG titres in serum from the onset of the rash. This is not a useful test in an aplastic crisis or in the immunocompromised.

Management and treatment

- As the infection is usually benign and self-limiting, treatment is generally supportive, with antipyretics and analgesia, as necessary.
- There is no effective antiviral therapy, but antibody is key to viral clearance.
- Patients with an aplastic crisis or immunodeficiency require admission, intensive monitoring, and packed red cell transfusions to treat the severe anaemia.
- Patients who are immunocompromised with chronic severe anaemia due to parvovirus B19 infection may be treated with IVIG. Regimens of 0.5g/kg for 3–5 days have been used. Controlled studies using this regimen have not been done.[2]

- Pregnant women with suspected infection or contact with erythema infectiosum should have serology checked. If parvovirus infection is confirmed in the contact and the mother is not immune, this may have implications for the fetus; the mother should be counselled and referred for a specialist opinion. Serial ultrasounds to monitor for hydrops fetalis may be indicated. If hydrops is diagnosed early, intrauterine transfusions can prevent the most severe outcomes.

Prevention

- 1° prevention of parvovirus B19 infection is currently not possible, as there is no commercially available vaccine. While vaccine candidates have been assessed in phase 1 trials, they have not progressed beyond this stage.
- Prevention of 2° cases of parvovirus B19 infection is difficult, because cases are infectious before the disease is usually diagnosed following the appearance of the rash. By the time the characteristic facial rash appears, the patient is no longer infectious, and, therefore, exclusion from childcare facilities, school, or work is usually unnecessary. As transmission is by respiratory droplets, handwashing precautions are likely to reduce the spread of infection.
- Pregnant parents of children at risk should be warned of this infection, so appropriate action can be taken if there is a contact.
- Pregnant health-care workers should be advised about the risk to their unborn child of caring for a child with parvovirus B19.
- In hospitals, prevention of 2° cases usually focuses on those at risk of severe complications: patients with haemolysis, immunocompromised patients, and pregnant women.
- In patients with a transient aplastic crisis, respiratory droplet precautions should be continued for 7 days.

Future research

- Although there has been a successful phase 1 trial, there is as yet no vaccine available. A recent candidate vaccine study was halted due to side effects.
- There are no antiviral drugs to treat parvovirus infection. An effective drug would be an important advance for high-risk patients or those who develop complications from parvovirus B19 infection.
- IVIG has been used to treat severe parvovirus B19 infection, but reports are limited to case reports and case series, with no controlled trials.
- There is no effective prophylaxis in high-risk patients after contact with parvovirus B19 infection. It is possible that IVIG could be used, but this needs further study.

What's new?

- As the indications for transplant, chemotherapy, and immune therapy increase, the severe consequences of parvovirus infection continue to be reported.
- There are increasing reports on the use of IVIG in severe parvovirus infection with a reduction in the viral load, although clinical correlation is less clear.
- A novel parvovirus human parvovirus 4 has been identified, although its clinical associations remain uncertain.

What's next?

- Development of a safe and effective vaccine.
- Controlled studies of IVIG in patients with severe parvovirus infection (e.g. in haemolytic anaemia and immunocompromised individuals).
- Further research on the clinical correlates of human parvovirus 4.

Key references

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2 Katragadda L, Shahid Z, Restrepo A, *et al*. Preemptive intravenous immunoglobulin allows safe and timely administration of antineoplastic therapies in patients with multiple myeloma and parvovirus B19 disease. *Transpl Infect Dis* 2013;**15**:354–60.

Chapter 98

Pertussis

See also Chapters 27, 44.

Name and nature of organism

- Pertussis is an infectious disease of the respiratory tract caused by *B. pertussis* or, less commonly, *Bordetella parapertussis* (rarely *Bordetella bronchiseptica* or *Bordetella holmesii*).
- *Bordetella* spp. are aerobic, Gram-negative coccobacilli that express tropism for ciliated epithelial cells.

Epidemiology

- Pertussis is an endemic disease, with epidemic peaks approximately every 3 years. The highest incidence, rates of complications, and case fatality rates are seen in infants, especially neonates.
- Pertussis vaccination programmes have led to a significant reduction in cases worldwide. However, it remains one of the principal causes of vaccine-preventable deaths, with an estimated 16 million cases and 195 000 paediatric deaths per year.
- WHO estimates that 80% of infants receive three doses of the pertussis vaccine in the first year of life. The impact of vaccination is demonstrated by comparisons between neighbouring countries with and without vaccination programmes, and within countries when vaccination programmes are interrupted (e.g. the UK in the 1970s and 1980s; Fig. 98.1).
- Vaccine-induced and natural immunity wane after 6–10 years, and pertussis in older or previously immunized patients is under-recognized.
- An ongoing rise in the number of non-paediatric cases, despite a sustained high immunization uptake, suggests persisting *B. pertussis* transmission and has led to changes in national immunization programmes to improve protection for unimmunized infants.

Pathogenesis

The disease process in pertussis is multifactorial and dependent on numerous toxins and virulence factors, of which pertussis toxin is considered the most pathogenic. Many of these factors are targets for antibodies and T cells, and they facilitate:

- Attachment to ciliated respiratory epithelium
- Survival within the respiratory tract by local immune response evasion and modulation

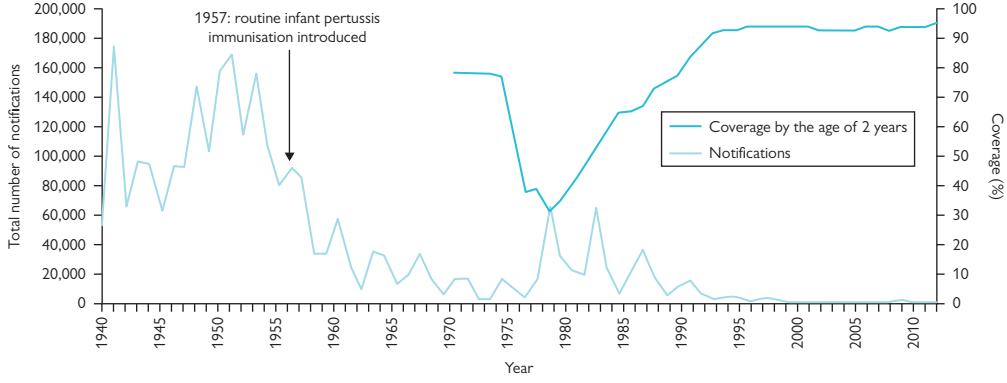

Fig. 98.1 Pertussis notifications (1940–2012, England and Wales) and vaccine coverage of children by 2 years (1970–2012, England only).

(Amirthalingam G, Gupta S, Campbell H. Pertussis immunisation and control in England and Wales, 1957 to 2012: a historical review. *Euro Surveill*. 2013;**18**(38):pii=20587. Available online: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20587>.)

- Avoidance of host immune defences by establishment of intracellular reservoirs within macrophages
- Local mucosal damage
- Systemic manifestations.

The principal factors included in acellular pertussis vaccines are:
- Pertussis toxin (PT)
- Filamentous haemagglutinin (FHA)
- Pertactin (PRN)
- Agglutinogens (fimbriae 2 and 3).

Other important factors include:
- Tracheal cytotoxin
- Tracheal colonization factor
- Adenylate cyclase toxin
- LPS
- Type III secretion system.

Transmission

- *B. pertussis* (and most strains of *B. parapertussis*) are human-only pathogens, with no environmental or animal reservoir.
- Transmission is by aerosol droplet from infected individuals to susceptible hosts.
- The incubation period is usually 7–10 days but may be up to 3 weeks.
- Untreated individuals are infectious from symptom onset for up to 3 weeks after paroxysm onset. Infectivity can be limited to 5 days by prompt treatment with appropriate antibiotics.
- Pertussis is highly infectious, with a 2° attack rate in susceptible household contacts of >80%.
- Symptomatic household contacts are the main source of infection for infants.
- There is no evidence for a prolonged *B. pertussis* carrier state, though asymptomatic individuals are well described.

Clinical features and sequelae

There are typically three stages of pertussis disease. Atypical disease is seen in young infants and those with a history of pertussis immunization or previous infection, and may be difficult to diagnose from clinical features alone.

Catarrhal

- Includes non-specific upper respiratory tract symptoms:
  - Rhinorrhoea
  - Sore throat
  - Conjunctivitis
  - Non-productive cough.
  - Occasional fever.
- This stage typically lasts for a few days up to 2 weeks.

Paroxysmal

- Cough becomes paroxysmal, i.e. bouts of forceful, continuous coughing.
- This causes venous congestion and may result in cyanosis or facial discoloration.
- There is commonly the production of profuse non-purulent secretions.
- The paroxysms may end with deep inspiration (whoop) and vomiting.
- Paroxysms may occur >30 times per 24 hours and are common at night.
- They can occur spontaneously or are precipitated by external stimuli, e.g. physical exercise, cold air, or feeding.
- Between episodes, there are few clinical signs—chest examination is usually normal, and the child is afebrile and may appear well.
- Very rarely, the spasms are so severe that ventilatory support may be required.
- This stage also typically lasts 2 weeks.

Convalescent

- The paroxysms gradually subside.
- If a viral URTI is acquired, relapse of paroxysmal cough may occur.
- This stage can last from 2 weeks to several months.

Atypical features

- In infants:
  - Apnoea
  - Cyanotic episodes
  - No cough
  - Poor feeding
  - Fever
  - Seizures
  - Sudden death.
- In the partially immunized:
  - Duration of catarrhal phase may be reduced
  - Paroxysms and/or whoop may not occur
  - Asymptomatic infection.
- In adolescents and adults:
  - Prolonged cough—may be the only symptom; chronic cough and post-tussive vomiting (if present) are key signs suggestive of pertussis.

Complications of pertussis are commonest in infants under 6 months of age who have high rates of hospitalization, severe illness, and death (~1% mortality, up to 3% in neonates). Other risk factors for severe disease include prematurity, co-infection with respiratory viruses, and pneumonia.

Major complications include:

- Bronchopneumonia, either due to *B. pertussis* or 2° infection. Fever is a good sign of pneumonia, as pertussis is usually afebrile
- Dehydration, metabolic alkalosis, and weight loss, due to decreased oral intake and vomiting
- Apnoea
- Herniae and rib fractures due to excessive paroxysms

- Pulmonary hypertension. Especially in younger infants and associated with hyperleukosis and high mortality
- Encephalopathy. Can be due to hypoxic injury during paroxysms or toxin-mediated
- Subarachnoid and intraventricular haemorrhage
- Seizures.

Minor complications include:
- Subconjunctival haemorrhage
- Epistaxis
- Facial oedema
- Interstitial or subcutaneous emphysema
- Ulceration of the tongue or surrounding area
- Otitis media.

Diagnosis

'Typical' pertussis may be diagnosed clinically, especially in an epidemic situation. Atypical cases, or those with a history of previous immunization or infection, may be more subtle and therefore under-recognized. Even within vaccinated populations, ~20% of cough of >2 weeks' duration in adolescents and adults has been shown to be due to *B. pertussis*. Diagnosis allows for disruption in disease transmission by early treatment with antibiotics.

Confirmation of the diagnosis or corroborative evidence may be obtained from a history of contact with a case and/or laboratory investigations. PCR assays have improved the laboratory diagnosis of pertussis, in addition to traditional culture and serology testing.

Respiratory specimens should be collected by NPA, nasopharyngeal swab, or pernasal swab. Throat and anterior nasal swabs (non-ciliated epithelium!) are unlikely to be helpful.

Culture of secretions

- Culture is highly specific and permits antibiotic susceptibility testing, but it is poorly sensitive.
- Sensitivity is affected by illness duration (55% sensitive in the first week of illness, compared to <10% by week 4), age of patient, prior antibiotics, and method and site of specimen collection.
- *B. pertussis* is a fastidious organism, requiring a selective culture medium (Regan–Lowe agar).
- Growth occurs over 3–7 days.
- Direct inoculation of the sample onto culture medium at the bedside increases sensitivity, but transport to the laboratory in an appropriate medium is more practical.

Polymerase chain reaction analysis

- More sensitive than culture, especially in late-stage disease and after initiation of antibiotic therapy.
- Highly specific.

- PCR enables rapid diagnosis of pertussis, but the validity of the results must be assured by careful controls.
- In the UK, the Bordetella reference laboratory at the Respiratory and Vaccine Preventable Bacteria Reference Unit (RVPBRU) offer a rapid turnaround service for hospitalized children under 1 year of age.

Serology

- Most useful in patients presenting in the convalescent phase when culture and PCR are rarely positive.
- The most widely used antibodies are anti-PT and anti-FHA.
- Serum anti-PT IgG >70IU/mL (ELISA) 2 weeks after disease onset is diagnostic. Other antigens and antibody classes (IgA, IgM) are not useful.
- Limited applicability, as difficult to interpret in those <3 months old (may not develop measurable antibodies and/or presence of maternal antibodies) or who have previously received pertussis vaccination (not recommended for diagnosis within 1 year of vaccination).

Leucocytosis due to lymphocytosis

Lymphocytosis is mediated by pertussis toxin and is due to the release of lymphocytes from extravascular sites into the blood. Lymphocytosis is prevented by anti-PT antibodies and therefore usually only occurs in unvaccinated individuals.

Management and treatment

The management of pertussis focuses on supportive care and preventing ongoing transmission.

Supportive

Oxygen therapy and gentle suction of pharyngeal secretions during paroxysms of cough. Nasopharyngeal tube or IV fluids may be required.

There is no evidence of any intervention reducing cough or illness duration, including corticosteroids, antihistamines, salbutamol, antibiotics, or pertussis-specific immunoglobulins.

Antibiotics

- Antibiotics given within 21 days of symptom onset eliminate the organism and prevent ongoing transmission; after this time, there is no benefit (unless 2° bacterial infection).
- *Bordetella* spp. are sensitive to macrolides, and co-trimoxazole can be used in cases where macrolides are contraindicated.
- Clarithromycin (7-day course) is preferred to erythromycin (7-day course) due to its convenient dosing, improved side effect profile, and good *in vitro* activity against the organism. There is no additional benefit of longer courses.
- Pregnant women diagnosed with pertussis in their third trimester are recommended to receive erythromycin or clarithromycin to prevent transmission following delivery.

Prevention

Vaccination

- Routine infant vaccination with whole-cell or acellular vaccines, usually combined with diphtheria and tetanus toxoids (DTaP) and other vaccine components (plus IPV, Hib, HBV), remains the mainstay of pertussis prevention.
- Whole-cell vaccine is more immunogenic but has higher reactogenicity, especially with booster doses, and has largely been replaced by acellular vaccines in the developed world.
- Acellular vaccines contain up to five pertussis antigens (see ➔ Pathogenesis, p. 737–9), improving immunogenicity, compared to those with fewer components, and are well tolerated.
- The concentration of antibody associated with clinical protection against pertussis is unclear, and it is therefore difficult to predict the effectiveness of different vaccines.
- The duration of protection following vaccination is 4–12 years, in the absence of natural or vaccine boosting.
- The recent increase in adolescent cases has led to the reassessment and adoption of different vaccination strategies to prevent transmission to those too young to be immunized.
- Strategies include:
  - Vaccination of mothers during pregnancy with Tdap (reduced diphtheria and pertussis antigen content, compared to DTaP), providing both direct and indirect protection to the infant. This approach has been employed in several countries, including the UK and Switzerland
  - Cocooning (vaccination of those in close contact with young infants). The effectiveness of this strategy is unclear, and its implementation is logistically challenging
  - Adolescent pertussis vaccination boosters have been integrated into the routine immunization schedules of several countries
  - Neonatal vaccination provides direct protection, but the effect on subsequent infant vaccination responses is unknown.

Post-exposure prophylaxis

- Due to the high risk of complications, PEP with antibiotics should be offered to infants under 1 year who are unimmunized or partially immunized. Exposed adults who are likely to have close contact with vulnerable infants should also receive chemoprophylaxis.
- The choice of antibiotic and course duration are the same as for treatment.
- Pertussis vaccination following exposure may be considered in children who are incompletely immunized or in an outbreak situation.
- Health-care workers who have not been recently immunized and are exposed to pertussis should receive a dose of pertussis vaccine (Tdap).

Isolation

Confirmed or suspected cases should be excluded from nursery or school for 5 days after commencing antibiotic therapy, or for 21 days from symptoms onset if not treated.

Future research

- Further studies are required to assess the optimal pertussis vaccination schedule to ensure ongoing protection for all ages.
- Defined immunological correlates of protection will allow the development and a better assessment of new pertussis vaccines.
- Continuing research into new PCR methods, including real-time PCR, may assist in the detection of pertussis, even in later stages.

Further reading

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Chapter 99

Plague

See also Chapters 42, 45.

Introduction

First documented in the Old Testament, historically plague has caused three large pandemics, known as the Black Death, and multiple epidemics, and it still causes widespread outbreaks, mainly in resource-poor countries. It also has the potential for use as a bioterrorist agent (it is a class A pathogen).

Name and nature of organism

- Gram-negative coccobacillus, *Yersinia pestis* (family *Enterobacteriaceae*).
- Originally *Pasteurella pestis*, it was renamed in 1967 after Alexander Yersin who first isolated the bacterium in 1894 and developed an antiserum for treatment.
- Pleomorphic facultative anaerobe, with three virulence plasmids: *pFra*—encodes the antiphagocytic capsular protein factor 1 (F1) and the murine toxin which enables the bacteria to survive in the flea gut; *pYV*—encodes the V antigen and the *Yersinia* outer proteins (Yops) which disrupt phagocytosis and inflammation; and *pPla*—encodes plasminogen activator, allowing bacterial spread by lysis of fibrin-containing clots.

Epidemiology

- Naturally zoonotic disease cycle, primarily affecting wild rodents.
- Humans are accidental hosts.
- Over 21 000 human cases of plague from 16 countries (97% in Africa) were reported to WHO between 2001 and 2009; mortality rate 7.4%.
- Endemic regions include: Congo, Madagascar, Zambia, Uganda, Mozambique, Tanzania, China, India, Peru, Malawi, Indonesia, and Vietnam.
- Disease foci in Europe lie around the Caspian Sea and Caucasus.
- Factors that favour hosts and vectors of the bacteria and increase disease prevalence include: civil unrest, wars, and deteriorating health services; global warming; and the expanding world population (with poorer sanitation/hygiene and increased risks of animal contact).

Transmission and incubation period

Transmission

- Three main routes:
  - Host to human via bite from vector (e.g. rat to person via rodent flea)
  - Direct inhalation or ingestion of bacterium
  - Close contact with infected tissue or body fluids (e.g. through broken skin or ingestion of poorly cooked meat).
- Most important vector is the Oriental rat flea (*Xenopsylla cheopis*).
- Main vector reservoir hosts are rodents and, depending on the area of infection, include: rats, gerbils, jirds, marmots, ground squirrels, and deer mice.
- Highly infectious nature, so only small number of organisms needed to cause disease (inhaled infectious dose is 100–500 organisms).
- *Y. pestis* may survive for long periods in soil, from which burrowing rodents then acquire the bacteria.

Incubation period

- Varies, depending on the transmission method and form of plague:
  - Via flea bite: 2–8 days
  - Via airborne/aerosol: 1–3 days.

Clinical features and sequelae

- Ninety-six per cent of plague is bubonic, and 3% pneumonic; other rarer forms include septicaemic, meningeal, pharyngeal, and GI.
- *Bubonic plague*—the flea bite is most often on the leg, usually unnoticed, and, 2–8 days later, after the bacteria migrate to the regional LN, the 'bubo' develops.
- Pathognomonic feature = bubo—classic large LNs (also seen in syphilis, TB, gonorrhoea).
  - Necrotic and haemorrhagic LN draining area of the skin containing the vector bite
  - Very tender with overlying erythema and pitting oedema
  - Two to 10cm, oval in shape
  - Flea bites on the upper limbs lead to axillary bubos, on the head and neck to cervical bubos
  - Fevers and chills develop, as the bacteria spread from the bubo into the bloodstream, and seed: liver, spleen, lungs, LNs, and bone marrow
  - Shock and DIC may develop, and, if untreated, death usually occurs in 3–6 days
  - The case fatality rate for bubonic plague is <50%
  - *Pneumonic plague*—infection is usually by aerosol spread from a sick animal or human, and, within 1–3 days, signs of severe pneumonia with haemoptysis develop. In untreated patients, case fatality is 100%, and death usually occurs within 3 days of the onset of symptoms
  - *Septicaemic plague*—may develop from bubonic plague or occur in the absence of lymphadenitis. Dissemination of the infection in the bloodstream results in meningitis, endotoxic shock, and DIC.

Complications

- ARDS or lung abscess.
- Superinfection of buboes (commonly staphylococcal or *Pseudomonas*).
- Vasculitis and gangrene of extremities.
- Lymphoedema.
- Polyarthritis.

Diagnosis

The initial symptoms are very similar to many commoner infections. Suspicion should be raised if there is:

- History of flea bites (only remembered in 10% people)
- Travel to an endemic plague area, with close contact with a potential animal reservoir
- Sudden increase in severe pneumonia cases in a previously healthy population, especially in areas of poor housing and health provision
- Contact with sick animals (e.g. camels, dogs, cats, squirrels, and carnivores).
- Take three sets of blood cultures during the first hour (before starting antibiotics), sputum, and/or bubo fluid.
- Label all specimens as *high-risk*, and inform the microbiology team of the suspicion of plague, so that laboratory staff may take appropriate containment precautions.
- Direct microscopy reveals bacilli with bipolar staining. Appropriate stains include Gram, Wayson, and Giemsa.
- Rapid diagnostic kits have been developed for high-incidence countries with limited laboratory capacity, including:
  - Biochemical test strips (*Y. pestis* is catalase-positive and oxidase-negative)
  - Dipstick assays (using immunochromatography) to detect F1 antigen.
- Clinical isolates may be misidentified as *Proteus* spp. or other *Enterobacteriaceae*. Biochemical tests are available to confirm the diagnosis, including antigen detection, antibody detection, PCR, and matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry.
- ELISA to detect IgM and IgG antibodies:
  - Acute and convalescent serum is useful in culture-negative cases (positive if 4-fold or higher rise in titre)
  - *Immediately inform: local and national authorities*.

Management and treatment

Plague is a notifiable disease and a public health emergency.

General

Population

- Eradicate fleas, rats, other vectors, and reservoirs associated with infected case.
- Available vaccines not recommended for immediate protection in outbreaks (takes 4 weeks to develop protective immune response).

- Strict respiratory infection control precautions when dealing with suspected or confirmed cases (human or animal).

Individual

- Keep in respiratory isolation, until effective antibiotics given for 2–3 days or until sputum culture-negative (if ever positive).
- Gangrenous areas may require amputation.
- Incision and drainage of buboes if large or fluctuant.

Antibiotics

- Antibiotics are most effective if given within the first 24 hours of symptoms.
- Antibiotics effective against plague include: gentamicin, doxycycline, tetracycline, co-trimoxazole, fluoroquinolones, and chloramphenicol.
- Gentamicin and doxycycline are first-line and equally effective, unless there is meningeal plague when chloramphenicol should be used due to better blood–brain barrier penetration.
- Resistance to antibiotics is rarely seen.
- Length of treatment:
  - Minimum of 14 days, and for at least 3 days after the last fever
  - If suspected meningeal involvement, then 21 days minimum
- Can convert to oral antibiotics (e.g. doxycycline) after 48 hours if symptoms are improving.
- Although fever and symptoms can settle in <1 week with appropriate treatment, a 1° bubo may take months to resolve.

Post-exposure prophylaxis

- Give to humans in close contact with an infected animal or body fluids or a case of pneumonic plague within the last 6 days.
- Ciprofloxacin is recommended for PEP.
- Complete a 7-day course.

Prevention

The main aim is to prevent contact with zoonotic foci.

Individual-led

- Insect sprays on exposed body areas and bedding.
- Flee bite-resistant clothing, especially on lower limbs.
- Avoid contact with known animal reservoirs, especially if dead or sick.
- Avoid visiting endemic plague regions.

Vaccines

- Live attenuated and killed whole-cell vaccines have existed for over a century, but both are reactogenic and no longer used.
- New vaccines are in development, including for bioterrorism situations, using recombinant subunits of the F1 capsule and the V outer membrane of *Y. pestis*. These have been found to be safe and immunogenic in phase 1 and 2 trials, and larger phase 3 trials are planned.

Future research

Keys areas for vaccine development involve anticipating an imminent bioterrorist attack, including having a vaccine effective against the pneumonic plague, which gives more immediate protection.

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Chapter 100

Pneumococcal disease

Organism

Pneumococcal diseases are those caused by the bacterium *S. pneumoniae*, also known as pneumococcus. *S. pneumoniae* is a Gram-positive α-haemolytic bacterium that can be identified in microbiological culture by its sensitivity to optichin and its solubility in bile.

Disease-causing pneumococci possess a polysaccharide capsule, which, as well as providing various virulence factors, also determines the serotype. There are currently >90 known serotypes of pneumococcus, only a proportion of which are known to be associated with disease in humans.

Pneumococcus can be carried asymptomatically in the nasopharynx. This is particularly common in young children.

Diseases caused by pneumococcus range in severity from non-invasive otitis media, sinusitis, and LRTI to invasive infections such as meningitis, SA, OM, peritonitis, and bacteraemic sepsis.

Disease involving infection of a normally sterile site is referred to as IPD.

Epidemiology

Incidence

Pneumococcal disease makes a major contribution to childhood mortality and morbidity worldwide, with ~800 000 deaths in children <5 years of age, estimated to be due to IPD, in the year 2000.

Pneumococcus is a leading cause of bacterial otitis media, pneumonia, and meningitis.

Since the introduction of childhood PCV in a number of countries, the incidence of invasive disease caused by serotypes contained in the vaccines (7-valent (PCV7), 10-valent (PCV10), or 13-valent (PCV13)) has declined both in vaccinated children (direct protection) and unvaccinated age groups (via herd immunity).

Age

Pneumococcal disease affects all age groups, with peaks of incidence in early childhood and old age. Children under 2 years of age are particularly vulnerable, thought, in part, to be a result of immaturity of the immune system, resulting in suboptimal immunity to encapsulated bacteria.

Sex

Risk of IPD is slightly higher in ♂.

Geography

Pneumococcal disease has a global distribution, with the highest incidence rates particularly associated with resource-poor settings (e.g. sub-Saharan Africa, India).

Seasonality

In temperate climates, there are peaks in disease incidence in winter months.

Risk factors

Immunity to pneumococcal disease is considered to be predominantly antibody-mediated. Aside from extremes of age, there are a number of well-established risk factors for pneumococcal disease and/or more severe pneumococcal disease. These include:

- Asplenia or splenic dysfunction (e.g. sickle-cell disease)
- 1° immunodeficiency (including defects of innate immunity, cell-mediated immunity, antibody, and complement)
- 2° immunodeficiency (e.g. HIV, malignancy, chemotherapy, BMT, immunosuppressive drugs (including prolonged high-dose steroids))
- Chronic respiratory disease (e.g. bronchiectasis, cystic fibrosis)
- Chronic kidney disease (e.g. nephrotic syndrome)
- Chronic liver disease (e.g. cirrhosis)
- Chronic heart disease (e.g. significant CHD)
- Cochlear implants
- CSF leak.

Preceding viral respiratory tract infection (especially influenza) can increase susceptibility to pneumococcal disease, with a proportion of the mortality associated with influenza epidemics being attributable to secondary pneumococcal infection.

Transmission and incubation period

- Transmission is most commonly via droplet spread from individuals with nasopharyngeal carriage.
- Carriage is considered to be a precursor to invasive disease.
- Invasive potential varies according to serotype.
- Duration of nasopharyngeal carriage can range from days to months and also varies according to serotype.
- Time from colonization to invasion is also variable.

Clinical features

Clinical signs or symptoms of pneumococcal disease are not specific to *S. pneumoniae* (i.e. they can occur in the context of other bacterial and viral infections) and depend on the site of infection, disease severity, age of the child, and co-morbidity.

Asymptomatic bacteraemia is rare but possible. Localizing signs may not occur in the context of young age or immunodeficiency.

Otitis media

Symptoms

Ear pain, pulling at ears, discharge from ear canal, irritability.

Signs

Bulging and erythematous tympanic membrane, exudate from ear canal, fever.

Pneumonia

Symptoms

Cough, chills, shortness of breath, chest pain, purulent sputum, decreased feeding.

Signs

Fever, tachypnoea, tachycardia, hypotension, hypoxia, drowsiness, respiratory distress, signs of consolidation or pleural effusion on chest auscultation.

Meningitis

Symptoms

Depending on age, include headache, neck stiffness, photophobia, fever, vomiting, irritability, drowsiness, decreased feeding, seizures.

Signs

Fever (or hypothermia), tachycardia, hypotension (if associated sepsis), hypertension and bradycardia (if associated raised ICP), decreased GCS, meningism, bulging fontanelle.

Bacteraemic sepsis

Symptoms

General malaise, lethargy, weakness, dizziness plus symptoms associated with a specific focus of infection.

Signs

Septic shock (fever, tachycardia, hypotension, poor perfusion, reduced urine output) and purpuric rash (similar to that more commonly associated with meningococcal sepsis) can also occur.

Osteomyelitis/septic arthritis

Symptoms

Pain, refusal to weight-bear or reluctance to use affected limb, joint swelling.

Signs

Tenderness, swelling, warmth and erythema at site of infection, limited range of joint movement, fever, tachycardia, limp.

Diagnosis

Diagnosis is made when there is clinical evidence of bacterial infection from examination findings, imaging (CXR, head CT), and laboratory investigations (blood tests, CSF analysis, sputum microscopy, BAL microscopy) plus identification of organism by culture and/or molecular methods.

Every attempt should be made to culture relevant sites prior to commencing antibiotic therapy.

Obtaining sputum samples from young children is often not possible which can limit the isolation of pneumococci contributing to LRTI. Pneumococcal pneumonia is usually not associated with bacteraemia. Reductions in the overall incidence of pneumonia following the introduction of PCV indicate that a substantial proportion of culture-negative cases are attributable to pneumococcus.

Additional laboratory investigations of use include:

- 16S ribosomal PCR and/or specific pneumococcal PCR performed on fluid from a sterile site (or a non-sterile site not usually colonized with pneumococcus (e.g. empyema fluid)
- Urinary pneumococcal antigen (though limited specificity for invasive disease in young children due to high rates of colonization)
- Detection of pneumococcal antigen from other sites (e.g. latex agglutination on CSF or pleural sample)
- MALDI-TOF mass spectrometry is useful for early identification of bacterial culture isolates prior to formal identification using standard microbiological techniques.

Management and treatment

Specific treatment of *S. pneumoniae* is with antibiotics. Choice of antibiotic, route of administration, formulation, dosing, and duration of therapy varies, according to age, site of infection, and clinical status of the child.

Levels of pneumococcal antibiotic resistance vary globally. In some regions, pneumococcus is still generally susceptible to penicillin, whereas, in other regions, resistance to penicillin can be as high as 40%. Resistance to multiple classes of antibiotics is increasingly documented (MDR pneumococcus).

Knowledge of local pneumococcal resistance patterns, as well as those of possible alternative causative bacteria, should guide empiric first-line antibiotic choices.

In areas with low incidence of resistance, amoxicillin is generally appropriate as first-line therapy of non-invasive disease, whereas a third-generation cephalosporin (ceftriaxone, cefotaxime) is generally recommended to treat presumed IPD while awaiting formal microbiological confirmation and information of *in vitro* antimicrobial sensitivity.

Appropriate second agents are recommended if there is concern regarding penetration of cephalosporin into the affected site or to provide additional cover for alternative possible causative organisms (e.g. *S. aureus*). A second agent (e.g. vancomycin) can be added when treating IPD in regions with high background prevalence of resistant pneumococcus, especially in the context of suspected pneumococcal meningitis.

Drainage of collections of pus or inflammatory fluid to limit mass effect/tissue destruction may be indicated, as antibiotic penetration may be poor (e.g. pleural fluid drainage, joint aspiration/washout, drainage of intracranial abscess).

It is generally recommended that proven pneumococcal meningitis should be treated for a total of 14 days of IV antibiotics, although trials have shown equal efficacy for shorter courses of antibiotics. For the duration of therapy for other specific sites of infection, see appropriate sections.

Sequelae

Sequelae can be short- or long-term, are similar to those of other invasive bacterial diseases, and depend on the site of infection.

Otitis media

Local extension to cause mastoiditis or intracranial spread of infection to cause meningitis or intracranial abscess is very rare.

Osteomyelitis/septic arthritis

Irreversible damage to joint or growth plate, resulting in limited range of movement, chronic pain, or limb length discrepancy.

Pneumonia

Parapneumonic effusion, necrotizing pneumonia, empyema, pneumothorax, pneumatocele.

Meningitis

Hydrocephalus, cerebral vasculitis, intracerebral abscess, subdural collection, ischaemic stroke, cerebral palsy, developmental delay, hearing and visual impairment, epilepsy.

Haemolytic–uraemic syndrome

IPD is a relatively rare cause of HUS.

Prevention

Vaccination

PCVs are highly effective at preventing IPD in healthy children and in risk groups. They also reduce pneumococcal carriage of vaccine serotypes, resulting in the protection of unvaccinated individuals (herd immunity).

The first licensed PCV was 7-valent (PCV7: serotypes 4, 6B, 9V, 14, 18C, 19F, 23F). Global roll-out of PCV7 has resulted in dramatic decreases in vaccine-serotype IPD.

Although the overall rates of IPD have decreased in countries using PCVs routinely, disease caused by non-vaccine serotypes have increased (replacement disease).

Higher-valency vaccines (PCV10: PCV7 serotypes plus 1, 5, 7F; and PCV13: PCV10 serotypes plus 3, 6A, 19A) have subsequently been licensed, and early surveillance data indicate that they are effective in reducing the burden of disease caused by non-PCV7 serotypes.

It remains to be seen whether significant replacement disease will occur following the introduction of PCV10 or PCV13.

Pneumococcal polysaccharide vaccine (PPV: serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F) is not effective in children under 2, is not associated with reduction in carriage, and does not lead to establishment of immune memory. Use of PPV also results in serological hyporesponsiveness to subsequent doses of PCV (although the clinical significance of this is yet to be demonstrated). For these reasons, PPV is not recommended in children, apart from those in specific risk groups in whom extended coverage is important, often with an additional recommendation to vaccinate with PCV prior to PPV.

Vaccination schedules vary from country to country but generally include universal pneumococcal vaccination (two or three doses in infants plus a booster in the second year of life) plus vaccination of older children in risk groups with one or both of PCV or PPV.

Prophylactic antibiotics and intravenous immunoglobulin

Prophylactic oral antibiotics are effective in the context of asplenia or reduced splenic function (e.g. sickle-cell disease) and also 1° or 2° immunodeficiency.

IVIG may be effective in specific circumstances, although its use should ideally be discussed with a specialist in infection and immunity or respiratory paediatrics.

Follow-up and outcome

Following an episode of IPD, a child should be assessed for risk factors for susceptibility.

Recurrent pneumococcal disease and vaccine-serotype disease, despite completion of the recommended PCV immunization schedule, are particular causes for concern.

Suggested baseline investigations include:

- Abdominal ultrasound (to assess for the presence of the spleen)
- Specific vaccine responses
- Lymphocyte subsets
- HIV test
- Serum IgG/A/M.

Additionally, the following might be considered:

- Complement function
- Mannose-binding lectin.

Interpretation of serum pneumococcal-specific IgG antibody (total and serotype-specific) is complex, requiring expertise in the field and awareness of the limitations of such assays.

For more specialized investigation of genetic causes of susceptibility (in the context of very severe or recurrent disease), referral should be made to a specialist in ID and immunology.

Following pneumococcal meningitis, children should have neurodevelopmental follow-up, and hearing assessment is essential.

Despite advances in supportive therapy, improved diagnostics, and awareness of antibiotic resistance, outcomes following pneumococcal meningitis remain relatively poor, with high case fatality rates and significant neurological sequelae.

Future research

Areas of future research include:

- Novel vaccine strategies (protein vaccines effective against all serotypes, whole-cell vaccines)
- Ongoing surveillance (carriage, disease, antibiotic resistance)
- New correlates of pneumococcal immunity following immunization
- New strategies to protect risk groups
- Newborn or maternal immunization in high-incidence regions
- Host genetic susceptibility
- Improved diagnostics.

Further reading

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Chapter 101

Pneumocystis pneumonia

See also Chapters 7, 34, 107.

Name and nature of organism

The classification of *Pneumocystis* has evolved. It was originally misclassified as a protozoan. Recent phylogenetic analyses place *Pneumocystis* within the fungal kingdom. *Pneumocystis* spp. are currently classified within the phylum *Ascomycota*, class *Pneumocystidomycetes*, order *Pneumocystidales*, and family *Pneumocystidacae*. *Pneumocystis* are atypical fungal organisms, as they are unable to grow *in vitro* in fungal culture media, are susceptible to a number of antiparasitic agents, and their cell wall contains cholesterol, rather than ergosterol. Human *Pneumocystis* now is called *Pneumocystis jirovecii* (versus *Pneumocystis carinii,* the species that infects rats). It is an obligate extracellular pathogen and exists in trophic and cystic forms.

Epidemiology

Pneumocystis is a ubiquitous organism, infecting a wide array of mammalian species, particularly rodents, and has a pulmonary tropism and pathogenesis. Infections are species-specific, and cross-species infections are not known to occur. The reservoir of the organism has not yet been defined. Exposure to *P. jirovecii* is common early during life, with >85% of healthy children acquiring antibody by 20 months of age. The clinical significance of colonization is not well understood. *P. jirovecii* pneumonia (PCP) can occur in epidemics, primarily affecting preterm and malnourished infants or children. Immunocompetent infants with the infection are either asymptomatic or have mild respiratory symptoms. Clinically significant disease occurs almost entirely in immunocompromised people with deficient cell-mediated immunity, particularly people with HIV infection, recipients of immunosuppressive therapy after solid organ transplantation and HSCT or treatment for malignant neoplasm, and children with 1° immunodeficiency syndromes. PCP remains one of the most important AIDS-indicator diseases among HIV-infected children. The highest incidence of PCP in HIV-infected children is in the first year of life, with a peak incidence at ages 3–6 months.

Transmission

The mode of transmission is not firmly established. Animal and human studies suggest that *Pneumocystis* is transmitted by the airborne route. Human-to-human transmission has been suggested. Vertical transmission is considered rare.

The incubation period in unknown, but reports of PCP outbreaks in transplant recipients have demonstrated a median of 53 days from exposure to clinically apparent infection. The period of communicability is unknown.

Clinical features and sequelae

Classically, PCP presents with a characteristic syndrome of subacute diffuse pneumonitis with fever, tachypnoea, and cough. The severity of these signs and symptoms can vary. Onset can be abrupt or insidious with non-specific symptoms such as mild cough, dyspnoea, poor feeding, diarrhoea, and weight loss. Some patients may not be febrile, but almost all have tachypnoea by the time pneumonitis is evident on chest radiograph.

- Physical examination is often surprisingly normal, even in the presence of significant disease and hypoxaemia. Tachypnoea, tachycardia, oxygen desaturation, and bilateral basilar rales, with evidence of respiratory distress may be seen.
- In HIV-infected children with pneumonia aged <6 months, respiratory rate >60 breaths/min, arterial percentage haemoglobulin saturation ≤92%, and absence of vomiting are independently associated with PCP.
- The mortality rate in immunocompromised patients ranges from 5% to 40% in patients treated and approaches 100% without therapy.

Diagnosis

Most children with PCP are hypoxic with low arterial oxygen pressure. Chest radiographs most commonly show bilateral diffuse parenchymal infiltrates with a 'ground glass' or reticulogranular appearance, but they also can be normal or have only mild parenchymal infiltrates. Rarely, lobar, cavitary, nodular, or military lesions, pneumothorax, or pneumomediastinum are seen. No combination of symptoms, signs, and chest radiographic findings is diagnostic of PCP.

A definitive diagnosis of PCP requires the visualization of the organism in pulmonary tissue or respiratory tract secretion specimens in the presence of pneumonitis. Open-lung biopsy is the most sensitive and specific diagnostic technique, but not recommended routinely. Bronchoscopy with BAL is the diagnostic procedure of choice for most infants and children. Sensitivity ranges from 55% to 97%. Fibreoptic bronchoscopy and transbronchial biopsy are recommended only when BAL is negative or non-diagnostic, despite a clinical picture consistent with PCP. Sensitivity ranges from 87% to 97%. Nasogastric aspirates, if positive, are of diagnostic value. Sputum induction procedure with hypertonic saline is less invasive but may be difficult in children <2 years. Sensitivity ranges from 74% to 83%.

Gomori methenamine silver, toluidine blue, and monoclonal immunofluorescence antibodies are useful for identifying the cyst wall. Giemsa and Wright stains depict the trophozoites and intracystic sporozoites. For each studied specimen, cyst wall, trophozoite, and immunofluorescence antibody stains are recommended.

PCR assays for detecting *P. jirovecii* infection are sensitive, but less specific than microscopic methods, and are not standardized in most centres.

Management and treatment

TMP-SMX is the drug of choice for PCP. Alternatively, IV pentamidine isetionate can be used. Mild to moderate PCP cases can be treated with atovaquone, dapsone/trimethoprim, and clindamycin/primaquine (Table 101.1).

A short course of corticosteroids is recommended in cases of moderate or severe PCP, starting within 72 hours of diagnosis. Doses for children vary between studies; however, a commonly used regimen is the following:

- For children <13 years of age: prednisone 1mg/kg/dose twice daily for the first 5 days of therapy; 0.5mg/kg/dose twice daily on days 6–10; and 0.5mg/kg/dose once daily on days 11–21
- For children ≥13 years of age: prednisone 40mg/dose twice daily for the first 5 days of therapy; 40mg/dose once daily on days 6–10; and 20mg/dose once daily on days 11–21.

Prevention

Regarding the isolation of hospitalized patients with PCP, standard precautions are recommended. Clinical data are limited to support extra isolation measures. Some experts recommend that high-risk patients should not be placed in a room with another patient with PCP.

Chemoprophylaxis is highly effective in preventing PCP among high-risk groups. Prophylaxis against a first episode of PCP are indicated for many patients with significant immunosuppression, including:

- *HIV-infected children*. The risk of PCP is associated with age-specific $CD4^+$ T-lymphocyte cell counts and percentages that define the degree of immunosuppression. Prophylaxis for PCP is recommended for all infants born to HIV-infected women with an indeterminate HIV status, beginning at 4–6 weeks of age until they are determined to be HIV-uninfected (usually 5–6 months of age). Children who are HIV-infected or whose HIV status is indeterminate should continue prophylaxis during the first year of their life. For children older than 1 year of age, prophylaxis should be considered in terms of the level of their immunosuppression, as indicated by their $CD4^+$ T-lymphocyte counts and percentages (Table 101.2)
- *Recipients of HSCT*. PCP prophylaxis is recommended to be initiated at engraftment (or before engraftment) and administered for at least 6 months. For children who receive ongoing or intensified immunosuppressive therapy or with chronic GVHD prophylaxis should be extended
- *Recipients of solid organ transplants*. Experts' suggestion for the duration of therapy ranges from 6 months to 1 year for renal transplants, and from 1 year to lifelong for heart, lung, and liver transplants

Table 101.1 Treatment regimens for *Pneumocystis jirovecii* pneumonia

Drug	*Dose*	*Comments*	*Adverse reactions*
Recommended regimen			
co-trimoxazole (trimethoprim/ sulfamethoxazole) (TMP-SMX), IV	3.75–5mg/kg/dose (TMP component) every 6 hours (for children >2 months)	Duration of therapy 21 days Patients with favourable response to initial IV therapy can be transitioned to oral treatment (same total daily dose of TMP-SMX in three or four divided doses) to complete a 21-day course Oral therapy should be reserved for patients with mild disease without malabsorption or diarrhoea	Rash, neutropenia, anaemia, thrombocytopenia, renal toxicity, hepatitis, nausea, vomiting, diarrhoea
Acceptable alternative regimens			
Pentamidine isetionate, IV	4mg/kg, once daily	Recommended for patients who cannot tolerate TMP-SMX or demonstrate clinical treatment failure after 5–7 days of TMP-SMX therapy In patients with clinical improvement after 7–10 days of IV therapy, an oral regimen (atovaquone or TMP/ dapsone) can be considered to complete a 21-day course	Pancreatitis, diabetes mellitus, renal toxicity, electrolyte abnormalities, hypoglycaemia, hyperglycaemia, hypotension, cardiac arrhythmias, fever, neutropenia

Atovaquone, orally*	750mg/dose twice daily (for ≥13 years) 30–40mg/kg/dose once daily (for <3 months and >24 months to 12 years) 45mg/kg/dose once daily (for 2–24 months) *Alternatively:* 12–20mg/kg/dose twice daily (for <3 months and >24 months to 12 years) 22.5mg/kg/dose twice daily (2–24 months)	Should be administered with food Co-administration with fluconazole and prednisone increases atovaquone concentration Co-administration with aciclovir, opiates, cephalosporin, rifampin, and benzodiazepines decreases atovaquone concentration	Rash, nausea, diarrhoea
Dapsone/TMP, orally*	Dapsone: 100mg/dose once daily (for ≥13 years) and 2mg/kg/dose once daily (for <13 years) TMP: 5mg/kg/dose three times per day	Effective in treating mild to moderate PCP Duration of therapy 21 days	Neutropenia, anaemia, thrombocytopenia, methaemoglobinaemia, rash, transaminase elevation
Clindamycin/primaquine*	Clindamycin: 600mg IV every 6 hours for 10 days, then 300–450mg orally every 6 hours to complete 21 days of treatment Primaquine: 30mg of base orally for 21 days (for patients >60kg) Clindamycin: 10mg/kg/dose every 6 hours Primaquine: 0.3mg/kg/day (paediatric doses)	Effective in treating mild to moderate PCP Primaquine is contraindicated in patients with glucose-6-dehydrogenase deficiency	Rash, nausea, diarrhoea

* Limited data on children.

Table 101.2 PCP chemoprophylaxis for HIV-infected children

Initiation of chemoprophylaxis	
1 to <6 years	$CD4^+$ cell counts <500 cells/mm^3 or $CD4^+$ percentage <15%
≥6 years	$CD4^+$ cell counts <200 cells/mm^3 or $CD4^+$ percentage <15%
Discontinuation of chemoprophylaxis	
1 to <6 years	For those who receive combination antiretroviral therapy for ≥6 months and have for >3 consecutive months: $CD4^+$cell count ≥500 cells/mm^3 or $CD4^+$ percentage ≥15%
≥6 years	For those who receive combination antiretroviral therapy for ≥6 months and have for >3 consecutive months: $CD4^+$ count ≥200 cells/mm^3 or $CD4^+$ percentage ≥15%

Note: Do not discontinue PCP chemoprophylaxis in HIV-infected children aged <1 year.

- *Children with haematologic malignancies (leukaemia or lymphoma), some non-haematologic malignancies, and children with severe cell-mediated immunodeficiencies*.

The duration of PCP prophylaxis varies, depending on individual circumstances.

2° prophylaxis should be given to all children with a history of PCP who are severely immunocompromised, until their immunity recovers sufficiently.

The recommended prophylactic regimen for all immunocompromised patients against *P. jirovecii* (for children ≥4 weeks of age) is Co-trimoxazole. The prophylactic dosage is 150mg/m^2 per day of the trimethoprim component (~5–10mg/kg per day) administered orally either every day (5–10mg/kg/dose once daily of trimethoprim) or on 3 consecutive days per week (2.5–5mg/kg/dose of trimethoprim twice per day, or every other day). The total daily dose should not exceed 320mg of trimethoprim.

For patients who cannot tolerate Co-trimoxazole, alternative choices are:

- Oral atovaquone: for 1–3 months and >24 months to 12 years, 30mg/kg/day; for >3 months to 24 months, 45mg/kg/day; and for ≥13 years 1500mg
- Oral dapsone: for children ≥1 month, 2mg/kg/day (maximum total dosage 100mg/day); or 4mg/kg/week (maximum total dosage 200mg/week), and
- Aerosolized pentamidine: for children ≥5 years, the dosage is 300mg once per month via Respirgard II nebulizer.

Up-to-date and new information

- Reclassification as fungus with new name. Now known as *Pneumocystis jirovecii*.
- PCP remains a major opportunistic disease in HIV-infected patients and an emerging problem in immunocompromised patients without HIV infections.

What's new?

- Development of novel, non-invasive diagnostic tests (PCR, (1,3)-β-D glucan, S-adenosylmethionine).
- There is an increasing understanding of the immune response to *Pneumocystis*.
- Although the clinical significance of *Pneumocystis* colonization remains to be elucidated, there is an association between colonization and pulmonary disease development and transmission.

What's next?

- Determining whether one single simple prophylaxis regimen is adequate for all children with immunocompromise at risk of PCP.
- New drugs with different modes of action are needed, as current drugs are associated with many side effects, and mutations have emerged.
- The combination of caspofungin and Co-trimoxazole is a promising therapeutic approach that needs to be assessed in controlled clinical trials.
- Biological markers to estimate the risk for PCP infection in non-HIV immunocompromised hosts are needed.

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Chapter 102

Polio

Name and nature of organism

- Poliomyelitis is caused by infection of the motor neurons of the CNS by poliovirus.
- Poliovirus is a positive-strand RNA virus of the family *Picornaviridae*, now classified with many Coxsackie virus A types as a species C human enterovirus.
- The virion consists of an icosahedral, non-enveloped protein capsid, composed of four capsid proteins (VP1, VP2, VP3, and VP4), which encapsulates the RNA genome.
- Poliovirus has a rapid replication cycle, with ~8 hours elapsing between infection and the release of progeny virions upon host cell lysis.
- There are three serotypes of the virus, designated types 1, 2, and 3. Infection gives immunity to the serotype, but immunity to one serotype does not protect adequately against the other two, so vaccines contain single strains of each serotype.

Epidemiology

- Humans are the only known natural host.
- Poliovirus infection occurs predominantly in summer and autumn in temperate climates, but year-round in tropical regions.
- Prior to the twentieth century, in a poor hygiene environment, exposure to infected faecal material will occur while the child is still protected by maternal antibody, and infection will be safely confined to the gut. Following the Industrial Revolution and improvements in hygiene and sanitation, children increasingly encountered poliovirus at older ages, without the benefit of passively conferred immunity, leading to epidemics of poliomyelitis. This gave rise to an alternative name of infantile paralysis of polio.
- Attempts to control poliomyelitis through vaccination programmes in 1950 have led to a dramatic fall in the incidence of poliomyelitis. The Global Polio Eradication Initiative (GPEI) began in 1988; since then, wild poliovirus (WPV) transmission has decreased by 99%, and currently WPV transmission remains endemic only in Afghanistan, Nigeria, and Pakistan. During 2014, outbreaks caused by importation of WPV type 1 (WPV1) cases have been detected in previously polio-free countries such as the Horn of Africa and the Middle East (Syria to Iraq). WPV type 3 (WPV3) cases have not been detected in Pakistan since April 2012, and in Nigeria since November 2012; therefore, there is possible eradication of WPV3. No WPV type 2 (WPV2) cases have been detected anywhere in the world since 1999.

Transmission and incubation period

- Transmission is primarily by the faecal–oral route.
- The virus enters through the GI tract. The 1° site of replication is in the M cell lining the mucosa of the small intestine; then the virus spreads to deep local lymph nodes, and a 1° viraemia occurs after 2–3 days. From the blood, the virus gets to multiples sites, including skeletal muscle, fat, liver, reticuloendothelial system, and bone marrow until to the CNS. Gut infections are silent; the 2° infection sites correspond to the minor disease, and CNS infections cause the major (paralytic) disease.
- The incubation period is generally between 7 and 14 days but can range from 3 to 35 days.
- Typically, the minor disease occurs 7 days, and the major disease 30 days, after infection.
- Patients are most infectious immediately before, and 1–2 weeks after, the onset of paralytic disease.

Clinical features and sequelae

- The most serious result of poliovirus infection is paralysis, although 90–95% of infection are asymptomatic but induce protective immunity.
- The minor disease occurs in about 5% of patients after 1–2 weeks after infection, also called 'abortive poliomyelitis'. Fever, malaise, anorexia, and headache are prominent features; sore throat, and muscle and abdomen pain may be present. The illness is short-lived, lasting up to 2–3 days.
- A small proportion of patients experiencing a major viraemia will manifest signs and symptoms of CNS invasion. These include:
  - Non-paralytic polio (1–2% of poliovirus infections) with specific features of aseptic meningitis. Patients experience the non-specific features of abortive poliomyelitis but, in addition, may complain of severe headache and neck, back, and lower limb pain. They may display nuchal rigidity and CSF lymphocytosis
  - Spinal poliomyelitis—characterized by acute flaccid paralysis 2° to the selective destruction of spinal motor neurons and subsequent denervation of the associated skeletal musculature. Children exhibit a biphasic illness, with 2–3 days of minor non-specific illness, followed by up to 5 days without symptoms. Abrupt onset of headache, fever, vomiting, neck stiffness, and intense muscle pain is followed, after 24–48 hours, by flaccid weakness and paralysis, which are usually asymmetrical. Multiple muscle groups and limbs may be involved, with proximal involvement usually more severe than distal. The lower limbs are involved more frequently than the upper limbs. Deep tendon reflexes may initially be hyperactive but are rapidly lost. Sensory loss has been described but is rare. Bladder paralysis and bowel ileus commonly occur but tend to improve over a few days
  - Bulbar poliomyelitis—characterized by paralysis of muscle groups innervated by cranial nerves. Patients present with dysphagia, nasal speech, and respiratory compromise 2° to involvement of the medullary respiratory centre

- Bulbospinal poliomyelitis—where both the brainstem and spinal cord are affected, resulting in a mixed clinical picture
- Paralytic poliomyelitis—occurs in 0.1–1% of all cases of poliovirus infections. Cranial nerve dysfunction is reported in 5–35% of paralytic polio cases. Respiratory compromise is an important complication, resulting from involvement of both the diaphragm and intercostal muscles, the medullary respiratory centre, and IXth, Xth, and XIIth cranial nerves affecting the pharyngeal, palatal, and vocal cord function. In the pre-vaccination era, mortality rates of up to 60% were reported, mainly due to respiratory compromise. With modern intensive care, mortality rates of 2–5% in children have been described
- Most cases of paralytic disease will show clinical improvement, but ~60% of affected individuals will experience a residual deficit. Complete recovery is rare if the paralysis is severe or ventilatory support is required. Patients who survive bulbar involvement often recover quickly to normal function
- Certain risk factors for paralysis have been identified. These include pregnancy, B-cell immunodeficiencies, strenuous exercise during the first days of the illness, and IM injections which seem to predispose to paralysis in the limb injected (provocation paralysis)
- Complications of infection include respiratory compromise, myocarditis, GI haemorrhage, and ileus
- Up to 30% of patients who have recovered from paralytic polio may experience new-onset weakness, pain, and atrophy in the previously affected muscle groups some 25–35 years after the 1° illness, referred to as the post-polio syndrome.

Diagnosis

- The virus may be cultured from throat and stool swabs.
- After initial replication in the mucosal epithelium, poliovirus is shed in nasopharyngeal secretions and saliva for 1–2 weeks, and in faeces for 3–6 weeks. Immunocompromised individuals have been shown to excrete poliovirus for prolonged periods of time, occasionally 3 years or more, and, in some extreme situations, for as long as 20 years after mucosal infection.
- WHO recommends the isolation and identification of poliovirus in the stool. Poliovirus concentrations are high in the first week after the onset of paralysis.
- Poliovirus may be isolated from 80% to 90% of specimens from acutely ill patients, and 20% of specimens after 3–4 weeks after the onset of paralysis.
- Isolation of virus from CSF is diagnostic but seldom achieved. CSF is often normal during minor illness, and, with CNS involvement, CSF may show raised cell count (10–200 leucocytes/mL) and mildly raised protein (40–50mg/dL).
- Neutralizing antibody can be detected in serum as early as 1 week post-infection, and a greater increase after 3–4 weeks from the onset of paralysis. A 4-fold rise in acute and convalescent IgG titres

demonstrates acute infection but cannot distinguish between vaccine and wild-type virus.
- RT-PCR for poliovirus can be performed for stool, throat swabs, and CSF specimens.

Management

- There is no specific antiviral therapy.
- Management is supportive:
  - Analgesia and bed rest in the acute phase to reduce extension of the paralysis
  - Decompression of the bladder, where indicated
  - Ventilatory assistance/tracheal intubation, where indicated
  - Avoid IM injections—risk of 'provocation paralysis' (see Clinical features, p. 765–6)
  - Physiotherapy during the recovery phase.

Prevention

- Vaccination is the only effective method of preventing poliomyelitis, and, since its introduction in the 1950s, there was a dramatic effect on the incidence of polio. The two types of polio vaccines most widely use are the trivalent inactivated polio vaccine (IPV) and trivalent live attenuated OPV.
- The first vaccine to be introduced was Salk's IPV in 1955. This immunized against all three strains of poliovirus and reduced the incidence of paralytic poliomyelitis in the US from 13.9 cases per 100 000 in 1954 to 0.5 cases per 100 000 in 1961.
- In 1961, Sabin developed monovalent live OPVs which were replaced by a trivalent OPV in 1963. These were seen to offer the advantage of superior immunogenicity, ease of oral administration, induction of local mucosal immunity, and the potential public health benefit of the spread of live vaccine (attenuated) viruses from immunized to unimmunized contacts. However, the genetic instability of the Sabin vaccine strains, combined with the potential for recombination with other viruses, allows reversion of attenuated strains to neurovirulence, leading to rare cases of vaccine-associated paralytic poliomyelitis (VAPP).
- VAPP is defined by WHO as poliomyelitis that occurs in a vaccinee between 7 and 30 days after a dose or in a close contact of a vaccinee between 7 and 60 days after receipt of the dose. VAPP is commonest after the first vaccine dose. Hypogammaglobulinaemic individuals have a 3000-fold higher risk of developing VAPP than healthy vaccinees. OPV is contraindicated in patients with immunodeficiency or household contacts of immunodeficient individuals.
- In addition to VAPP, a further consequence of OPV is the development of vaccine-derived polioviruses (VDPVs). A VDPV is defined as a Sabin poliovirus with ≥1% of genetic variation, compared to the prototype sequence (reflecting sustained viral replication over at least 1 year

in one or more persons). These viruses can be further subdivided into two subtypes: circulating VDPV (cVDPV) when the reversion to neurovirulence is associated with person-to-person transmission, and immunodeficiency-related VDPV (iVDPV) caused by prolonged virus replication in an immunodeficient individual. Individuals with deficient B-cell immunity may fail to clear the virus after OPV vaccination and may continue to excrete the virus for prolonged periods (months to decades).

- Outbreaks of cVDPV, with sustained transmission in affected communities, have occurred primarily in areas where poor vaccine coverage has led to diminished herd immunity and have involved all three serotypes (including serotype 2 which has been eradicated in its wild form). These outbreaks have been interrupted with widespread targeted vaccination programmes using OPV.
- IPV does not run the risk of VAPP or VDPV but, in its current form, may be prohibitively expensive in the developing world.
- The reasons for failure, to date, of the global initiative to achieve its goal are multiple. Interruption of vaccination programmes due to military conflicts, local cultural or political misconceptions regarding the vaccine, and fears of VAPP impact on herd immunity all predispose to local outbreaks. Reintroduction of the virus into previously polio-free countries has occurred through travel. Low OPV vaccine efficacy has been reported in certain states in India, with children requiring multiple doses to achieve levels of population immunity to stop poliovirus transmission.
- The GPEI Strategic Plan for 2013–2018 is to: (1) interrupt all poliovirus transmission, (2) progressively withdraw OPV and introduce IPV, (3) certify polio eradication, and (4) transition assets and infrastructure to routine immunization programmes as part of the GPEI legacy.
- To obtain a progressive withdrawal of OPV, WHO has recommended that all 124 countries currently using only OPV introduce at least one dose of IPV before the global withdrawal of serotype 2 OPV in 2016. A 1- or 2-dose schedule, potentially administered intradermally with a reduced antigen content, may make this affordable.

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Chapter 103

Molluscum contagiosum and other poxviruses

See also Chapters 4, 19, 24, 34, 37, 38.

Molluscum contagiosum

Name and nature of organism

- Common self-limiting cutaneous wart-like eruption in children and young adults.
- Can cause problems in the immunocompromised host.
- Large, double-stranded DNA virus of the poxvirus group.
- Four distinct genotypes have been identified.
- Type 1 is the commonest cause of the condition in children.
- Type 2 is commonest in adults (often sexually transmitted).
- The virus replicates in the cytoplasm of epithelial cells.

Epidemiology

- Very common worldwide infection.
- Humans are the only host.
- In a Dutch GP survey, there was an incidence of 2.4 per 1000 person-years, mainly in children.
- An Australian seropositivity study in 357 people showed an overall seropositivity rate of 23%.
- It is estimated that <5% of children in the US have clinical evidence of molluscum contagiosum infection.
- Prevalence may be higher in tropical areas.
- Age distribution is bimodal; most cases occur in preschool children.
- Cumulative incidence of infections in young children is 17%.
- Infection is rare in children <1 year of age.
- Infection in young adults is predominantly sexually transmitted, with a ♂:♀ ratio of 3.3:1.
- Infection is more prevalent in individuals with impaired cellular immunity, such as HIV infection, where the prevalence increases with decreasing CD4 count, and in those with skin disease, e.g. eczema.
- Relationship between atopic dermatitis and molluscum contagiosum remains uncertain.

Transmission

- Mode of transmission is by direct skin-to-skin contact, being involved in contact sports, living in close proximity, sharing of fomites, and sexual contact.
- Incubation period is typically 2–7 weeks (range 1–26 weeks).

- Transmission is increased from disrupted skin lesions following scratching, which may also lead to auto-inoculation. Period of infectivity unknown, but probably while lesions present.
- Auto-inoculation is believed to be the commonest cause of anogenital lesions in infants and young children.
- However, the possibility of sexual abuse should be considered.
- Vertical transmission has been reported.

Clinical features

- Skin lesions are smooth papular lesions with a pearly appearance and often central umbilication.
- Papules usually are <5mm in diameter but can be as big as 2cm, particularly in the immunocompromised host.
- Typically, a patient may have 20–40 lesions.
- Lesions tend to occur in clusters or sometimes in lines.
- The lesions may be anywhere on the body, except the palms and soles.
- Oral mucosal involvement is rare.
- Disrupted lesions can discharge a waxy infectious white material.
- There are no systemic features to the infection.
- 2° bacterial infection can occur. Lesions on the eyelids can be troublesome, particularly in patients with AIDS in whom the lesions become confluent and induce keratoconjunctivitis.
- Nine to 47% of the patients develop molluscum dermatitis. A short course of topical steroids can be used.
- Gianotti–Crosti syndrome may occur in association with molluscum contagiosum.

Diagnosis

- The appearance of the lesions is highly characteristic, and it is rare that tests need to be performed to confirm the diagnosis—look for the central umbilication.
- Where tests are required, a lesion can be punctured, and the core material examined either by light microscopy, to show the characteristic intracytoplasmic inclusion bodies, or by EM.
- Histopathology reveals eosinophilic cytoplasmic inclusion bodies within keratinocytes.
- Molecular diagnostic assays are available, but not used widely.

Management and treatment

- In the immunocompetent host, the infection runs a benign, self-limiting course. Individual lesions heal spontaneously in 3 months.
- New lesions will continue to appear, and the whole episode of infection may last from 8 to 18 months.
- Recurrences are rare.
- Scarring is unusual, unless there has been a lot of scratching or 2° infection.
- In immunocompromised individuals, the lesions may persist for a longer period of time and may enlarge and become disfiguring.

- In the vast majority of cases, no treatment is required. Treatment is only required in those with immunosuppression. No one treatment has been found to be convincingly effective.
- Surgical treatment involves curettage of individual lesions following topical anaesthesia. This is effective but may result in scarring.
- Cryotherapy has also been used—but is painful.
- Topical treatments include cantharidin (a topical blistering agent) and podophyllotoxin (an antimitotic agent), and the antiviral agent cidofovir.
- Imiquimod, KOH, salicylic acid, and topical retinoids have also been used, although the efficacy of the agents is uncertain.
- Based on some randomized trials, if treatment is desired, cryotherapy, curettage, cantharidin, and podophyllin should be considered as first-line therapeutic options.
- In very severe cases associated with underlying immunocompromised states, systemic therapy with antivirals, such as cidofovir, or with immune modulators, such as cimetidine or interferon alfa, has been used.
- In HIV-positive patients, the use of ART is helpful by correcting the CD4 lymphopenia.
- Treatment of genital lesions in adolescents/adults to prevent sexual transmission should be considered.

Prevention

- Isolation and exclusion from school are not justified.
- Transmission of infection can be reduced by avoiding the sharing of bath towels, sponges, or clothes and minimizing skin-to-skin contact.
- Individuals with molluscum contagiosum should be encouraged not to scratch the lesions, which increases their infectivity.
- In those with lesions confined to a limited area, covering of lesions with bandage or tape prior to participation in contact sports may reduce the likelihood of transmission.

Future research

- Development of an *in vitro* culture system for the virus would help in the development of antiviral agents.
- Where therapy is indicated, controlled clinical trials are required to determine optimal treatment regimens.

Other poxvirus infections

Smallpox

- Natural smallpox was eradicated in 1977 after a global immunization campaign. The virus is believed to be held in only two research laboratories in the US and Russia due to the potential for bioterrorist release. The clinical picture is of a widespread bullous eruption, similar to chickenpox, but with a marked peripheral distribution.

Monkeypox

- Only seen in rural Africa, e.g. Zaire, after animal-to-human contact.
- Severe illness, similar to smallpox, with high mortality.

Cowpox and orf

- Reported in Europe and Central Asia following animal contact. Causes localized vesicles that ulcerate. In orf, these may be 2–3cm in diameter.

Other reported uncommon zoonotic poxviruses

- Bovine popular stomatitis virus.
- Paravaccinia virus.
- Deerpox and sealpox viruses.
- Tanapox virus.
- Yatapoxviruses.

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Chapter 104

Prion diseases

Name and nature of organism

- Caused by unconventional transmissible agents called 'prions'.
- Prions are derived from a normal cellular protein (PrP^C).
- Normal function of the prion proteins is not well understood.
- Prions are characterized by their infectious properties.
- When the normal cellular protein PrP^C, which is largely of an α-helical form, is transformed into a β-sheet form, referred to as PrP^{Sc} ('Sc'—scrapie), disease may manifest.
- Each of the PrP^{Sc} conformations seems to be associated with a specific illness leading to neuronal injury and death.
- In sporadic CJD, the misfolding of PrP^C to PrP^{Sc} is likely to happen spontaneously.
- In genetic prion diseases (PDs), PrP^C is encoded by *PRPN* gene which is located on chromosome 20p13.
- In acquired forms, PrP^{Sc} is transmitted accidentally or iatrogenically.

Classification

Based on the clinical manifestations and species in which they occur, PDs are classified into human and animal disease. Currently, there are five forms of human PD recognized:

- Kuru
- CJD:
  - Sporadic CJD (sCJD)
  - Iatrogenic CJD (iCJD)
  - Familial CJD (fCJD)
  - Variant CJD (vCJD)
- Gerstmann–Straussler–Scheinker syndrome (GSS)
- Fatal insomnia:
  - Familial (fFI)
  - Sporadic (sFI).

Epidemiology

Human prion diseases

- Annually, there are ~6000 cases worldwide.
- There is no marked difference in incidence between the sexes.
- The majority of human PDs (85–90%) fall into the sCJD category.
- fCJD and iCJD account for 5–15% and 1% of total cases of CJD, respectively.

- ~60 cases of sCJD occur each year in the UK.
- Over the period 1990–2006, the average crude annual mortality rate from sCJD was <1 per million persons in the UK.
- Annual number of vCJD peaked in 2000 with 28 cases and is currently in steep decline. A total of 224 cases have been reported, and most of them occurred in the UK.

Bovine spongiform encephalopathy

- The first confirmed case occurred in the UK in 1996.
- Since then, >180 000 cattle have been affected in the UK.
- Several other countries have also reported BSE cases.
- The origin of BSE, though not fully established, was epidemiologically and experimentally linked to the use of meat and bone meal in cattle feed.
- The epidemic was brought under control by restricting, and later prohibiting, the use of mammalian meat and bone meal in farm animals.

Transmission and incubation period

- Efficiency of transmission depends on the route of inoculation and species difference between the donor and the host.
- Species barriers, largely inhibiting transfer between species, are observed in PDs.
- PDs can be experimentally transmitted through the brain and spinal cord, eye, lung, liver, kidney, spleen, lymph node tissues, and CSF.
- Cases of transfusion transmission of vCJD have been reported.
- Several modes of iatrogenic transmission of CJD have been recognized:
  - Corneal and dura mater grafts account for the vast majority of cases
  - Liver transplants
  - Cadaveric pituitary-derived gonadotropin and human growth hormone (hGH)
  - Use of contaminated EEG depth electrodes and neurosurgical instruments
  - Proven surgical routes for transmission have now been largely eliminated.
- Enteral transmission, the probable mode of transmission in most cases of vCJD, appears to be the least efficient.
- Secretions and excretions have not been demonstrated to transmit infection.
- PDs are not known to be transmitted from mother to child during pregnancy or childbirth.
- Familial disease is inherited as a result of genetic mutations.
- PDs typically have long incubation periods.
- The incubation period is influenced by:
  - Route of infection (central inoculation, leading to a more rapid onset of disease than peripheral inoculation)
  - Strain
  - Dose
  - Species difference (transmission between species tends to have a longer incubation period).

Clinical features and sequelae

Kuru

- Observed in the Foré population of New Guinea and found to be 2° to mortuary feast (transumption) rituals of the tribe.
- Gradually, it disappeared once mortuary feasts were discontinued in the 1960s.
- The mean incubation period is ~12 years.
- The disease occurs in predictable stages:
  - Ataxia, tremors, and postural instability observed in the early phase
  - Loss of ambulation, involuntary movements, including myoclonus, choreoathetosis, and fasciculations appear in the sedentary stage
  - Progressive dementia, frontal release signs, cerebellar-type dysarthria usually observed in the terminal phase.
- Death occurs within 9–24 months from the onset of the illness.

Creutzfeldt–Jakob disease

CJD has four major forms. All forms of CJD are progressive and are fatal. Currently, there are no treatments that have been shown to halt progression or to reverse the disease.

Sporadic Creutzfeldt–Jakob disease

- sCJD accounts for most PD cases in humans.
- Cause is unknown.
- There is no association with a genetic mutation or evidence for exposure to a PD agent.
- It is a disease of middle and old age. Occurrence before age 40 or later than 70 is uncommon.
- Characterized by rapidly progressive mental deterioration and myoclonus, although clinical presentation can be variable.
- Onset usually is subacute.
- First symptoms can be subtle behavioural or psychiatric and constitutional symptoms (fatigue, vertigo, headache, hypersomnia).
- Extrapyramidal signs, such as nystagmus and ataxia, occur in approximately two-thirds of patients.
- More prominent psychiatric symptoms and prolonged clinical course observed in older patients.
- Typical neuropathologic features: neuronal loss, gliosis, vacuolation, and deposition of PrP^{Sc}.
- Death usually occurs within 1 year of illness onset. Median survival 7–8 months.

Familial Creutzfeldt–Jakob disease

- Shows an autosomal dominant inheritance pattern and accounts for 5–15% of CJD patients.
- The substitution of lysine for glutamine in codon 200 is the commonest *PRNP* gene mutation.
- >15 *PRNP* mutations manifest as fCJD.
- It also occasionally exhibits ‘generational skip’ and occurs in a seemingly sporadic pattern.

- Clinical features of fCJD are generally similar to those of sCJD.
- Age at onset is younger, and progression is usually slower than in sCJD.

Iatrogenic Creutzfeldt–Jakob disease

- >400 cases have been reported since 1950.
- CJD surveillance reported that, in 2000, all incident cases of iCJD were from infections acquired before 1985.
- Estimated mean incubation time of 9–10 years has been reported.
- Homozygosity for a polymorphism at codon 129 in *PRNP* is a risk factor for iCJD.
- Patients with iCJD are often younger than sCJD patients.
- The symptoms are similar to other forms of CJD, but more rapidly progressive in the iatrogenic form.

Variant Creutzfeldt–Jakob disease

- Originally called new variant CJD (nvCJD), is a form of CJD first described in the UK in 1996.
- It was aetiologically linked to the contemporary epidemic of BSE.
- It is distinct from the other forms of CJD in its epidemiology, clinical profile, and neuropathology.
- Five cases have been reported to be acquired through blood or blood product transfusion.
- Patients are much younger at the onset of the disease. Median age ~27 years.
- Mean disease duration is about 14.5 months.
- Sensory abnormalities may be seen early and include dysaesthesia and paraesthesiae of the face, hands, feet, and legs.
- As the disease progresses, other neurologic signs including gait ataxia, and dysarthria appear, quickly followed by cognitive impairment, involuntary movements, immobility, unresponsiveness, and mutism.
- Paresis of upward gaze was noted in 50% of the patients, an uncommon sign in other forms of CJD.

Gerstmann–Straussler–Scheinker syndrome

- Rare familial form of PD.
- At least 15 *PRNP* mutations can cause GSS. Codon 102 mutation is the commonest.
- The main characteristics are a subacute development of the disease (several years in many cases) and the presence of multicentre PrP plaques on histopathological examination.
- The illness starts at about the age of 40, with progressive cerebellar ataxia and/or parkinsonian disorder as the main symptoms.
- Oculomotor or pyramidal signs and dementia develop later.

Familial fatal insomnia

- Rare form of PD reported in a few families in France, but also in other parts of the world.
- FFI is caused by a single *PRNP* point mutation D178N.
- Onset usually occurs in the fifth and sixth decades.
- The disease duration is ~1–1.5 years.

- Clinical features, in particular, associate a severe insomnia with significant delusions, vegetative symptoms (loss of circadian rhythms, dyspnoea, loss of thermoregulation), motor impairment, myoclonia, and dementia.
- On neuropathological examination, gliosis is predominant in the anterior and dorso-median thalamic nuclei.

Bovine spongiform encephalopathy

- First reported in British cattle in 1986, it later spread to several other countries.
- It is a slowly progressing fatal disease, affecting the CNS of cattle.
- The source of BSE remains unclear.
- It is believed that BSE occurred as a consequence of feeding scrapie-infected sheep products to cattle.
- Alternatively, BSE may be due to the meal derived from cattle tissue containing a pre-existing, but unrecognized, bovine prion.
- There is increasing evidence supporting the possibility that vCJD represents bovine-to-human transmission of BSE.
- The duration of the clinical course of BSE in cattle is typically 1 or 2 months but ranges from 7 days to 14 months.
- The most commonly observed signs are apprehension, hyperaesthesia, and ataxia.

Diagnosis

- At present, no diagnostic test exists for the detection of PDs in live animals or humans.
- The main criteria include clinical and neuropathological features, including the presence of prions, and the infectivity in homologous and/or heterologous species.
- Diagnosis is supported by various tests such as specific EEG changes, detection of neuronal enzymes and specific proteins in CSF, and diagnostic changes on MRI.
  - Routine CSF and other laboratory studies are usually normal.
  - Several CSF biomarkers, such as 14-3-3 protein, total tau (T-tau), neuronal-specific enolase (NSE), and S100β, have been used to diagnose some PDs. Specificities of each marker vary greatly.
  - A typical EEG in sCJD shows periodic sharp or triphasic wave complexes occurring approximately once every second.
  - MRI has been shown to be highly specific and sensitive (92–95%) for sCJD.
  - Neuropathologic examination reveals spongiform degeneration in the cerebral cortex, basal ganglia, and thalamus, with relative sparing of the brainstem and cerebellum in CJD patients.
  - Due to the apparent absence of a nucleic acid component, PDs are impossible to diagnose using PCR.
  - The absence of an inflammatory or immunological reaction means that antibody or cell culture assays used to diagnose other infectious diseases are of no use.

- The pathological form of the prion protein PrP^{Sc} may be detected by EIAs or ELISA.
- The only reliable molecular marker for PDs is PrP^{Sc} that accumulates in the CNS and, to a lesser extent, in lymphoreticular tissues.
- Post-mortem examinations remain an essential element in confirming the clinical diagnosis and the cause of death as PD.

Differential diagnoses

- Cerebral vasculopathies (ischaemic, amyloid, inflammatory, vascular lymphoma).
- Chronic encephalitis, including Hashimoto's encephalitis, viral encephalitis, and SSPE.
- Alzheimer's disease and other dementias (usually in older patients).
- Paraneoplastic encephalitis.
- Encephalopathy (e.g. anoxic brain damage—obvious from the history and accompanied by watershed infarction).
- White matter diseases (e.g. multiple sclerosis—should be differentiated by imaging).

Management and treatment

- No effective treatment has been identified for human PDs.
- Care is supportive.
- Normal social and clinical contact, non-invasive clinical investigations (e.g. X-ray imaging procedures), diagnostic tests, or interventions involving non-infective tissues (e.g. blood tests) with PD patients do not present a risk to health-care workers, relatives, or the community.
- Isolation of patients is not necessary; they can be nursed in the open ward or at home using universal precautions.
- Nursing care to prevent the complications of immobility, such as pressure sores, is important.
- Care givers should be made aware of possible psychiatric symptoms, and the need to address emotional, psychological, and social issues of the patient and relatives.

Prevention measures

- PD agents exhibit an unusual resistance to conventional chemical and physical decontamination methods.
- Some infectivity may persist under standard hospital or health-care facility autoclaving conditions.
- Prion proteins are extremely resistant to high doses of ionizing and UV irradiation, and some residual activity has been shown to survive for long periods in the environment.
- Infection control measures are required in handling tissues of suspected or potential cases.

- All high- and low-infective PD infectious health-care waste should be disposed of according to the stipulated national standards.
- As mother-to-child transmission is not observed in PDs, no particular precautions need be taken during pregnancy.
- Childbirth should be managed using standard infection control procedures.
- Relatives and caregivers of PD cases should be advised on safety precautions, as appropriate. Otherwise disposable equipment must be used.
  - So far, no cases due to accidental exposure of such nature have been reported.
- Proper screening of donors of human cells, tissues, and tissue-derived products can minimize the spread of PD through such products.
- Ban on the feeding of protein derived from ruminants (e.g. cattle, sheep, and goats) to any ruminant.
- Ban on the use of bovine offal in food chains.

Key areas of uncertainty

- Despite extensive research, the precise nature of the infectious agent, pathogenesis, and mode of transmission remain unclear.
- The means whereby the pathological form of the prion protein crosses the species barrier and converts the prion protein of the new host is also uncertain.
- Precise ante mortem diagnostic tests, the development of a 'vaccine', and effective treatments for all forms of CJD are priorities.

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Chapter 105

Rabies

See also Chapters 14, 42, 45.

Name and nature of organism

- Rabies is a zoonosis caused by a rhabdovirus that can affect the nervous system of all mammals, including humans, causing an acute encephalomyelitis and leading to painful death in almost all cases.
- Caused by the RNA rhabdovirus, genus *Lyssavirus* (*Lyssa*—Greek God of raging fury/madness) (this genus has seven genotypes, of which type 1 represents the classic rabies virus). The virus causing clinical rabies in bats is distinct from that causing rabies in dogs.
- Less frequently, rabies may result from infection with rabies-related *Lyssavirus*, including European bat lyssaviruses (EBLVs).
- A strain of rabies called European bat lyssavirus 2 (EBLV-2) has been found in UK Daubenton bats.

Epidemiology

- WHO estimates that over 55 000 people die from rabies each year (95% in Asia and Africa).
- The epidemiology of human rabies mirrors the disease prevalence in the local animal population.
- Rabies in animals is found in all continents, except Antarctica.
- Individual countries report being rabies-free in terrestrial animals.
- Animal rabies is predominantly found in dogs but may affect all mammals. It has been found in cats, foxes, skunks, and bats.
- In Europe, the main indigenous animal reservoirs are:
  - Eastern Europe/borders with the Middle East: dogs
  - Central/Eastern Europe: fox
  - North-Eastern Europe: racoon
  - Pan-Europe: insectivorous bat.
- Most human deaths result from a bite from an infected dog; 30–60% of those bitten by dogs are children <15 years.
- Children, especially from poorer backgrounds, are more likely to play outdoors with dogs. As they are shorter than adults, they are more likely to be bitten and scratched around the head and face, and will therefore have a worse clinical outcome.
- The European incidence is <5 cases per year. From 2008 to 2009, there were four reported cases of human rabies: two in Ukraine, one in the Russian Federation, and one in the UK. The former two countries reported 960 and 632 cases of rabies in domestic animals, respectively, while the UK case was imported.

- In the UK, the last case of human rabies from an indigenously affected terrestrial animal occurred in 1902.
- There was a fatal case of human rabies from an indigenous bat in Scotland in 2002, and imported cases occurred following a dog bite in Goa in 2005 and South Africa in 2008.[1]
- Wound cleansing and immunization performed as soon as possible after potential exposure prevent clinical onset of rabies in nearly all cases, but, once symptoms appear, the disease is usually fatal.

Transmission and incubation period

- Rabies is spread by the saliva of an infected animal.
- Transmitted to humans through bites, scratches, licks on broken skin, or mucous membranes.
- Rabies has rarely been transmitted through inhalation of contaminated aerosols from infected bats in caves and through organ transplantation from an unrecognized rabies case.
- Incubation period is generally between 3 and 12 weeks but may range from a few days to years, depending on the salivary viral load, inoculation site (quicker if closer to the brain), and the viral strain.
- There is a shorter incubation period for inhalational, face, and upper body exposure.
- Experimental studies indicate dogs may shed the virus (and hence be infectious) for 13 days before the onset of symptoms. Bats may be infected without symptoms.
- The virus enters the body through transdermal inoculation (infectious virus in saliva from a rabid animal), penetrating the skin through a bite or scratch, or direct contact with mucous membranes or broken skin.
- The rhabdovirus binds to cell receptors. It may directly infect nervous cells or replicate within striated muscle cells.
- The virus moves via retrograde axoplasmic transport at 1–40cm/day to the CNS where rapid viral replication occurs. The virus then travels via anterograde axoplasmic flow within peripheral nerves, with infection of neighbouring tissue (such as the salivary glands) en route.
- There is salivary viral shedding from the new victim when symptoms are manifest, thus completing the infectious cycle.

Clinical features

- Initially, there is a prodromal phase from 2 to 10 days of non-specific symptoms of fever, malaise, headache, and anxiety. There may be pain or paraesthesiae at the site of exposure.
- Then there are two distinct presentations:
  - *Encephalitic ('furious')*—presents with agitation, delirium, hydrophobia. May also demonstrate hyperventilation, hypersalivation, and priapism. Progresses to fluctuant conscious level and generalized convulsions. This leads to coma and death, usually within a week of onset of symptoms

- *Paralytic ('dumb' rabies)*—more commonly seen after bat exposure and looks clinically similar to Guillain–Barré syndrome, with an ascending flaccid paralysis and extreme weakness at the site of exposure, but coma, incontinence, and myxoedema are present in the former, but not the latter.[2]

Diagnosis

- The early diagnosis is difficult if no classic history of exposure is obtained.
- Specialist laboratories may be able to detect the virus in the CSF or saliva by culture or PCR.
- Brain biopsy in an animal may show the virus in the brain tissue.
- In England, the Virus Reference Division of PHE has expertise with the diagnosis of rabies in humans. Colindale also issues PEP immunoglobulin. Clinicians working in different countries need to familiarize themselves with national pathways to access post-exposure immunoglobulin.
- Laboratory diagnosis supported by DFA of hair follicles (on a full-thickness skin biopsy taken from the nuchal hairline), virus PCR, brain biopsy for histology (cytoplasmic inclusion bodies consistent with Negri bodies), and PCR. Antibodies against the virus can be detected in the CSF and serum. Several specimens (saliva, skin, serum, CSF) and different testing methods may be required to reach the diagnosis in a suspected case, since the sensitivity of any single test is limited.[3]

Treatment

- There is no specific antiviral therapy for rabies.
- Four patients have been reported to survive rabies.
- There is no proven standard treatment, although combinations of rabies immunoglobulin, vaccination, ribavirin, amantadine, interferon alfa, and ketamine have all been used.
  - A case was reported from Milwaukee, US, in 2005 of a 15-year-old girl bitten on her hand by a bat, who cleaned her wound immediately but did not seek medical advice, and then developed fatigue, diplopia, ataxia, and paraesthesiae 1 month later. She was treated by induced coma to buy time for the immune response to develop and was given amantadine and ribavirin. Rabies vaccine was not administered, and an LP, 8 days into the illness, showed rabies antibody. She was discharged home at 76 days and, at 5-month follow-up, was alert and communicative, but with an unsteady gait and choreoathetosis.[4]
- Given the high mortality of rabies, treatment is often palliative. Sedatives, neuromuscular blockade, narcotic analgesics, and antiepileptics may offer symptomatic relief. The 'Milwaukee protocol', as the induced coma therapeutic option is now known, has never been successfully replicated, despite attempts in at least 24 other patients. The current protocol uses ketamine and midazolam which may help

alleviate dysautonomia and suffering, but coma induction is not routinely recommended.
- Patients with rabies should be barrier-nursed to avoid potential health-care worker and family contact exposure to infectious material.
- All suspected human rabies cases should be notified to the appropriate local public health team.

Prevention

Pre-exposure

- Avoid exposure by being careful around dogs and bats.
- Pre-exposure vaccination is recommended for travellers to high-risk countries, laboratory workers handling the virus, and those who frequently handle imported animals.
- Pre-exposure immunization involves three immunizations by the deep IM or subcutaneous route with the inactivated vaccine at 0, 7, and 21- to 28-day intervals.
- Animal vaccination helps with environmental control (easier in domestic animals).

Post-exposure

- Washing the site of exposure aggressively with repeated irrigation and soap can reduce the risk of developing clinical rabies by 50–90%.
- Avoid suturing wounds and occlusive dressings.
- The slow time course of rabies with slow axoplasmic viral transport to the CNS allows time for successful intervention with PEP.
- PEP includes both the vaccine and rabies immunoglobulin (RIG) (human or equine).
- In previously unimmunized individuals, the vaccine should be given on days 0, 3, 7, 14, 30, and 90, and RIG 20IU/kg (most infiltrated into the exposure site and the residual given by parenteral injection).
- Two vaccine booster doses at 0 and then 3–7 days, rather than RIG, are indicated for patients completely vaccinated pre-exposure.
- Three inactivated vaccines are currently available in Europe for human rabies prophylaxis: a human diploid cell culture vaccine (HDCV; Imovax®, Sanofi Pasteur); a purified vero cell rabies vaccine (PVRV; Verorab®, Sanofi Pasteur); and a purified chick embryo cell vaccine (PCECV; Rabipur®, Novartis Vaccine and Diagnostics).[5]
- The vaccine does not contain live organism and cannot cause rabies disease.
- RIG is obtained from pooled immunized and screened donors.
- There have only been seven reported failures of PEP before the onset of symptoms when both the vaccine and RIG have been used according to the WHO protocol.
- WHO guidelines state, if the biting animal remains well under quarantined observation after 10 days, there is no risk of rabies transmission, and the vaccine course can be stopped.[6]
- The modern cell culture vaccine is safer than nerve tissue-based vaccines.

Future research

- Monoclonal antibodies as vaccines/therapy.
- Intradermal vaccine as pre-exposure prophylaxis.

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Chapter 106

Respiratory syncytial virus

See also Chapters 17, 27, 44.

Name and nature of organism

- RSV is a negative-sense, single-stranded RNA paramyxovirus of the genus *Pneumovirus*.
- There are two main immunodominant surface glycoproteins—the F fusion protein and the G attachment protein, which divide RSV into two antigenic subtypes A and B.
- The incubation period is 2–8 days, with 4–6 days being most commonly observed.

Epidemiology

- RSV is the commonest viral cause of bronchiolitis and severe respiratory illness in infants and young children. It has very predictable yearly epidemics worldwide, identifiable in virtually every country—from November to March in temperate climates, and during the rainy season in tropical climates.
- The sharp winter peaks demonstrate limited variability in respect of timing or size—most notably the Christmas/New Year period in temperate climates. The sharpness of the disease peak appears to be latitude-related, flattening closer to the equator. Severe RSV disease is commonest in younger infants in the first 6 months of life in Europe, and the second 6 months of life in Africa.
- ~20% of paediatric admissions for LRTI in the UK are due to RSV. The annual UK incidence of RSV-related hospital admissions is 28.3/1000 for infants, and 1.3/1000 for children between 1 and 4 years. Mortality is estimated at 0.1%. All children will have been infected by 2–3 years of age. The length of hospital stay for RSV bronchiolitis varies markedly across Europe.
- 1° infection induces an immune response with the production of specific antibodies, but it does not prevent repeated infections each year, although these are usually much milder. Antigenic variation both between the main subgroups and within each subgroup may be one of the factors in enabling RSV to cause reinfections. RSV A and B may co-circulate during an epidemic, but the specific proportions of the two groups will vary each year and also by location. Despite both RSV and influenza A outbreaks being prevalent in winter months, their peaks seldom overlap.
- Risk factors for severe lower respiratory disease include CHD, prematurity, immunodeficiency, and respiratory or neuromuscular conditions. Passive smoking is also a risk factor. Elderly patients and immunosuppressed patients can also suffer from severe disease.

Transmission

- Spread is by large droplets of secretion from an RSV-infected person, by direct hand-to hand contact, or via contaminated surfaces and objects. Studies suggest that aerosol spread via small particles is less important outside families, as infection does not occur at distances >1.8m (6ft) from an infected person. The virus can remain viable on surfaces for about 4–7 hours.
- Clinical severity dictates the duration and degree of viral shedding. RSV can be shed for prolonged periods, up to 4 weeks in young infants and 6 weeks in immunocompromised patients. Older children and adults shed the virus for 3–4 days.
- Transmission between infants and staff may be more important than between infants, in hospitals, childcare centres, and institutions. At home, infants are usually infected via an older sibling with few symptoms. Studies demonstrate that increasing family size correlates with increasing incidence of disease.

Pathophysiology

- Inoculation is via the upper respiratory tract. The nose and eye are more effective routes, compared with the mouth. After inoculation, RSV is confined to the respiratory mucosa, spreading down the lower respiratory tract by fusion of the infected cells with uninfected cells. This results in giant masses of cells with multiple nuclei known as syncytia—hence the name respiratory syncytial virus.
- A marked peribronchiolar cellular infiltrate occurs in RSV bronchiolitis. In the early stages, this consists of monocytes, lymphocytes, eosinophils, and neutrophils. In the later stages of the infection, T lymphocytes predominate with monocytes. An inflammatory cascade is triggered, involving a wide range of immunoregulatory and inflammatory molecules, including toll-like receptors, chemokines, cytokines, and surfactant proteins. Extensive research continues in this area to try to delineate the fine balance between protective effects of the immune process and disease severity.
- Subsequent necrosis of the epithelium and submucosal oedema of small airways occur; mucus plugging is also present, all of which contribute to hyperinflation and/or collapse of lung tissue. Ventilation–perfusion mismatches occur. Full recovery may take several weeks. In RSV pneumonia, studies have demonstrated an interstitial infiltration of mononuclear cells, with a more generalized involvement of bronchioles, bronchi, and alveoli.

Clinical features

- RSV begins as an URTI, quickly followed by signs of respiratory distress with tachypnoea, a typical bronchiolitic cough, occasional wheeze, but more commonly end-expiratory crackles, recession, and hyperinflation.

Older children present with an RSV viral pneumonia or a viral-induced wheeze picture.

- Acute illness gets worse, stabilizes, then usually resolves within 7 days, but infants may cough and wheeze post-recovery. High-risk infants may quickly progress to respiratory failure. Preterm infants may present with apnoea or non-specific signs of sepsis. Older children and adults will have symptoms similar to a cold (cough, runny nose, low-grade fever). Less commonly, RSV can also cause croup, ear infections, conjunctivitis, pneumonia, and laryngitis.

Diagnosis

- The availability of a rapid RSV test is useful for infection control measures and facilitating cohorting of patients for bed management. NPA immunofluorescence testing is the routine test available in hospitals. It has an estimated 60–90% sensitivity in acute illness. The diagnosis of bronchiolitis is a clinical one.
- CXR findings include hyperinflation and focal areas of collapse, which may rotate between different areas of the lungs during the course of the disease.

Management and treatment

- Most children can be managed at home. Hospitalization should occur in children needing fluids/oxygen or ventilatory support. Generally, a respiratory rate in an infant of over 60 breaths/min and/or taking less than two-thirds of normal feeds is a good marker for needing admission. Oxygen saturation <90% also mandates admission.
- Antibiotics are not required in the great majority of infants. Bacterial secondary infection is very rare.
- Where possible, milk feeds should be continued via a nasogastric tube, but, when these are not tolerated, IV fluids may be required. Oxygen should be delivered by nasal cannulae or a head box to ensure saturations are >93%. Supportive treatment is the only management option available. Studies have shown that adrenaline, bronchodilators, and oral, inhaled, and IV steroids offer no benefit, and a recent NICE analysis does not support their use in the acute phase. There is very little evidence of benefit for chest physiotherapy.
- Around 2% of admitted infants with RSV bronchiolitis require short-term ventilation due to apnoea or respiratory failure. Underlying prematurity, chronic lung disease, cardiac disease, or neurological problems are associated with longer intensive care stays. Medical management is supportive. Many treatments have been tried in PICU. None are of proven benefit.
- Ribavirin should only be considered as IV therapy in immunocompromised children with severe RSV disease in the intensive care setting where it may have a very small effect on reducing the length of ventilation and hospital stay.

Complications

- Studies have shown that RSV infections in infancy may result in long-term respiratory problems, with recurrent wheezing, reactive airways disease, and 'asthma', which may persist into adolescence. This risk is increased if parents smoke, so clear advice and support for stopping smoking should be given to all parents of a child diagnosed with RSV bronchiolitis.
- Children who have been hospitalized with RSV disease require more frequent hospital outpatient attendances for respiratory complaints. Recent studies have shown that regular inhaled corticosteroids do not reduce these late respiratory complications, so smoking advice is the only possible therapeutic intervention to prevent subsequent respiratory disease.

Prevention

- Hospitalized infants with RSV should be isolated or cohorted. Particular attention should be paid to standard infection control measures such as handwashing with alcohol-based gels, aprons, and cohort nursing.
- Currently, passive immunization with palivizumab, an IM monoclonal antibody, is the only licensed option available for certain high-risk groups. This is given monthly, usually for 5 months, over the winter RSV season. The original studies demonstrated a 55% reduction in RSV hospitalization in those deemed high-risk. Its cost-effectiveness remains debatable. Systematic reviews are in agreement that the potential costs of palivizumab nearly always outweigh any potential savings generated by reduced hospital admissions. Mortality from RSV bronchiolitis is now extremely low, even in high-risk groups.
- National guidance varies, based on local epidemiology and hospital costs.
- In the UK, the Joint Committee on Vaccination and Immunisation advise palivizumab to be considered for the prevention of RSV only in:
  - Infants with chronic lung disease (oxygen dependency for at least 28 days from birth) who have the following specific risk factors:
    - —Infants born up to 30 weeks premature who are <3 months old at the start of the RSV season
    - —Infants born up to 26 weeks premature who are <6 months old at the start of the RSV season.
  - Infants with chronic lung disease with a sibling at school or in day care, including:
    - —Infants born at ≤35 weeks' gestation, and <3 months at the start of the RSV season
    - —Infants born at ≤30 weeks' gestation, who are <6 months at the start of the RSV season
    - —Infants born at ≤26 weeks' gestation, who are 9 months at the start of the RSV season
    - —Infants with haemodynamically significant acyanotic CHD <6 months old.
  - Children with SCID until they achieve immune reconstitution.

- Prophylaxis of RSV using palivizumab is not, in the UK, considered a cost-effective strategy for other preterm infants and children with CHD, except for the groups mentioned.

Future research

- The development of a safe, effective RSV vaccine is a worldwide priority. Vaccine development has been slow, following deaths due to an apparently enhanced immunological response to wild RSV after vaccination with an early formal inactivated RSV vaccine.
- An active vaccine will need to be deliverable within the routine 1° immunization schedule if it is to have any practical effect, as the average age of hospital admission with RSV bronchiolitis is <3 months. Live attenuated strains, vector-based, and viral protein subunit-/DNA-based candidates are currently in development. A live attenuated RSV/parainfluenza vaccine delivered intranasally is in clinical trials.
- There have been rapid and exciting developments in antiviral agents, with a number of agents entering clinical trials.

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Chapter 107

Human herpesvirus 6 and 7

See also Chapters 14, 20, 34.

Nature and name of organisms

- HHV-6 and 7 are closely related herpesviruses that cause a similar spectrum of disease. This chapter describes HHV-6 in detail and refers to HHV-7 when there are important differences.
- HHV-6 has a linear, double-stranded DNA of about 160kb. Two major variants A and B have been identified. Variant B is the type associated with the common clinical manifestations in childhood. The virus preferentially infects $CD4^+$ T lymphocytes but is also found in monocytes, macrophages, brain, and kidney cells.
- HHV-7 has a genome of ~145kb and has close homology to HHV-6, and both are more closely related to CMV than to other herpesviruses.

Epidemiology

- Infection is acquired in early childhood. 1° infection with HHV-6 typically occurs between 6 months and 3 years of age.
- At birth, up to 80% of infants have detectable maternal-derived antibody. In spite of this, neonatal infection has been reported, indicating that humoral immunity is not completely protective.
- Seropositivity rates for HHV-6 climb from a nadir of 5–10% at 6 months to a peak of 80–90% by the age of 2 years. The seroconversion rate is highest between 6 and 12 months of age. Antibody titres have been reported to fall in later life.
- Epidemiological studies around the world have shown similar rates of acquisition, apart from some isolated indigenous communities where rates of seropositivity may be ≤10%.
- HHV-7 tends to be acquired later than HHV-6. The median age of seroconversion is 2 years. HHV-7 shows a similar pattern of high titres in early childhood which declines in adult life.

Transmission

- Infection is transmitted by respiratory droplets from asymptomatic carriers, most likely family members, who carry latent virus in their saliva.
- ~1% of the population carries chromosomally integrated HHV-6 (CI-HHV-6). CI-HHV-6, transmitted through germ cells, accounts for the majority of congenital HHV-6 infection and is typically asymptomatic.
- Congenital HHV-7 has not been reported.
- HHV-6/7 has been isolated in cervical secretions and may lead to perinatal infection.
- HHV-7 may also be transmitted via breast milk.
- Transmission occurs all year-round.

Incubation period

- The mean incubation period for HHV-6 is 9–10 days.

Clinical features

Exanthem subitum/roseola infantum

- Exanthem subitum, also known as roseola infantum or sixth disease, is the classical clinical syndrome associated with HHV-6 and 7.
- Typically, a disease of infants and young children. There is abrupt onset of a high persistent fever, which may be complicated by seizures. The fever lasts 3–5 days, and a rash appears on defervescence. The rash is characterized by small, discrete blanching pink macules, predominantly on the trunk, with later extension to the limbs.
- The viral syndrome may be clinically indistinguishable from meningitis or bacterial sepsis.
- HHV-7 causes an identical clinical syndrome and has been shown to be the cause of a second episode in children with previous HHV-6 infection. Subclinical infection often occurs; T-cell clones against HHV-6 react with HHV-7, and this may protect children from clinical disease with a subsequent HHV-7 infection.

Non-specific febrile illness

- Most young children with acute HHV-6 infection do not present with classical exanthem subitum, but with a high fever (lasting 3–5 days), coryza, and signs of an URTI.
- Pharyngitis, inflammation of the tympanic membranes, puffy eyes, palpebral conjunctivitis, diarrhoea and vomiting, lymphadenopathy, and a maculopapular rash are all reported.
- In a survey of 1653 children <3 years presenting to an emergency department with acute febrile illness, 160 (9.7%) had evidence of 1° HHV-6 infection.

Febrile seizures

- 1° infection with HHV-6 in young children is estimated to carry a risk of febrile seizure in the region of 30%.
- HHV-6 has been identified in one-third of children <2 years presenting with a first febrile convulsion.

Encephalitis

- HHV-6 has been associated with encephalitis of varying severity in otherwise healthy patients, in some cases mimicking HSV infection.
- Case series of adult and paediatric patients with encephalitis show a prevalence of HHV-6 in the CSF of 1–3% of patients.
- HHV-6 infection has been linked to subsequent mesial temporal lobe epilepsy.
- Isolated cases of HHV-7-associated encephalitis have been reported.

Infection of immunocompromised hosts

- HHV-6 was first isolated from immunocompromised patients with lymphoproliferative disorders.
- It infects a variety of immune cells, having a particular tropism for $CD4^+$ T cells. Evidence suggests that infection impairs the immune response, in particular inhibiting IL-12 production and consequently inhibiting antiviral activity.
- HHV-6/7 have not been clearly associated with severe disease in children living with HIV.
- Among children with haematological malignancy, HHV-6 viraemia is common and is a marker for impaired cellular immunity. In this population, co-infection with HHV-6 and CMV has been associated with lymphopenia, anaemia, and more frequent episodes of febrile neutropenia.
- HHV-6 reactivation post-HSCT has been documented in 30–70% of cases and typically occurs within 2–4 weeks of transplant. It has been associated with CMV reactivation, an increased incidence of acute GVHD, and increased non-relapse mortality. HHV-6/CMV co-infection post-HSCT increases the risk of CMV-related disease.
- HHV-6 reactivation also occurs post-solid organ transplant and has been associated with fever, elevated transaminases, and bone marrow suppression in liver transplant patients.
- Post-transplant acute limbic encephalitis (PALE) is a clinical syndrome seen in patients after either HSCT or solid organ transplantation. It is characterized by neuropsychiatric symptoms, in particular anterograde amnesia, personality change, and irritability. The CSF may be normal or demonstrate mild pleocytosis and elevated protein. There is a strong association with HHV-6 in the CSF. Treatment with ganciclovir/foscarnet has been associated with a decrease in the CSF viral load and clinical improvement. The prognosis is variable. Some patients with PALE are left with permanent neurological deficit.

Other associations

- HHV-6 has been reported as a rare cause of fulminant hepatitis. Other associations include pneumonitis, myocarditis, and haemophagocytic syndrome. However, as this virus may reactivate during acute illness, its role in the pathogenesis of these condition remains uncertain. Previously suggested associations with Kawasaki disease and with multiple sclerosis have been discounted.

Diagnosis

- In most cases, no laboratory diagnosis is made, or the child has recovered by the time a diagnosis is made.
- Leucopenia with relative lymphocytosis is common.
- Acute and convalescent serology will show a rising antibody titre.
- In the acute phase, HHV-6/7 DNA can be detected in peripheral blood mononuclear cells by PCR and culture. The viruses can also be detected in throat swabs and the CSF.
- HHV-6 is kept latent by cell-mediated immunity but can reactivate intermittently, usually asymptomatically.
- Discriminating 1° HHV-6 infection from CI-HHV-6 can be difficult and requires examination of serial viral PCR titres and their interpretation in light of the clinical context. CI-HHV-6 is expressed in all cells in the body and can be detected in the patient's hair follicles.

Treatment

- In most cases, only symptomatic treatment is needed.
- In immunocompromised patients who have co-infection with CMV and HHV-6, treatment of CMV infection with foscarnet or ganciclovir appears to also suppress the HHV-6 viral load.
- Aciclovir has no activity against HHV-6/7.
- There is no trial evidence of benefit from these drugs in generalized or limbic encephalitis, but, in view of the potential severity of the illness, antiviral treatment should be given when HHV-6 encephalitis is suspected.

Prevention

- There is no vaccine against HHV-6/7. As in most cases, the viruses cause mild illness, and it is unlikely that mass immunization would be considered, even if an effective vaccine were produced.
- Some transplant units routinely monitor patients post-transplantation for HHV-6, along with CMV and EBV. Treatment is not given routinely to asymptomatic or mildly symptomatic patients with a detectable HHV-6 viral load, but, where a rising viral load is associated with a significant clinical problem, antiviral treatment might be considered.

Future research

Future research will help to clarify the importance of HHV-6/7 in the immunocompromised host and may identify further clinical syndromes that can be attributed to these pathogens.

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Chapter 108

Rotavirus

See also Chapters 12, 17.

Name and nature of organism

- Rotavirus is a double-stranded, non-enveloped RNA virus.
- It belongs to the *Reoviridae* family of viruses. On EM, the appearance is of a wheel (Latin *rota*) with spokes.
- Group A rotaviruses are the major cause of infection worldwide.
- Seven serotypes G1–4, 9, and P1 are thought to cause the majority of disease in the US and Europe, although, in sub-Saharan Africa, these account for <70% of infection, and G8, as well as other P serotypes, appear to be important causes of disease in those regions.

Epidemiology

- Rotavirus is the commonest cause of severe gastroenteritis in children worldwide.
- Data from the WHO European region identified that, before the introduction, in some countries, of the rotavirus immunization programme, rotavirus infection caused an estimated 6550 deaths and 150 000 hospital admissions each year in children aged <5 years. Hospital admission rates were similar across income groups.
- Seven countries, mostly in the low- and lower middle-income groups, accounted for 93% of estimated deaths. Disease burden varied dramatically by income level in the European region. Rotavirus vaccination in Azerbaijan, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan, and Turkey could potentially prevent 80% of all regional rotavirus deaths.
- Rotavirus is an important cause of mortality in children in the resource-poor world where ~400 000 children <5 years die from rotavirus infection yearly.
- The number of deaths from rotavirus in the UK, as well as in other Western European countries, is low, with a total estimated number of 200/year across Europe, in the absence of rotavirus vaccination programmes.
- Rotavirus infection is ubiquitous worldwide, and, by the age of 5 years, almost every child will have been exposed and become infected, of which fewer than half will have clinically apparent infection.
- Although the mortality rate in the developed world is low, rotavirus is an important cause of morbidity. Before the introduction of rotavirus vaccination in July 2013 in the UK, it is estimated that rotavirus was responsible for 2.5% of all hospital admissions annually; 20% of adult

household contacts develop disease, causing lost workdays, with the knock-on economic impact, as well as the direct cost to the health service. In Western Europe and the UK, it has been estimated that there are, respectively, around 90 000 and 15 000 admissions due to rotavirus in children each year.

- In Western Europe and the UK, rotavirus is the commonest pathogen responsible for nosocomial infection and an important cause of increased morbidity and mortality in hospitalized children, particularly neonates.
- Rotavirus infections show marked seasonality. In temperate climates, the disease occurs in late winter months, with the epidemic overlapping with the respiratory viruses.
- This seasonality is less pronounced in tropical climates but tends to occur during the drier, cooler months of the year.

Transmission and incubation period

- Transmission is faecal–oral in nature, and so breaking the transmission cycle is heavily dependent on meticulous hand hygiene. Humans are the only reservoir for infection, and the virus is excreted solely in faeces.
- As an unenveloped virus, it can survive for long periods on fomites such as toys, hard surfaces, and door handles. This increases the risk of transmission and needs to be remembered when instituting infection control programmes in the hospital setting and breaking the cycle of infection in nurseries and day-care centres.
- Although animals can be infected with rotavirus, spread is species-specific, and animal-to-human spread of disease has not been documented.
- Rotavirus is shed in high concentrations in the stool of infected patients, and shedding begins just prior to the development of diarrhoea.
- Virus can be shed in the stool for up to 2 weeks after infection in the immunocompetent patient, and, in immunocompromised hosts, it has been isolated from stool >1 month after the onset of symptomatic disease.
- Asymptomatic shedding of the virus, both in adults and children, has been described and can be a cause of ongoing transmission. This explains the rapid spread of infection in the family setting and in day-care centres.
- Incubation period is usually around 2–3 days.

Clinical features

- The clinical picture ranges from a short-lived mild GI illness to severe dehydration, lactic acidosis, electrolyte abnormalities, and, if these conditions are not managed properly, death. A low serum bicarbonate is often seen.
- The disease typically starts abruptly, with high fever and watery, non-bloody diarrhoea. Vomiting often precedes the development of diarrhoea and fever.

- Complications, such as seizures and encephalitis, have been described, although it seems unlikely that the CNS signs are a result of direct infection of the CNS with rotavirus. The typical duration of illness is 3–8 days.
- Immunocompromised children develop more severe and prolonged infections.

Sequelae

Long-term sequelae are very rare, of which the most important is ongoing chronic diarrhoea as a result of damage to the intestinal mucosa during the infection. Cow's milk protein and lactose intolerance are unlikely but may be seen, which can last 3–6 months.

Diagnosis

- A number of tests exist for the diagnosis of rotavirus infection.
- The most commonly used ones are antigen detection assays, PCR, and cell culture isolation.
- Antigen detection assays are very specific, but false positives do occur in neonates and patients with underlying chronic intestinal diseases.
- EM is useful in the direct identification of the virus.
- Cell culture is the gold standard for detecting rotavirus. It has the advantage of identifying the infective strain but is time-consuming and requires specific expertise. It is used mainly as a research tool.

Management and treatment

- Supportive therapy is the only effective management strategy of rotavirus diarrhoea.
- There is no effective antiviral agent for the treatment of rotavirus infection.
- Rehydration and the correction of electrolyte imbalances are key to management. ORS has revolutionized the treatment of diarrhoea worldwide and has had a marked impact on the reduction of mortality from rotavirus in the developing world.
- Persistent diarrhoea and poor weight gain may represent post-rotavirus enteropathy. The differentiation between a mild recovering post-rotavirus enteritis and true cow's milk protein and lactose intolerance may be difficult. The key is growth, rather than persistent diarrhoea. Failure to grow post-rotavirus should be investigated and may require a temporary change to a diet free from cow's milk protein and lactose.
- In the clinical, childcare centre, and home settings, meticulous handwashing and disinfection of fomites, such as door handles and taps, are vital to contain infection and prevent spread among patients or family members. The use of soap and water should be used, followed by a 70% ethanol solution, to inactivate the virus and break the transmission cycle.
- There are two vaccines currently available in Europe and the US. A new effective vaccine has been developed and licensed in India.

- A monovalent human vaccine (Rotarix®, GSK biologicals) is licensed in >100 countries and has been introduced into the routine vaccination schedule in countries worldwide, including South America, Africa, and Asia. Efficacy in the prevention of severe rotavirus gastroenteritis is ranging from around 50% in low-resource settings to >90% in more developed countries.
- An oral pentavalent bovine–human reassortant vaccine (RotaTeq®, Merck) was licensed in the US in 2006 and is now approved in 90 countries worldwide. It has a similar efficacy rates as Rotarix® in preventing severe rotavirus-induced gastroenteritis.
- Rotavirus vaccination is recommended by the scientific societies in most developed countries. It has been included as part of the routine schedule in the US, Australia, and in several European countries, including the UK where it is funded from 2013.
- In June 2009, WHO recommended the introduction of rotavirus into all national immunization programmes worldwide.
- Effectiveness studies in developed countries have shown a dramatic reduction (around 75–85%) of hospitalization rates due to rotavirus infections. In the UK rotavirus vaccination was introduced in July 2013, and by early 2014 a coverage of more than 90% was reached. A drop by more than 70% of cases of rotavirus infections was reported in the season 2013–2014. A 90% drop was then observed in the subsequent winter season.
- Post-licensing surveillance for Rotarix® and Rotateq® has detected a very small increased risk of intussusception (1–5/100 000 infants vaccinated), mainly within the first week after the first dose. Despite this small increased risk, WHO, FDA, European Medicines Agency (EMA), and all scientific authorities consider that the benefit of rotavirus vaccination outweighs the possible risk of intussusception, and therefore the vaccination continues to be strongly recommended.

Future research

- Improved post-licensing surveillance mechanisms to detect very rare events.
- Monitoring of changes in the prevalent circulating pathogenic rotavirus strains worldwide.
- Understanding the mechanism of rotavirus vaccine efficacy in different global settings.
- Development of new effective vaccines for developing countries.
- Safety and efficacy of vaccination of immunocompromised children.

Further reading

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Chapter 109

Rubella

See also Chapters 10, 30, 34.

Name and nature of organism

- Rubella is caused by the rubella virus, an RNA enveloped virus in the *Togavirus* family.
- It is usually a mild disease in children, but infection in early pregnancy can be transmitted to the developing fetus, with serious outcomes, including fetal death or congenital rubella syndrome (CRS), characterized by multiple defects affecting the heart, eyes, and ears.

Epidemiology

- Humans are the only host for rubella.
- In the absence of comprehensive rubella immunization programmes, rubella was a common childhood infection and endemic worldwide; epidemics occurred about every 4–9 years.
- Worldwide, it is estimated that >100 000 infants are born with CRS each year, mostly in developing countries.
- Circulation of infection can be interrupted with effective rubella immunization programmes.
- WHO published a global strategic plan for measles and rubella in 2012, with elimination targets already achieved in WHO Region of the Americas by 2010. WHO Europe set a target for rubella and CRS elimination (<1 case of CRS/100 000 births) by 2015.[1]
- Since the introduction, in 1988, of the combined MMR vaccine for young children of both sexes in the UK, the incidence of rubella infection has declined substantially. Fewer than 20 infants with congenital rubella were reported in the UK between 2000 and 2013.

Transmission and incubation period

- Transmission is by direct contact or droplet spread.
- The infectious period is from about a week before to up to a week after the onset of the rash.
- The incubation period is about 14–21 days.
- Infants with congenital rubella may continue to excrete the virus for ≥6 months after birth.

Clinical features and sequelae

- Up to half of all cases of rubella infection are asymptomatic, and, in the remainder, the disease is rarely serious.
- In children, there is usually little, if any, prodrome, but, in adolescents and adults, low-grade fever, malaise, headache, conjunctivitis, sore throat, and cough may precede the rash, if it occurs, by up to 5 days.
- At all ages, there may be a generalized lymphadenopathy, usually the suboccipital, post-auricular, and cervical nodes.
- The pink–red maculopapular rash appears first on the face and spreads rapidly to the rest of the body. The rash then disappears from the face, coalesces on the trunk, and is gone by day 4.
- The lymphadenopathy may take longer to resolve. The rash may appear similar to measles, scarlet fever, or parvovirus B19.
- Transient arthritis or arthralgia is sometimes associated with rubella infection in adults and adolescents, particularly in women.
- Other rare complications include purpura (with normal or low platelet counts) that is usually self-limiting. Rubella encephalitis is extremely rare.

Congenital rubella

- The risks associated with rubella are highest in non-immune women who acquire infection in the first 10 weeks of pregnancy, at which stage transmission to the fetus is extremely likely, and the probability of damage, frequently severe and multiple, is about 90%.[2]
- The likelihood of transmission diminishes, as pregnancy progresses, and, after about 13 weeks' gestation, damage is usually confined to SNHL; maternal infection after the sixteenth week of pregnancy is not normally associated with any adverse effects.
- Clinical manifestations of congenital rubella include fetal death and stillbirth, growth retardation, cardiac anomalies (septal defects, patent ductus, pulmonary artery stenosis), eye involvement (cataract, microphthalmia, retinopathy), sensorineural deafness, thrombocytopenia, and jaundice.

Diagnosis

- Clinical diagnosis of rubella infection is uncertain and should not be relied on, particularly if a pregnant woman is, or has been, in contact with the suspected case.
- The virus can be recovered from the nasopharynx and the urine in the acute phase, and a clinician notifying a case of rubella will normally be asked to take an oral fluid sample for PCR.
- Since 2000, <100 confirmed cases of rubella in children and adults have been reported annually in the UK.
- Routine antenatal testing for rubella susceptibility does not distinguish between recent and past infection, and is not diagnostic—its sole purpose is to indicate whether or not a woman requires post-partum vaccination with MMR to protect future pregnancies. Women with rubella IgG antibodies detectable at 10IU/mL or more are reported to

have detectable antibody, and those with antibody levels <10IU/mL are reported not to have detectable antibody and advised to have rubella immunization after delivery.
- Any pregnant woman with a rubella-like rash or contact with suspected rubella should be investigated as soon as possible and managed in accordance with current guidelines.[3] Normally, a serum sample for rubella-specific IgM and IgG testing would be requested, with a subsequent serum sample taken 10–14 days later. No pregnant woman should have rubella diagnosed on the basis of a single positive rubella-specific IgM alone. Confirmation of maternal infection is on the basis of detection of rubella virus or RNA in a clinical sample, the detection of rubella IgM with low-avidity IgG in serum, and/or a significant increase in rubella IgG in serum samples taken 10 days apart. Close consultation between the clinician managing the woman and the virologist is essential to ensure proper timing of samples and correct interpretation of results. Confirmed infection in early pregnancy is an indication for offering a termination of pregnancy.
- Congenital rubella can be confirmed in an infant by virus isolation or PCR on clinical specimens.

Management and treatment

- There is no specific treatment for rubella; treatment should be based on alleviating any symptoms.
- Individuals with congenital rubella should have regular clinical review, so that any late-onset problems, e.g. deterioration in sight or hearing, or the development of autoimmune conditions, such as diabetes or thyroid disorders, are identified and managed appropriately.

Prevention

- A child with confirmed rubella should be kept away from school or nursery for 6 days after the first symptoms, and contact with pregnant women should be avoided, if possible.
- The main prevention strategy relies on:
  - Ensuring high uptake of the combined MMR vaccine among children to maintain herd immunity in the community and prevent circulation of rubella infection
  - Ensuring women are not susceptible to rubella when they become pregnant.

Vaccination strategy

See the NHS immunization information website (available at: <http://www.nhs.uk/Conditions/vaccinations>).
- A live attenuated vaccine has been available for over 40 years. The original approach in the UK was to ensure individual protection by allowing the

virus to circulate among children, with vaccination offered to all schoolgirls at around age 11–14 to protect those who had not acquired infection naturally. Rubella vaccine was also promoted for health professionals and susceptible women of childbearing age. In 1988, the strategy changed when MMR vaccine was introduced for all children at 13 months of age, with the aim of preventing circulation of all three diseases. A second MMR dose was subsequently introduced for children aged 3–5 years.

- Both the vaccine and the disease are thought to provide lifelong protection for most individuals, but reinfection does sometimes occur; there have been a few cases of congenital rubella in infants born to women known to have been immune in the past, though this is rare.
- Rubella vaccine should not be administered during pregnancy, but there is now substantial evidence to suggest that, though the vaccine virus can cross the placenta, it does no harm. Inadvertent vaccination in pregnancy is therefore not considered to pose a risk, and termination of pregnancy is not recommended under these circumstances. Women who are rubella-susceptible at antenatal screening should not be immunized during pregnancy but offered MMR vaccine as soon as practical after delivery, preferably before discharge from the maternity unit. If anti-D immunoglobulin is required, the two may be given at the same time, but at different sites.

Migrants

People migrating to the UK from countries where rubella vaccination is not routine or has not been long-standing are at particular risk of being susceptible to rubella, and they should be tested for rubella antibodies and/or offered MMR vaccine.

Health-care staff

All health-care staff, ♂ and ♀, should be screened for rubella, and immunized if susceptible.

Surveillance of congenital rubella

- Surveillance of congenital rubella was established in 1971 to monitor the impact of the newly implemented vaccination programme. Prior to that, there was no routine monitoring, but studies suggested that about 200–300 children were born with congenital rubella damage in the UK every year, and many more in epidemic years. During the 1970s, >50 children a year were reported to the National Congenital Rubella Surveillance Programme (NCRSP), but there was probably substantial under-reporting. Several hundred terminations associated with rubella disease or contact were also reported every year (Fig. 109.1). The number of affected pregnancies declined slowly during the late 1970s and 1980s, but much more rapidly after the introduction of MMR.[4]
- Between 2000 and 2013, <20 UK-born infants were diagnosed and reported altogether. About half of these infants were born to women who acquired the infection abroad, usually in their country of origin in early pregnancy, and more than half of the remainder had mothers who, though they acquired infection in the UK, were themselves born abroad.

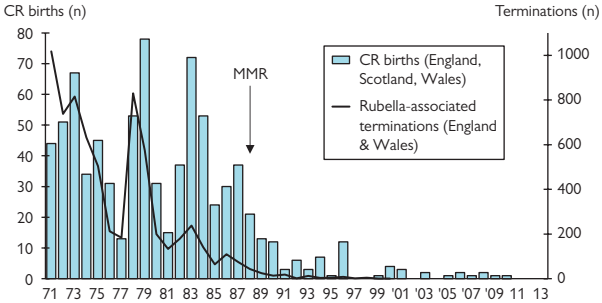

Fig. 109.1 Congenital rubella births (NCRSP) 1971–2013 and rubella-associated terminations* (ONS) 1971–2000.

Source data from The National Congenital Rubella Surveillance Programme and the Office for National Statistics.

Notification of cases of rubella and congenital rubella

Rubella in children and adults is a notifiable disease in the UK and should be reported through the normal channels. In addition, infants born with congenital rubella should be notified to the NCRSP by paediatricians on the BPSU's monthly surveillance card.

Future research

- Long-term immunity of MMR, as the maternal age at pregnancy increases.
- Impact of the historic drop in MMR uptake rates in the UK.

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Chapter 110

Salmonellosis

See also Chapter 122.

Name and nature of organism

- *Salmonellae* are typical members of the *Enterobacteriaceae* family: motile, non-encapsulated, facultatively anaerobic Gram-negative bacilli.
- There are >2500 antigenically distinct serotypes of *Salmonella* in nature. They represent serotypes of a single species *S. enterica*.
- The correct nomenclature is *S. enterica*, followed by the serotype (e.g. *S. enterica* subspecies enterica serotype Enteritidis). This is commonly abbreviated *Salmonella* Enteritidis.
- *S. enterica* is subdivided into six subspecies: *S. arizonae, S. choleraesuis, S. gallinarum, S. paratyphi, S. pullorum*, and *S. typhi*.
- *Salmonella* serotype is defined by the serogroup antigens known as the somatic (O) antigens, the flagellar (H) antigens, and the virulence (Vi) antigen. Most serotypes causing human disease are divided among O antigen groups A through E (Table 110.1). H antigens can be either phase 1 (non-specific) or phase 2 (specific). The (Vi) antigen is a heat-labile polysaccharide found on *Salmonella* Typhi, *Salmonella* Dublin, and *Salmonella* Paratyphi C.
- *Salmonella* spp. can survive refrigeration and sometimes heating; they may remain viable at ambient or reduced temperatures for weeks. They are killed by heating to 54.4°C for 1 hour or 60°C for 15min.
- All pathogenic *Salmonella* spp., other than *Salmonella* Typhi, produce gas. Most of them ferment glucose, maltose, and mannitol but do not use lactose or sucrose.
- Clinical disease caused by typhoidal serotypes (*Salmonella* Typhi and *Salmonella* Paratyphi A and B) differs generally from that caused by other *Salmonella* serotypes which are collectively called non-typhoidal salmonellae (NTS).

Epidemiology

- *Salmonella* spp. infect a variety of animals, including poultry, livestock, and pet reptiles, and rodents.
- The 1° source of *Salmonella* infections (95% of cases) is food-borne transmission, especially from dairy and poultry products.
- Worldwide estimates of NTS range from 200 million to 1.3 billion, with estimated deaths of 3 million each year.
- The true burden of NTS in the US is calculated to be 520 cases per 100 000, compared with 13.4 cases per 100 000 of laboratory-confirmed cases annually.

Table 110.1 Common *Salmonella* serotypes included in major serogroups

Serogroup	Serotypes
A	*Salmonella* Paratyphi A
B	*Salmonella* Paratyphi B
	Salmonella Typhimurium
	Salmonella Derby
	Salmonella Heidelberg
	Salmonella Agona
C1	*Salmonella* Paratyphi C
	Salmonella Choleraesuis
	Salmonella Infantis
	Salmonella Montevideo
C2	*Salmonella* Newport
C3	*Salmonella* Santiago
D1	*Salmonella* Typhi
	Salmonella Enteritidis
	Salmonella Dublin
E1	*Salmonella* Anatum
E2	*Salmonella* Newington
E3	*Salmonella* Illinois

- *Salmonella* causes ~1.4 million illnesses and 600 deaths annually in the US.
- The highest incidence rates occur in children younger than 1 year and in individuals older than 70 years.
- *Salmonella* infection occurs more frequently in the warmer months of the year.

Transmission and incubation period

- The transmission of salmonellae to a susceptible host usually occurs via consumption of contaminated foods. *Salmonella* spp. have been isolated from 50% of poultry, 16% of pork, 5% of beef, and 40% of frozen egg products in retail stores.
- Poultry, ducks and turkeys are the most significant reservoirs of food-poisoning salmonellae in the UK.
- *Salmonella* infections associated with reptile exposure are becoming commoner. Up to 90% of reptiles and amphibians harbour *Salmonella* in their GI tracts, and 6% of non-typhoid disease is related to direct contact with these animals.

- In addition, infected persons without symptoms, or chronic carriers, serve as reservoirs and sources of continuous spread.
- Intra-familial spread to infants can occur through contaminated food, although person-to-person spread is unusual outside of nurseries or hospitals.
- Nosocomial infections have been related to contaminated medical equipment and diagnostic or pharmacologic preparations, particularly those of animal origin.
- The estimated inoculum size required to cause symptomatic disease is 10^5–10^{10} organisms.
- The incubation period usually is 6–72 hours, but it depends on the inoculum size, bacterial virulence, and host immunocompetence.

Clinical features and sequelae

Although NTS organisms can cause a wide range of clinical illness, there are three major consequences of infection: gastroenteritis, bacteraemia with or without focal infection, and asymptomatic carriage.

Acute gastroenteritis

- The commonest clinical manifestation of infection with non-invasive *Salmonella* serotypes is diarrhoea, often accompanied by headache, malaise, nausea, vomiting, and crampy abdominal pain.
- The onset is usually abrupt, and the clinical course short and self-limiting.
- The site of infection usually is the small intestine, but colitis can occur. Diarrhoea usually is moderate in volume and, depending on the serotype, may be grossly bloody.
- Moderate fever is common with *Salmonella* gastroenteritis in most of the children.
- Diffuse, non-focal abdominal tenderness is commonly present.
- These symptoms usually resolve in ~1 week without antibiotic therapy.
- ~5% of individuals with GI illness caused by NTS will develop transient bacteraemia.

Bacteraemia with or without metastatic focal infection

- Some *Salmonella* serotypes (e.g. *Salmonella* Typhi, *Salmonella* Paratyphi, *Salmonella* Typhimurium, *Salmonella* Enteritidis, *Salmonella* Newport) have a particular propensity to invade the bloodstream and cause bacteraemia.
- It is usually associated with fever, chills, myalgias, anorexia, and weight loss lasting for days or weeks.
- Depending on the patient's age, geographical location, and *Salmonella* serotype, 2–45% of infections are bacteraemic.
- After early infancy, invasive cases are less common in children than adults (4.1% versus 8.7%).
- Bacteraemia occurs more commonly in the neonatal and early infant periods (30–50%) than in older children. The true risk of bacteraemia developing in the first year of life is likely to be 2–6%.

- The risk for development of focal infections during bacteraemia is higher (36%) in children with compromised immunity due to underlying conditions than in previously healthy children (2.5%). Certain 1° innate deficiencies can particularly predispose to such complications.
- Almost any organ can be affected. The commonest sites are bones (particularly in sickle-cell anaemia) and the CNS.
- OM is often found in long bones, costochondral junctions, and the spine.
- Of NTS meningitis, 50–75% occur in the first 4 months of life.
- Meningitis has a high morbidity, with acute hydrocephalus, seizures, ventriculitis, abscess, subdural empyema, and cerebral infarction.
- Mortality rates from meningitis have been 40–60% in the past, even with appropriate treatment; more recent data suggest that the mortality rate is now much lower. Relapses, even after prolonged therapy, occur commonly.
- A feared complication of *Salmonella* bacteraemia in adults is the development of infectious endarteritis, especially that which involves the abdominal aorta.

Asymptomatic carrier state

- Non-typhoidal infection is associated with excretion for a mean of 5 weeks, although children younger than 5 years old, elderly patients, and patients with biliary tract disease are more likely to become chronic carriers. Virtually all permanent carriers are adults.
- A chronic carrier state occurs in 0.2–0.6% of patients with NTS.
- Most chronic carriers are asymptomatic.

Diagnosis

- Salmonellae can be recovered on blood or chocolate agar or other selective media from cultures of blood, stool, urine, CSF, and material from foci of infection.
- Most diagnostic laboratories identify the organism as *Salmonella* by biochemical tests and partially determine the antigenic structure with different Poly-O and Poly-H antisera.
- Serologic testing has no role in the diagnosis of NTS.
- Molecular techniques used primarily in epidemiologic studies include DNA hybridization studies, phage typing, chromosome analysis, and plasmid analysis.

Treatment

- For most patients, oral rehydration is all that is necessary to treat *Salmonella* gastroenteritis. Antibiotics have no part to play in the management of asymptomatic infection or uncomplicated diarrhoea.
- Randomized, placebo-controlled, double-blind studies showed no significant differences in the length of illness, diarrhoea, or fever between any antibiotic regimen and placebo; some antibiotics prolong *Salmonella* detection in the stool.

- However, antimicrobial therapy is recommended for patients who are proven or suspected to be bacteraemic/septicaemic or who are at increased risk of invasive disease, including infants younger than 3 months of age and people with chronic GI tract disease, malignant neoplasms, HIV infection, haemoglobinopathies, or other forms of immunocompromise.
- If antimicrobial therapy is indicated, ampicillin, amoxicillin, or Co-trimoxazole is recommended for susceptible strains. If resistance is suspected or proven, ceftriaxone, cefotaxime, fluoroquinolones, or azithromycin should be used (Table 110.2).
- The duration of therapy has not been defined, but 5–7 days is usually effective for uncomplicated illness caused by NTS.
- For septicaemia caused by NTS, 10–14 days of therapy is recommended, although data suggest that shorter courses with some drugs may be adequate (Table 110.3).
- If reduced susceptibility to ciprofloxacin is suspected or confirmed, ceftriaxone or, in uncomplicated disease, oral azithromycin should be given. If the organism is sensitive and the child is improving, oral amoxicillin or azithromycin is recommended.
- For extra-intestinal focal infections caused by *Salmonella* spp., the duration of antibiotic therapy usually is 4–6 weeks to prevent relapses (Table 110.3). A third-generation cephalosporin (e.g. ceftriaxone, cefotaxime) is an appropriate choice.

Table 110.2 Commonly used antimicrobial therapy

Ampicillin, amoxicillin
Trimethoprim–sulfamethoxazole
Third-generation cephalosporin (ceftriaxone, cefotaxime)
Fluoroquinolone (ciprofloxacin or ofloxacin)
Azithromycin

Table 110.3 Treatment duration for *Salmonella* infection

Uncomplicated disease or gastroenteritis, if indicated: 5–7 days
Extra-intestinal disease, including bacteraemia: 10–14 days
Acute osteomyelitis: 4–6 weeks
Meningitis: 4 weeks

Prevention

- Clean water, sanitation, an appropriate use of antibiotics, careful food processing, and storage and hygienic handling of foodstuff are the keys to prevention.
- Notification of public health authorities and determination of the serotype are of 1° importance in the detection and investigation of outbreaks.
- Hospitalized children with *Salmonella* gastroenteritis should be isolated until stool cultures are negative.

Future research

- The epidemiology and mechanisms of NTS carriage and disease in areas of high HIV prevalence are poorly understood and merit further studies utilizing the use of molecular approaches.
- Large, well-designed trials are needed to compare fluoroquinolones, especially in children, with first-line antibiotics in community or outpatient settings, with adequate follow-up and monitoring of adverse events and resistance.
- The development of vaccines effective against NTS to reduce the burden of invasive NTS disease in areas of the world such as Africa.
- Effective measures to eradicate *Salmonella* carriage are needed.

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Chapter 111

Scabies

See also Chapters 34, 38, 41.

Name and nature of organism

- A mite *Sarcoptes scabiei* variety (var.) *hominis*, belonging to the class *Arachnida* (*Scabere*—Latin—to scratch!).
- The adult ♀ mite is ~0.4mm by 0.3mm, the ♂ being smaller at 0.2mm by 0.15mm, with four pairs of legs. The body is white, with bristles and spines on the dorsal surface.
- The mite is an obligate human parasite, living burrowed into the skin.
- After mating, the ♂ mite dies. The ♀ lays two or three eggs each day in the burrows in the epidermis. A total of 40–50 eggs are laid during the remainder of the ♀ mite's life, which lasts 4–6 weeks in total.
- A larva emerges after 3–4 days. After a number of moults, it becomes a nymph and, after further moults, an adult mite. Development from egg to adult takes about 10–15 days.
- Less than 10% of eggs become mature mites.
- The average infestation is with 12 mites. Individuals who are immunocompromised may be heavily infested, with thousands, or even millions, of mites—crusted or Norwegian scabies.

Epidemiology

- Scabies affects all ethnic and socio-economic groups globally.
- In many tropical and subtropical areas, scabies is endemic.
- In industrialized countries, scabies occurs as sporadic cases and institutional outbreaks, particularly in elderly people.
- There are about 300 million cases of scabies worldwide each year.
- Poverty, overcrowding (especially bed sharing), malnutrition, and poor hygiene are all predisposing factors.
- It has been claimed there are cyclical rises in the incidence approximately every 20 years, but this is disputed.
- Infestation is commonest in young children and becomes less frequent with increasing age. A UK study showed the incidence to rise again in the 80+ age group.
- It seems to be commoner in winter.
- In some countries, it is commoner in rural populations, whereas, in others, it is commoner in urban areas. This may be related to the frequency of predisposing factors.
- In one area of Poland, the reported prevalence ranged from 7.9 to 80 per 100 000 people.

Transmission and incubation period

- On warm skin, mites crawl at about 2.5cm a minute (fast!). They are unable to jump or fly.
- Away from a human host, in bedding, clothing, etc., they can survive for 24–36 hours under average conditions. However, transmission is most likely if contact of the materials with the human host was very recent.
- Spread is mainly by direct skin-to-skin contact such as prolonged hand-holding, sharing a bed, sexual intercourse, etc. Therefore, it occurs mainly within households.
- Casual contact is rarely important; however, carers of those with scabies may become infected.
- A large study in Sheffield (UK) about 40 years ago found that infested schoolchildren and teenagers, especially girls, were the commonest route of introduction into households.
- Thirty-eight per cent of family contacts within a household became infested. The 2° attack rate was highest for preschool children (49%), and lowest for men (30%). This may be related to the closeness and duration of contact.
- In the case of a first infection, once infestation has occurred, symptoms usually occur 7–27 days later, but the incubation period may be longer.

Clinical features and sequelae

- The probable cause of the symptoms is an immune response, immediate and delayed-type hypersensitivity, to the mites and their products (saliva, eggs, and faeces).
- The main symptom is itching which does not necessarily occur at the site of the burrows. It tends to be worse at night.
- Erythematous papules, excoriation, and sometimes vesicles are most likely to occur at the interdigital spaces, flexor surfaces of the wrists, axillae, waist, periumbilical skin, scrotum, feet, and ankles.
- In young children, the palms, soles, face, neck, and scalp are often affected.
- Very young children often have widespread eczema-like lesions, particularly on the trunk, and there may be multiple crusted nodules on the trunk and limbs.
- In infants, the commonest lesions are papules and vesicopustules, which are particularly common on the palms and soles.
- Pinkish brown nodules are particularly seen with scabies in babies.
- The distribution of lesions tends to be symmetrical.
- Using a magnifying glass, linear burrows can be seen in the interdigital spaces, and on the wrists and ankles.
- The skin may develop bacterial infection due to damage caused by scratching.

Crusted or Norwegian scabies

- These are heavy infestations, found particularly in immunocompromised individuals.
- The skin lesions most commonly seen are hyperkeratotic crusted nodules and plaques.
- The nails are frequently thickened, with subungual debris.
- 2° bacterial infection with *S. aureus*, GAS, or peptostreptococci can occur.
- Glomerulonephritis, septicaemia, and death may follow infection.
- In some communities, the 2° infection is an important cause of rheumatic fever and rheumatic heart disease.

Diagnosis

- Usually based on the clinical presentation, including itching worse at night, the distribution of the skin lesions, and contact with other cases. Burrows may be seen.
- Differential diagnosis includes bites from insects such as midges, fleas, and bedbugs; and infections such as folliculitis, impetigo, tinea, and some viral exanthemata.
- Diagnosis is more difficult with 2° bacterial infection.
- Confirmation of the diagnosis can be made by gently scraping the skin off a burrow with a blunt scalpel blade or needle. The mite may stick to the scalpel or needle point and may be seen with the naked eye. If not seen, the sample can be examined under a microscope or sent to a laboratory. This method is only about 50% sensitive. As yet, there are no reliable laboratory tests in routine use.

Management and treatment

- For classic scabies, topical permethrin is the treatment of choice in most countries and is very effective.
- A 5% preparation should be applied to the whole body. Even though the manufacturers recommend exclusion of the head and neck, these areas should be included. Particular attention should be paid to the webs of the fingers and toes, and it should be brushed under the edges of the nails. It should be washed off after 8–12 hours. If the hands are washed during this time, it should be applied again. It can sting. The treatment should be repeated 7 days later.
- Topical lindane (gammabenzene hexachloride) is equally effective but is no longer used in many affluent countries because of concerns about potential neurotoxicity.
- Benzyl benzoate is less effective and should be avoided in children, as it is an irritant.
- Topical malathion may be as effective as permethrin, but evidence is limited.

- Oral ivermectin (as a single dose) appears to be as effective as topical malathion; however, it is not licensed for use in children in many countries and has no clear benefit over permethrin.
- Crusted scabies should be treated with topical permethrin and oral ivermectin.
- There is evidence of *in vitro* resistance to ivermectin when used frequently in scabies-endemic communities.
- 2° bacterial infection should be treated with an appropriate antibiotic.
- Even in the presence of effective treatment, itching may persist for up to 6 weeks. If it continues beyond this, re-treatment is indicated, as it is likely to indicate continuing infestation.
- Treatment for pruritus with oral histamines has not been shown to be effective but, given at night, may help sleep.

Prevention

- As classic scabies is not highly infectious, it is unnecessary to exclude infested children from school.
- Asymptomatic household contacts, sexual partners, people that share a bed, and close contacts (those who have had >5min of direct, continuous skin-to-skin contact with the affected person) are generally advised to receive a single treatment of topical permethrin; however, a recent Cochrane review found no evidence to support this.
- Although there is little evidence that scabies can be spread by bedding, as opposed to physical contact, it is recommended that clothes and bedding that have had contact with an infested individual within the previous 72 hours should be machine-washed at 50–60°C and machine-dried. If this is not possible, they may be kept in a sealed plastic bag for 72 hours. Either method should kill the mites.

Future research

Research into new treatments for sufferers and contacts is required. Alternatives to clinical diagnosis and microscopy are needed.

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Chapter 112

Schistosomiasis

See also Chapters 3, 41, 42.

Name and nature of organism

- Schistosomes are flat worms of the trematode family.
- The adult schistosome is an unsegmented, leaf-like organism, 1–2cm in length, and is either ♂ or ♀. They have an average lifespan of 3–7 years, although they can live for as long as 30 years.
- They have an amazingly complex life cycle with both parasitic (snail and humans) and free-living forms (cercariae).
- Cercariae are shed by the snail into water and penetrate the human skin to transform into schistosomulae, which travel through veins, via the lungs, to the liver where they differentiate into the sexual form. They pass down the portal system to the bowel or bladder to mate and deposit eggs (ova). These are passed in the stool or urine into freshwater and hatch into miracidia that invade snails.
- The ova released by the ♀ worm are distinctive, oval in shape with a hook, the placement of which varies, depending on the species.
- Schistosomiasis causes a number of different clinical syndromes, depending on the infecting species, the infective load, the distribution of ova, and the host response to them.
- Disease can be both acute and short-lived, or chronic with long-term sequelae.
- There are five main species which cause disease in humans: *S. mansoni, S. haematobium, S. japonicum, S. mekongi*, and *S. intercalatum*.

Epidemiology

- Schistosomiasis is found almost worldwide and is an important cause of chronic ill health in resource-poor settings, affecting 250 million people.
- Around 200 000 people die from schistosomiasis annually.
- Although commoner in people who live in endemic areas, particularly rural areas, brief exposure to infected water can result in infection.
- Infection in endemic areas among local communities occurs in childhood, but the peak prevalence and severity of disease occur between the ages of 15 and 20.
- Acute infection is more commonly seen in returning travellers, while chronic manifestations of the disease and the development of immunity to infection are seen in endemic regions.
- Generally, only one adult worm pair persists in a host. The severity of disease is related to the egg load produced.

- Although schistosomiasis infection is widespread, different species are responsible for disease in different regions.
- Each species of schistosome has a predilection for a specific snail species as its intermediate host. It is the presence and location of these snail species which determine the geographical distribution and species of the schistosome.
- *S. mansoni* (intestinal/hepatic) and *S. haematobium* (bladder/renal) account for 95% of all infections.
- *S. mansoni* is widespread through Africa, parts of the Caribbean, the Middle East, and South America (Brazil, Venezuela).
- *S. haematobium* is endemic throughout Africa, Mauritius, the Middle East, and some areas of India, and it is also found in the eastern Mediterranean region.
- *S. japonicum* (GI and hepatic disease) is widespread throughout East Asia and the Pacific region.
- *S. mekongi* is confined to a small area in the Mekong river delta in South East Asia.
- *S. intercalatum* is limited to West and Central Africa.
- In the UK, there are around 50–100 cases reported each year, with Malawi and Zimbabwe the commonest countries of origin.

Transmission and incubation period

- Humans (particularly young children) are the principal hosts in the life cycle, with water snails being the intermediate hosts.
- Freshwater becomes infected from human faeces and urine, in which schistosomal ova are excreted.
- Miracidia are hatched from these eggs into the water where they infect snails, the intermediate hosts.
- The asexual life cycle takes place in the snail where the miracidia multiply as sporocysts. These mature into cercaria, which are then released into the water.
- Cercaria have bifurcated tails, which allow them to propel through the water and seek the definitive host—humans. They enter the host through the skin, shedding their tails at this point, and are now known as schistosomulae. The life cycle continues with the migration of these organisms into blood and lymph vessels.
- The adult worms develop in arterial blood vessels, primarily of the lungs and liver. This process takes 4–6 weeks, and both ♂ and ♀ worms develop. Adult worms live in a state of permanent copulation and produce ova, but they do not replicate themselves in the human host.
- The ♀ worm sits within the groove of the adult ♂ worm, and, 1–3 months after the development of the adult worms, the ♀ begins to release ova into the circulation, which are then excreted either in the faeces or urine. The life cycle begins again.
- The incubation period is thus 4–8 weeks. However, symptoms related to the entry of the cercaria through the skin can cause a more acute syndrome.

Clinical features

- Different species of *Schistosoma* cause different clinical syndromes, the reason for its variable clinical presentation.
- Many infections are asymptomatic and go undetected.
- Symptomatic disease is commoner in travellers who are non-immune.
- People who live in endemic areas are more likely to suffer from chronic schistosomiasis and the sequelae.
- Severity of disease is related to the infective burden.
- The majority of the clinical features and underlying pathology of schistosomiasis are related to the *Schistosoma* eggs and the host response to them.
- In the initial stages of infection, when the cercariae penetrate the skin, the first presentation can be one of dermatitis (swimmer's itch). In endemic areas, where exposure and infection with cercariae are repeated, this can be severe. This presentation can also be caused by a delayed hypersensitivity reaction, which is immune-mediated, in addition to the immediate allergic reaction more commonly associated with this phenomenon.
- Katayama fever is an immune-mediated syndrome occurring about 2–8 weeks after infection with *S. mansoni* or *S. japonicum*. It presents with non-specific symptoms of fever, chills, myalgias, arthralgias, headaches, and dry cough. It can resemble many other infections which present non-specifically such as malaria (endemic in similar geographic regions), viral infections, or serum sickness. Lymphadenopathy and hepatosplenomegaly can also be part of the syndrome. The presence of eosinophilia helps in the diagnosis but is not consistent. Pulmonary infiltrates can be seen on CXR. Ova are infrequently found, as this clinical presentation coincides with the early production of ova, making diagnosis more difficult.
- Dysuria associated with terminal haematuria is a common presentation of *S. haematobium*.
- Intestinal symptoms and signs, bloody diarrhoea, abdominal pain and cramping, and poor appetite are common presentations of all species of *Schistosoma*, although much rarer in *S. haematobium* infection which generally presents with urinary symptoms.
- Hepatic symptoms and signs are the predominant clinical features of *S. mekongi* and can occur with other species of *Schistosoma* as well. Marked hepatosplenomegaly is a hallmark of infection. Ascites and varices can occur and are important causes of morbidity and mortality.
- Occasionally, neurological disease occurs, presenting as transverse myelitis, seizures, limb pain, increased ICP, or focal impairment.
- Pulmonary involvement, manifesting most commonly as dyspnoea, can occur.
- Weight loss, poor appetite, fatigue, and iron deficiency anaemia are commonly associated with all types of infection.

Sequelae

- Anaemia, fatigue, malnutrition, and growth restriction are important and common sequelae of chronic infection in endemic areas.
- Depression of cognitive function has been noted in children.
- Ongoing bladder inflammation is a risk factor for bladder cancer, more prevalent in areas where *S. haematobium* is endemic, and is related to chronic inflammation caused by the deposition of ova in the bladder wall.
- Deposition of ova in the genitourinary tract is also a risk factor for the acquisition of HIV in young adults, particularly young women.
- Hepatic infection can be a prelude to hepatic fibrosis and portal hypertension, with an increased risk of oesophageal varices.
- In patients with ongoing intestinal disease, polyps, ulcers, and intestinal strictures can develop.
- With heavy infestations affecting the lungs, pulmonary hypertension and cor pulmonale can occur.
- Infertility, both ♂ and ♀, is a rare consequence of chronic *S. haematobium* infection.
- 2° bacterial infection is a common complication of schistosomiasis.
- Co-infection with the hepatitides is common and can cause more severe morbidity related to liver damage.
- Malaria and schistosomiasis have similar geographical distributions and can occur concurrently. The two diseases have variable effects on each other, with some suggestion that, in younger children, schistosomiasis has a protective effect against severe malarial disease.

Diagnosis

- Non-specific findings on blood film include eosinophilia in up to 70% of patients, usually early in the disease process.
- Iron deficiency anaemia occurs in patients with chronic infection.
- Abnormal liver transaminases can be found in patients with hepatic sequestration of ova.
- Haematuria, either macroscopic or microscopically detected on dipstick, is almost pathognomonic of *S. haematobium* infection in children who live in endemic areas.
- Isolation and identification of ova is a simple and definitive method of diagnosis, although this is not sensitive early in the disease process or in light infections.
- *S. haematobium* eggs can be seen in urine specimens, as well as faecal samples, and, although similar in size to those of *S. mansoni*, have a large terminal, rather than lateral, spine. *S. intercalatum* is similar to *S. haematobium*, but much larger. *S. japonicum* and *S. mekongi* are similar, but smaller.
- Rectal snips have a better sensitivity for the detection of ova than faecal samples, even in *S. haematobium* infection.

- The use of concentration techniques for both urine and faeces increases the sensitivity of detection of ova in these samples. Yield is greater in samples taken in the middle of the day or after exercise.
- Serology is a useful means of diagnosis, though more expensive, and becomes positive later in the disease process. Antibodies are produced to the schistosomal ova, so tests are seldom positive before 4–6 weeks after infection and sometimes are absent for much longer. Serology does not differentiate between present and past infection, so it is most useful when positive in travellers to confirm diagnosis, and when negative in residents of endemic areas to rule out infection.

Treatment

Praziquantel is the most widely used drug available for treatment of all types of schistosomiasis. It has very few side effects and is usually effective as a single oral dose in one or two divided doses. It has no effect on ova and immature worms, and so a repeat dose 6–12 weeks later is sometimes necessary if the first dose is given early in the infection. Ova can continue to be shed for 4–6 weeks after successful treatment.

Artesunate can be used in endemic areas and is safe to use in children.

Prevention

There is no vaccine for prevention, so public health programmes are based on:

- Advice to travellers about avoidance of wading or swimming in freshwater lakes or rivers in endemic countries—particularly Lake Malawi
- Eradication programmes: elimination of snail species, the intermediate hosts, is an important strategy for breaking the life cycle of *Schistosoma* spp. and decreasing transmission of disease, and it is effective when used in conjunction with mass treatment of communities with praziquantel.

Future research

- Antigen detection assays are currently being developed.
- PCR tests are in the development phase and look promising, with good sensitivity and specificity.
- New therapeutic strategies and drugs are required and are an important focus for future research.

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Chapter 113

Shigellosis

Name and nature of organism

- Shigellosis, also called bacillary dysentery, is caused by *Shigella* spp.—Gram-negative bacilli that belong to the family *Enterobacteriaceae*.
- *Shigella* comprises four species or serogroups:
  - Serogroup A: *S. dysenteriae*—produces shiga toxin or verotoxin
  - Serogroup B: *S. flexneri*
  - Serogroup C: *S. boydii*
  - Serogroup D: *S. sonnei*.
- With the exception of *S. sonnei*, all the other serogroups are further divided into serotypes.
- The bacteria invade the intestinal epithelium, causing cell death and triggering localized inflammation and necrosis.
- The reservoir for infection is the human GI tract.

Epidemiology

- It is estimated that *Shigella* serogroups infect over 200 million people and cause >1 million deaths each year worldwide.
- The major burden of disease is in resource-poor countries; children aged 1–4 years account for 70% of cases and 60% of deaths. Illness in infants <6 months is uncommon.
- Shigellosis is endemic in conditions of overcrowding, poor sanitation, and inadequate water supply (especially in confined populations such as refugee camps).
- In tropical areas, there is a seasonal peak of shigellosis, usually before the rainy season starts, when water supplies are low.
- *S. flexneri* is the most frequently isolated serogroup worldwide, accounting for 60% of cases in resource-poor countries.
- In Europe, the incidence of shigellosis has fallen dramatically in the past 20 years; in most countries, <2000 cases per year are reported.
- *S. sonnei* is endemic in Europe and accounts for around two-thirds of all shigellosis cases.
- *S. boydii, S. dysenteriae*, and most *S. flexneri* infections are imported from outside Europe.
- Epidemics of *S. dysenteriae* occur particularly in confined populations and affect all age groups. *S. dysenteriae* type 1 causes the most severe form of disease, including toxic megacolon and HUS, with a case fatality rate of up to 20%.

Transmission and incubation period

- Shigellae are resistant to gastric acid, and the infective dose is very low; ingestion of 10–100 bacteria is sufficient to produce disease.
- In Europe, transmission is mainly direct faecal–oral from people with diarrhoea, especially in households, schools, and nurseries.
- The organism can survive in the environment for over 2 weeks in favourable conditions; thus, indirect transmission via contaminated fomites, food, or water can also occur.
- The 2° attack rate in households may be as high as 40%.
- Outbreaks occur in crowded conditions with poor sanitation.
- Occasionally spread via food or water that has been contaminated by people with shigellosis.
- Incubation period: 1–7 days, usually 12–96 hours.
- Period of communicability: during the acute illness and for up to 4 weeks afterwards. Rarely, the carrier state persists for months, e.g. in malnourished or immunocompromised children.
- Antimicrobial treatment usually reduces the duration of carriage to a few days.

Clinical features and sequelae

- The spectrum of shigellosis ranges from mild watery diarrhoea to full-blown dysentery with fever, abdominal pain, and severe diarrhoea with blood, mucus, or pus. The infection primarily affects the colon, and less frequently the terminal ileum.
- The bacteria invade the intestinal mucosa, resulting in mucosal ulcerations and confluent colonic crypt abscesses. Despite the intense superficial destructive process in the colonic epithelium, bacteraemia and disseminated infection are relatively rare.
- Nausea, vomiting, headache (± meningism), lethargy, confusion, and convulsions (mainly in small children) may occur and have been attributed to a neurotoxin.
- Less common presentations include a morbilliform rash and conjunctivitis (which may be confused with measles), and pneumonia.
- Dehydration and electrolyte imbalance are the main cause of death. There is a high mortality rate in neonates and infants.
- *S. sonnei* usually causes mild illness that is self-limiting within a few days, except in immunocompromised patients.
- The other *Shigella* serogroups cause more severe disease; *S. dysenteriae* type 1 causes the most serious illness.
- HUS is a complication of *S. dysenteriae* type 1, caused by the production of shiga toxin.
- Reactive arthritis occurs in up to 5–10% of patients 2–5 weeks after the dysenteric illness, especially in patients with HLA-B27.

Diagnosis

- There are many microbiological causes of gastroenteritis, and it is not possible to diagnose shigellosis on clinical grounds alone.
- *Shigella* serogroups can be cultured from faeces or rectal swabs.
- Culture media that are selective for *Shigella* are used to enhance sensitivity.
- Faeces samples should be cultured as soon as possible after collection to obtain the best diagnostic yield.

Management and treatment

- Supportive treatment: rehydration and correction of electrolyte imbalance.
- Antibiotic therapy is usually recommended for shigellosis, because it rapidly terminates infectivity. May also:
  - Shorten the duration of illness
  - Lessen the severity of illness in patients with underlying conditions
  - Reduce the risk of complications.
- The choice of antibiotic therapy should be based on the knowledge of local susceptibility patterns (MDR is increasingly common), and adjusted if resistant. There are high rates of plasmid-mediated antibiotic resistance globally.
- Ampicillin or amoxicillin is no longer recommended as empiric therapy, because resistance is common.
- Options for empiric treatment include co-trimoxazole, ciprofloxacin, or azithromycin.
- For children admitted to hospital with severe shigellosis, a third-generation cephalosporin, e.g. cefotaxime or ceftriaxone, is recommended.
- Short courses of antibiotic therapy are effective in most cases; longer courses may be required for children who are immunosuppressed or seriously unwell.
- Antimotility drugs, such as loperamide or diphenoxylate, are not recommended, as these may worsen symptoms and increase the risk of toxic dilatation of the colon.
- Avoid analgesics, such as codeine, that have an antimotility effect.

Prevention

- Good hygiene and sanitation.
- Hospitalized patients should be isolated using enteric precautions.
- Exclude children from school or nursery until 48 hours after first normal stool.

- Exclude children from swimming pools for 2 weeks following the last episode of diarrhoea.
- In many countries, shigellosis is a notifiable infectious disease.
- In resource-poor countries, breastfeeding affords important protection to infants.

What's new?

- As with many other Gram-negative bacteria, antibiotic resistance among *Shigella* spp. is increasing; resistance to ciprofloxacin, and even azithromycin, is now common in some countries.
- There is new evidence of the global spread of *S. sonnei* clonal groups, linked to growing international travel and cross-border food trade.

What's next?

- Rapid molecular diagnostic techniques that can detect *Shigella* and other enteric pathogens directly in faeces or rectal swabs are becoming available. This could allow a microbiological diagnosis to be made within hours, rather than 2–3 days required for conventional tests. Further work is required to determine the accuracy and cost-effectiveness of these techniques.

Future research

- Vaccination probably offers the best prospect for controlling shigellosis; several candidate vaccines are currently in development.
- In the absence of an effective vaccine, more research into the control and treatment of antibiotic-resistant shigellosis is required.

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Staphylococcal infections, including meticillin (INN)-resistant *Staphylococcus aureus*

Name and nature of organism

- Staphylococci are among the most frequently encountered causes of localized and systemic bacterial infections, as well as being ubiquitous commensals of the skin and mucosa. Staphylococci are Gram-positive cocci, which characteristically appear in clusters (*staphyle* —Greek for bunch of grapes).
- Staphylococci are subdivided by the coagulase test into *S. aureus* (coagulase-positive) and other species that are coagulase-negative. These are less virulent, acting as opportunistic pathogens in patients who are immunocompromised and/or have invasive devices.
- *S. aureus* is a major human pathogen. Most strains remain sensitive to commonly used antibiotics (except penicillin) and are referred to as MSSA (meticillin-sensitive *S. aureus*). Meticillin is an old β-lactam antibiotic, similar to flucloxacillin, that is now no longer used clinically; susceptibility to meticillin denotes susceptibility to flucloxacillin. MRSA are strains that are resistant to meticillin (and therefore flucloxacillin); these strains are also often resistant to other drug classes, e.g. macrolides.
- *S. aureus* can produce multiple exotoxins that are either membrane-active or superantigens.

Methicillin-sensitive *Staphylococcus aureus*

Epidemiology

- Carried by around 30% of the population at any one time.
- The nose is the commonest carriage site.
- Other carriage sites include the throat, axillae, perineum, and GI tract.
- Can also be carried by pets and other animals.
- Acts as an opportunistic pathogen when the body's defences are breached.

Measures that have been successful in preventing BSI with MRSA have had no impact on MSSA BSI. MSSA remains one of the commonest causes of both community- and hospital-acquired bacteraemia in children; the highest incidence, by far, is in infants aged under 1 year.

Risk factors for infection with *S. aureus*:

- 1° immunodeficiencies, especially those with neutrophil dysfunction, e.g. hyper IgE syndrome, CGD
- Acquired immunodeficiencies, especially neutropenia
- Skin or mucosal damage
- Recent surgery
- Presence of a foreign body, e.g. intravascular catheter
- Cystic fibrosis.

Different strains of *S. aureus* produce different virulence factors, some of which are associated with characteristic infectious syndromes.

Transmission and incubation period

Infections may be endogenous or exogenous.

- Endogenous infections occur when commensal bacteria become invasive.
- Exogenous infections are acquired from other persons (occasionally animals).

Transmission may be via direct contact with a colonized or infected individual or indirect contact with a contaminated environment; *S. aureus* can survive on surfaces for at least 24 hours.

Staphylococcal food poisoning is caused by preformed exotoxin (enterotoxins) in food, because symptoms do not depend on multiplication of bacteria in the host; symptoms develop quickly (typically 2–6 hours after ingestion). The source is nearly always a colonized food handler; contaminated food is then stored under inappropriate conditions, allowing *S. aureus* to multiply and produce enterotoxin.

Clinical features and sequelae

Less serious infections

- Superficial skin infections:
  - Folliculitis, furuncles (boils), carbuncles (confluent boils with sinus formation), cervical adenitis
  - Neonatal septic spots, breast abscesses, omphalitis
  - Impetigo: *S. aureus* is the main pathogen in both types of impetigo:
    - Non-bullous (70% of cases). Mainly affects the face and limbs, often commencing in an area of traumatized skin
    - Bullous. More commonly affects the trunk; more rapidly progressive with larger and multiple bullae. Commonest in infants
  - Infected atopic dermatitis: *S. aureus* common in exacerbations, but clinical significance in the absence of an overt infection is not certain
  - Surgical site infections.
- UTIs (especially urinary catheter-associated).
- Ocular infections: conjunctivitis, dacrocystitis, endophthalmitis.

Serious infections

- BSI (note that up to 20% of blood culture isolates represent contamination from skin colonization, although this proportion can be reduced by careful skin preparation and blood collection).
- Pneumonia:
  - 1° (see ➔ PVL-producing *Staphylococcus aureus*, p. 825)
  - 2° to viral infections, especially chickenpox, influenza
  - Ventilator-associated.
- Device-related infections (e.g. CVCs).
- Endocarditis (native valve and prosthetic valve).
- Peritoneal dialysis-associated peritonitis.
- OM, SA, discitis, pyomyositis, psoas abscess.
- Meningitis:
  - Shunt-associated or post-trauma
  - Uncommon cause of 1° bacterial meningitis, mainly in neonates.

Specific virulence factor-related conditions

Staphylococcal food poisoning

Abrupt onset of vomiting 2–6 hours after ingestion of food, followed by abdominal pain and watery diarrhoea. Usually self-limiting, with resolution of symptoms within 8 hours.

Toxic shock syndrome

Rapid-onset multisystem superantigen-mediated disease. Two forms:

- Menstrual: strongly associated with strains that produce TSST-1
- Non-menstrual: usually associated with enterotoxins.

Staphylococcal scalded skin syndrome

Caused by strains of *S. aureus* that produce exfoliatin toxins A and B, which cleave desmosomal junctions in the epidermis.

- Initial infection (which may be trivial), followed by:
  - Acute fever
  - Diffuse tender erythroderma: redness accentuated around the eyes and mouth, and in flexures
  - Clear bullae which form and rupture, leading to separation of sheets of skin
  - Nikolsky sign: intact-appearing skin is easily denuded by rubbing.

Panton–Valentine leukocidin-producing Staphylococcus aureus

PVL production is strongly associated with virulence and transmissibility. Invariable feature of community-associated MRSA (see later), but most PVL-producing strains are not MRSA.

Characteristic infections

- Skin and soft tissue infections:
  - Recurrent and/or unusually severe
  - Pain and erythema are prominent
  - May progress to necrosis and intravascular thrombosis.

- Necrotizing pneumonia. Suspect when:
  - Airway bleeding/haemoptysis
  - Hypotension
  - Flu-like illness (temperature >39°C, tachycardia, myalgias)
  - Leucopenia
  - High CRP (>200mg/L)
  - Gram-positive cocci on Gram stain of sputum
  - CXR—multilobular infiltrates
  - Raised serum creatinine kinase.
- OM, SA, pyomyositis.

Diagnosis

- May not be necessary to collect samples in infections of superficial sites where *S. aureus* is the likely pathogen, unless unusually severe, recurrent, or unresponsive to empiric therapy.
- Gram stain of clinical material (especially from sites that are normally sterile) may be useful in making a presumptive diagnosis.
- Culture of *S. aureus* from the site of infection is the mainstay of diagnosis.
- Blood cultures are often positive in deep-seated infections; always look for a likely focus of infection when *S. aureus* is isolated from blood cultures and thought to be significant.
- Because *S. aureus* is a common skin commensal, not all cultures will be clinically significant; treat only where clinical evidence of infection.
- Once *S. aureus* has been cultured:
  - Antibiotic sensitivities are required, especially to distinguish between MSSA and MRSA
  - Further tests may be required to identify specific virulence factors or to investigate possible outbreaks.

Management and treatment

Less serious infections

- Superficial pyodermas and eye infections: generally respond to topical antimicrobials.
- Impetigo: topical fusidic acid is widely used, although there are increasing reports of resistance. Resistance may be due to selection of resistant mutants during treatment or mediated by a transmissible gene. The risk of resistance in 1° care is probably overstated. However, use of topical fusidic acid in hospitals is not recommended, because systemic fusidic acid is used in the treatment of serious *S. aureus* infections (see ➔ Serious infections, p. 827).
- Other established topical antibiotics (neomycin, mupirocin) are used for MRSA decolonization, and their widespread use for other indications is not recommended.
- Retapamulin is a novel topical pleuromutilin antibacterial. It appears to be effective, with a low risk of resistance, but is expensive.

- Topical antiseptics, e.g. 1% hydrogen peroxide in stabilized cream, are an alternative to topical antibiotics. They have comparable efficacy and carry no risk of antibiotic resistance.
- Widespread or severe impetigo may require treatment with oral antibiotics, usually flucloxacillin or a macrolide.
- Exacerbations of atopic dermatitis: topical corticosteroids are the mainstay of treatment. Although *S. aureus* is frequently isolated from such patients, there is little evidence that the addition of an antibiotic hastens recovery, unless there is clear evidence of infection.

Serious infections

Flucloxacillin (or a first-generation cephalosporin) remains the mainstay of treatment of invasive infections with MSSA. Sometimes combined with another agent, although there is little evidence to support this approach:

- Fusidic acid or rifampicin penetrate well into difficult sites, e.g. bone. Never used as monotherapy because of the high rate of emergence of resistant mutants
- Aminoglycosides (e.g. gentamicin) sometimes recommended, especially for endocarditis. Recent work suggests that, even at a low dose, the risks of nephrotoxicity may outweigh any benefits.

A macrolide, clindamycin, or a glycopeptide are the alternatives to flucloxacillin for patients who are penicillin-allergic.

PVL-producing Staphylococcus aureus infections

- *Mild to moderate infections*—flucloxacillin or clindamycin.
- *Serious skin and soft tissue infections*—aggressive surgery where indicated: clindamycin and/or a glycopeptide.
- *Pneumonia*—clindamycin plus linezolid plus rifampicin; consider IVIG.
- *Bone and joint infections*—clindamycin plus linezolid or rifampicin.

Prevention

- The ubiquity of *S. aureus* means that it is not realistic to avoid it. Nevertheless, general good hygiene should be encouraged.
- Where children have recurrent skin infections, whole family decolonization may be considered: mupirocin nasal ointment three times daily, together with daily antiseptic baths (chlorhexidine gluconate 4% or octenidine), for 1 week. There is no point treating one family member!
- Surgical antibiotic prophylaxis with agents active against *S. aureus* where appropriate.
- Little evidence that regular surveillance cultures (e.g. nose swabs) are useful in high-risk patients (e.g. children with long-term lines or peritoneal dialysis catheters). However, antiseptic (e.g. octenidine) baths, once or twice weekly, may help prevent *S. aureus* colonization that could progress to infection.
- Long-term antibiotic prophylaxis for some groups of high-risk patients (e.g. cystic fibrosis).
- Screening and/or decolonization treatment of close contacts of PVL cases.

Methicillin-resistant *Staphylococcus aureus*

Epidemiology

- Two broad types of MRSA (Table 114.1):
  - Health care-associated: the commonest in the UK. In the UK, dominated by two epidemic hospital strains—EMRSA 15 and 16.
  - Community-associated: much less common in the UK, but prevalent in other parts of the world, including some southern European countries and the US (especially the USA 300 clone). These strains also produce PVL and are therefore more virulent.

In Europe, MRSA infection in children is much less common than in adults. In the UK, there are <100 BSIs per year; most of these are linked to either NICU or PICU admission and/or indwelling CVCs.

Table 114.1 Hospital-associated MRSA versus community-associated MRSA

	Health care-associated	Community-associated
Typical patients	Elderly; neonates; chronically ill patients who are frequent health-care attendees	Young healthy people
Transmission	Within health-care settings; little spread among household contacts	Community-acquired; spreads within families and institutions where close contact
Infection sites	Sites of nosocomial intervention	Often spontaneous; skin commonest
Antibiotics	Usually resistant to several antibiotic classes	Usually resistant only to β-lactam antibiotics

Diagnosis

- As with MSSA, culture, together with antibiotic sensitivity testing, is the mainstay of diagnosis.
- Use of chromogenic culture media allows a presumptive diagnosis to be made in 18–24 hours.
- Real-time PCR can be used as a screening or diagnostic test for MRSA, giving results in 1–2 hours. However, these tests are expensive, and their PPV is low in low-prevalence populations such as children.

Treatment

- Glycopeptides (e.g. vancomycin, teicoplanin) are the main treatment.
- Linezolid may have more favourable pharmacodynamics and could offer better outcomes in some types of infection. It is available for oral administration.

- For strains that are sensitive, clindamycin is sometimes suitable (preferred to macrolides, because emergence of resistance requires two mutations).
- Routine use of >1 agent is not recommended. However, addition of a second agent, e.g. rifampicin or fusidic acid (if sensitive), is indicated where single-agent therapy has failed or for bone and joint infections or meningitis. Use of >1 agent is also indicated for severe infections with PVL-producing community-associated MRSA (see earlier).
- Newer agents, e.g. daptomycin, should be used after specialist advice only.
- Decolonization treatment is with 5–7 days of nasal mupirocin three times daily plus a daily antibacterial body wash (4% chlorhexidine gluconate or octenidine), as for MSSA.

Prevention

- In contrast to MSSA, MRSA is not ubiquitous and is more preventable.
- Health care-associated MRSA is controlled by isolation, decolonization, and appropriate prophylaxis of MRSA-positive patients.
- Many countries now have a policy of screening at least high-risk hospital admissions for MRSA. Few children are at high risk of MRSA, e.g.:
  - Multiple previous admissions/chronic underlying condition
  - High-risk surgery (cardiac/transplantation, etc.)
  - All PICU and NICU admissions.
- Community-associated MRSA is currently rarely seen in Europe. However, the US approach has been around preventing and managing the five Cs:
  - Contaminated items
  - Close contact
  - Crowding
  - Cleanliness
  - Cuts and other compromises to skin integrity.

Coagulase-negative staphylococci

Epidemiology

- Around 30 species, none of which produce the coagulase enzyme (clots rabbit plasma!) that *S. aureus* produces.
- Ubiquitous low-virulence skin commensals. Act as opportunistic pathogens in patients who are immunocompromised and/or have indwelling devices. *S. epidermidis* is the commonest species, but there are many others. Slime production is an important virulence factor: interferes with opsonophagocytosis and impedes antibiotic penetration.

Transmission

Many infections are endogenous. Direct or indirect person-to-person spread in hospitals is also possible.

Clinical features and sequelae

- Almost exclusively HAIs:
  - Late-onset neonatal infections on NICUs: BSIs, pneumonia. May be associated with a poorer long-term neurodevelopmental outcome in these patients than was originally thought
  - BSI in neutropenic patients
  - Device-related infections: intravascular devices, CSF shunts, prosthetic joints, peritoneal dialysis catheter-related peritonitis
  - UTI: especially catheter-associated. *Staphylococcus saprophyticus* is a cause of UTI in older girls
  - Endocarditis (usually post-operative or prosthetic valve).

Diagnosis

Isolation of the bacterium from a site that is normally sterile. The challenge is to distinguish true infection from contamination. Isolation of the same bacterium (e.g. based on antibiogram) on >1 occasion and/or in association with other laboratory markers of infection increases the certainty that CoNS are pathogenic. In the neonatal setting, ~50% of CoNS bacteraemias are probably clinically significant.

Management and treatment

S. saprophyticus is usually sensitive to most anti-staphylococcal antibiotics.

Other species and strains causing invasive infections are usually multiply antibiotic-resistant. Glycopeptides (e.g. vancomycin, teicoplanin) are the mainstay of treatment; however, strains that have reduced susceptibility or are resistant to these agents do occur.

Occasionally, addition of a second agent (e.g. rifampicin in meningitis) is indicated. Newer anti-Gram-positive antibiotics (e.g. linezolid, daptomycin) should only be used on specialist advice.

Prevention

No specific measures can protect against acquiring CoNS, although good hygiene practices in hospitals can help prevent the spread of nosocomial strains.

The most important preventative measure is good care of indwelling medical devices, the main foci of infection.

What's new?

- Recognition that a large proportion of MSSA bacteraemias in children may be preventable.
- Although still not as prevalent as in the US, community-associated MRSA is becoming commoner across Europe.
- More paediatric experience of newer drugs, such as linezolid and daptomycin, but these drugs should still only be used on specialist advice.

What's next?

- Increased use of decolonization regimens to prevent systemic *S. aureus* infections in high-risk patients.
- Improved (more sensitive and specific) PCR detection of PVL, MRSA, and MSSA.

Future research

- Use of screening and decolonization treatment to prevent HAI with MSSA in children.
- Rapid diagnosis of MRSA and MSSA, so that effective antibiotic treatment is given.
- Better data on distinguishing true infection due to CoNS from contamination, especially in the neonatal setting.

Further reading

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Chapter 115

Streptococcal infections

See also Chapters 1, 6, 7, 8, 15, 16, 25, 26, 27, 29, 31, 33, 34, 37, 40.

Name and nature of organism

Streptococci are Gram-positive cocci. They grow in chains (e.g. group A/B streptococci and viridans streptococci) or as diplococci (*S. pneumoniae*). According to the type of haemolysis produced around colonies growing on blood agar, streptococci are classified into two main groups:

- β-haemolytic streptococci (= pyogenic streptococci): colonies are surrounded by a zone of complete haemolysis on blood agar. The cell wall contains Lancefield group-specific antigen which defines the following medically important groups:
  - Group A: *S. pyogenes*
  - Group B: *Streptococcus agalactiae*
  - Groups C and G: *Streptococcus dysgalactiae* and *Streptococcus equisimilis* (now classified as one species *S. dysgalactiae* subspecies *equisimilis*)
- α-haemolytic or viridans streptococci: colonies on blood agar are surrounded by a zone of greenish colour due to altered haemoglobin (partial haemolysis). Of medical importance in this group are:
  - *S. pneumoniae*
  - *Streptococcus anginosus* (previous *Streptococcus milleri*) group
  - Other viridans streptococci colonize the oral cavity and may be associated with dental or other oral infections, endocarditis, and disease in immunocompromised patients.

Beta-haemolytic streptococci

Streptococcus pyogenes (group A *Streptococcus*)

Epidemiology

- GAS is the commonest cause of bacterial tonsillopharyngitis in children between 5 and 15 years of age, accounting for 15–30% of cases.
- GAS is a significant cause of invasive bacterial infections, including soft tissue infections and sepsis.
- Up to 20% of children carry GAS asymptomatically.
- In temperate climates, the incidence of GAS infection peaks during winter and early spring, coinciding with the influenza season.

Transmission

- GAS is transmitted via respiratory droplets, usually from a contact with GAS pharyngitis. Occasionally, GAS spreads via contaminated food.

- Impetigo is acquired by direct person-to-person contact. Colonization of healthy skin usually precedes infection. Any minor (even unrecognized) skin break may result in infection. Yet since GAS does not penetrate intact skin, it can be a normal skin colonizer as well.

Incubation period

- One to 5 days for streptococcal pharyngitis, and 7–10 days for impetigo. May be shorter (12–24 hours) in cases with direct inoculation of organisms (e.g. childbirth or penetrating trauma).

Period of communicability

- When untreated, infectivity lasts for 7–21 days.
- Treatment with antibiotics reduces infectivity to 24 hours.
- Some children carry GAS in the pharynx for weeks or months and may be contagious for this time, yet the risk of transmission is low in the absence of acute infection.

Clinical features

- Purulent pharyngotonsillitis is the commonest GAS infection. It may be complicated by otitis media, sinusitis, suppurative cervical lymphadenopathy, or tonsillar, retropharyngeal, or peritonsillar abscesses (quinsy). Meningitis or brain abscess are rare complications, resulting from direct extension of an ear or sinus infection or from bacteraemic spread.
- Three or four positive, out of four, Centor criteria (fever, anterior cervical lymphadenopathy, tonsillar exudate, absence of cough) are suggestive for GAS pharyngitis (four criteria ~50% risk).
- Scarlet fever is usually accompanied by pharyngitis. It has a characteristic confluent erythematous 'sandpaper-like' rash, which is caused by one or more of several erythrogenic exotoxins. The rash usually starts on the head and neck and is accompanied by circumoral pallor and a strawberry tongue. The rash expands rapidly over the trunk, followed by the extremities, and ultimately desquamates; the palms and soles are usually spared.
- The skin is the second commonest site of GAS infections, i.e. impetigo, erysipelas, and cellulitis. Eczema, minor trauma, burns, and VZV infection are predisposing conditions.
- Invasive infections are defined by the occurrence of GAS at a normally sterile body site. Important examples are bacteraemia and pneumonia with empyema. Necrotizing fasciitis is characterized by severe focal pain (may be very localized, extreme tenderness), which is often, and especially in the early stage, disproportionate to cutaneous findings, fever, tachycardia, malaise, myalgias, diarrhoea, anorexia, and hypotension, and spontaneous gangrenous myositis.
- Streptococcal TSS is associated with shock and multi-organ involvement, including rapidly progressive renal failure, and may or may not be associated with bacteraemia. The commonest portals of entry are the skin, vagina, and pharynx. However, the focus cannot be ascertained in about 50% of cases.

- Neonatal GAS infection results from transmission from the mother (puerperal fever) or from nosocomial acquisition from medical personnel. Early-onset disease causes severe sepsis and pneumonia, while late-onset neonatal disease can cause severe soft tissue infections.
- Perianal and vulval infections may be seen in young children with marked erythema, itching, and bleeding.

Sequelae

- Acute rheumatic fever (ARF) occurs 2–3 weeks following initial pharyngitis. According to the revised Jones criteria, the diagnosis of rheumatic fever can be made in the presence of two major criteria (i.e. migrating polyarthritis of the large joints, carditis, subcutaneous nodules, erythema marginatum, Sydenham's chorea) or one major criterion plus two minor criteria (i.e. fever, arthralgia, raised ESR or CRP, leucocytosis, ECG abnormalities, a previous episode of rheumatic fever, or inactive heart disease). Evidence of a recent GAS infection is a prerequisite, yet serologic parameters alone can be difficult to interpret. Chorea and indolent carditis may be isolated findings, indicative of ARF. ARF remains an important public health problem in resource-poor countries.
- Post-streptococcal glomerulonephritis (PSGN) occurs with an estimated incidence of 10–30 new cases per 100 000 individuals per year, with the highest incidence between 5 and 15 years. PSGN develops about 10–14 days after pharyngitis or, more commonly, a skin infection with a nephritogenic GAS strain. The clinical spectrum varies from asymptomatic microscopic haematuria to acute nephrotic syndrome with frank haematuria, oedema, hypertension, and acute renal failure.
- Paediatric autoimmune neuropsychiatric disorders (PANDAS) describes the usually rapid onset or exacerbation of obsessive–compulsive or tic disorders following GAS infection. This association remains highly controversial.

Diagnosis

- *Culture* of GAS from normally sterile sites is diagnostic. Throat culture is the gold standard for the diagnosis of acute GAS pharyngitis (sensitivity 90–95%).
- *Rapid antigen detection tests (RADTs)* are 'near-patient tests'. RADTs have a specificity of ≥95% and a sensitivity of 65–90%, yet they may be highly variable in untrained hands. Throat culture should be performed in children with a negative RADT only, if the disease is suggestive of GAS infection. Yet neither culture nor RADT can differentiate between acute GAS pharyngitis and GAS carriers with intercurrent viral illness.
- *Serology*: anti-streptococcal antibody tests, including anti-streptolysin S and anti-deoxyribonuclease B (DNase B), are useful in the diagnosis of streptococcal sequelae such as ARF. The antibody response occurs 2–3 weeks after the onset of infection. Serology is not helpful in the diagnosis of acute GAS infection. Single serological testing cannot discriminate between recent or previous infections, and the antibody response may be aborted by antibiotic therapy.

Management and treatment

Invasive group A streptococcal infection

- Supportive (often intensive) care is essential. Established severe GAS infection is treated with a combination of IV benzylpenicillin plus clindamycin. Clindamycin inhibits protein synthesis, in particular synthesis of bacterial toxins and of the antiphagocytic M-protein. In necrotizing fasciitis, debridement of affected tissue is essential. Antibiotic treatment should be started with a broad-spectrum β-lactam (e.g. piperacillin/tazobactam), in combination with clindamycin, as organisms, other than GAS, may be involved.
- The use of IVIG may be considered as adjunctive treatment in streptococcal TSS or necrotizing fasciitis in severely ill patients, although evidence for its therapeutic effect is missing.

Non-invasive group A streptococcal infection

- Treatment with penicillin or amoxicillin, unless contraindicated.
- GAS remains uniformly susceptible to penicillin. Resistance to erythromycin is currently around 5% in the UK (>25% resistance rates have been reported from Scandinavia and other European countries). Clindamycin may be effective in erythromycin-resistant strains.
- The great majority of children with pharyngitis do not need antibiotics or a throat swab.
- Systematic reviews suggest that antimicrobial treatment of GAS pharyngitis:
  - Reduces the duration and severity of illness by only around 1 day
  - Reduces infectivity (to 24 hours) and transmission to contacts
  - Reduces the incidence of ARF, acute suppurative complications (such as quinsy), and potentially PSGN. BUT prevention of suppurative complications is no longer regarded as a sufficient sole reason for antibiotic therapy (very high number needed to treat).
- Oral penicillin therapy has to be continued for 10 days in order to achieve pharyngeal eradication.
- Other β-lactam antibiotics have no proven advantage above penicillin in children and are therefore not recommended.
- In penicillin allergy, a 10-day course of erythromycin or clarithromycin may be given.

Prevention

- Handwashing is the single most important measure to reduce cross-infection.
- If GAS is diagnosed in a newborn baby or its mother, both baby and mother must be treated.
- In the case of invasive GAS infection, prophylaxis may be offered to close contacts with underlying risk factors. For this purpose, as well as for surveillance purposes, invasive GAS infections have to be notified to public health authorities.
- 2° prophylaxis for patients who have had rheumatic fever (without residual heart disease) should be continued for 5 years or until the twenty-first birthday, whichever is later, and may have to be lifelong for patients with recurrent ARF or persistent valvular disease.

Streptococcus agalactiae (group B *Streptococcus*)

Organism

- Grows easily on a variety of media; detection from genital/GI tract specimens is optimized using selective media.
- Serotypes: nine type-specific capsular polysaccharides (Ia, Ib, II–VIII; five serotypes account for 95% of invasive disease); can be further classified, according to surface localized protein antigens.

Epidemiology

- GBS infection is the leading cause of neonatal sepsis in Europe. Rare cause of invasive disease in children, but increasingly reported in pregnant women, immunocompromised, and elderly adults.
- GBS colonizes the genitourinary or GI tract of ~20% of pregnant women.
- Around 50% of infants born to colonized women will get colonized during birth, and 1% of these may develop early-onset GBS disease (<7 days of age) in the absence of intrapartum antibiotic prophylaxis.
- Infection usually occurs within the first 3 months of life; 50–60% occur <7 days of age, and 90% of the latter occur on day 1 of life.
- GBS infection occurring later in infancy (after the first 90 days of life) is typically associated with a history of extreme prematurity or immunodeficiency.

Transmission

- Transmission from mother to baby may occur *in utero* or during passage through the birth canal.
- Exposure to GBS in hospital, home, or community may result in late-onset disease.

Clinical features and sequelae

- GBS infection is classified by age of onset into:
  - *Early-onset infection*—defined as <7 days of age, but the majority present within 24 hours of birth
  - *Late-onset infection*—usually occurs at 4–5 weeks of age (range 7–89 days).
- Sepsis without a focus of infection occurs in 80–85% of cases of early-onset GBS disease. Signs of sepsis are non-specific and include irritability, lethargy, respiratory distress, hypoxia, temperature instability, poor perfusion, and hypotension.
- Pneumonia occurs in ~10% of cases of early-onset disease. It may be accompanied by septicaemia. In preterm infants, clinical findings may be very similar to those of respiratory distress syndrome due to surfactant deficiency. Pleural effusions are commoner in GBS pneumonia than in hyaline membrane disease.
- Meningitis may be associated with early-onset GBS infection (7%) or with late-onset infection (25–30%). In late infection, the onset is more insidious, and septicaemia is less common. Clinically apparent seizures are more likely to occur in late-onset disease.
- Late-onset disease may present as pneumonia, meningitis, osteomyelitis (classically of the humerus in a baby, it may be misdiagnosed as 'Erb's

palsy'), cellulitis, neck adenitis, and abscesses. Rare presentations include endocarditis, myocarditis, pericarditis, pyelonephritis, endophthalmitis, and brain abscess.

Diagnosis

- Identification of Gram-positive cocci in chains in specimens from normally sterile sites in a neonate is an indication of GBS infection, but a positive culture result is necessary for definitive diagnosis. Intrapartum antibiotic prophylaxis may inhibit growth of GBS from blood or CSF cultures, thereby reducing the sensitivity of the culture.
- RADTs for GBS in body fluids, other than CSF, are not recommended due to lack of specificity.
- Molecular tests exist but have not yet been established in clinical practice.

Management and treatment

- Supportive care and antimicrobial therapy, combined with drainage of abscesses.
- Benzylpenicillin or amoxicillin plus an aminoglycoside is recommended if GBS infection is suspected, since subinhibitory concentrations of aminoglycosides synergize with penicillins in GBS killing. Cephalosporins are also effective. When GBS infection has been confirmed and a clinical response is documented, benzylpenicillin can be given as single therapy.
- Treatment duration for GBS bacteraemia is 10 days.
- Treatment duration of GBS meningitis is 14 days after sterilization of the CSF, which should (ideally) be confirmed by a repeat LP 48 hours after the start of treatment.

Prevention

- Intrapartum antibiotic prophylaxis reduces the risk of neonatal GBS infection by interrupting transmission to newborn infants during delivery and potentially by indirect treatment of the infant. In Europe, both 'risk-based strategies' and antenatal maternal swab-based 'screening strategies' have been successfully implemented. Intrapartum prophylaxis should be offered to mothers with:
  - A previous delivery of an infant with GBS disease
  - GBS isolated in the urine or vagina at any time during pregnancy
  - Chorioamnionitis
  - Preterm delivery
  - Prolonged rupture of membranes
  - Pyrexia during labour.
- GBS vaccines are in development.

Lancefield group C or G streptococci

These are primarily pathogens of horses, cattle, and pigs, which have adapted to the human host. *S. dysgalactiae* subspecies (Lancefield group C or G) may cause epidemic sore throat in schools, nurseries, and other institutions. They are associated with unpasteurized milk. Skin infections are less common; endocarditis, septicaemia, or meningitis are very rare.

Alpha-haemolytic streptococci

Viridans (alpha-haemolytic) streptococci other than *Streptococcus pneumoniae*

- The *S. anginosus* (previously *milleri*) group and *S. bovis* are the most important members of this very heterogeneous group. Other viridans streptococci are often not identified further by clinical laboratories but simply reported as 'α-haemolytic' or 'viridans' streptococci.
- 'Viridans' streptococci are part of the normal oral flora, e.g. *S. mitior, S. sanguis, S. mutans, S. salivarius*.
- The *S. anginosus* group, which comprises *S. anginosus, Streptococcus constellatus*, and *Streptococcus intermedius*, inhabits the oropharynx, GI tract, or vagina.
- *S. bovis* is primarily found in animals but may be found in the human intestinal tract. It may be α-haemolytic or non-haemolytic and reacts with Lancefield group D antigen.

Epidemiology and clinical features

- The *mutans* group of streptococci contributes to dental caries.
- Viridans streptococci are a cause of subacute endocarditis in patients with pre-existing valvular damage (CHD or rheumatic fever). Dental or other surgical procedures in the mouth cause transient bacteraemia. Viridans streptococci have a particular ability to adhere to platelets, fibronectin, fibrinogen, and laminin, which are present on damaged heart valves.
- Viridans streptococci cause sepsis in immunocompromised patients, particularly in patients with mucositis or central line infections.
- *S. bovis* is associated with endocarditis and with underlying malignancies.
- The *S. anginosus* (previously *milleri*) group may cause dental, brain, liver, abdominal, and pelvic abscesses, when organisms move from the colonizing sites to deeper tissues.

Transmission

- Derived from the patient's own flora.

Treatment

- Resistance to penicillin is increasing among viridans streptococci (20–30% in the UK from 2004–2008, HPA data). Treatment of endocarditis may include penicillin or vancomycin ± gentamicin, according to results of susceptibility testing.
- *S. bovis* is generally susceptible to penicillin. As for other viridans streptococci, treatment of endocarditis needs to be planned with an ID specialist or microbiologist.
- The *S. anginosus* group remains sensitive to penicillin. Macrolide resistance is currently around 10%. The treatment of choice is penicillin or amoxicillin. Cephalosporins are second-line choices. For initial empirical therapy, metronidazole should be added, as mixed infections with anaerobes are not uncommon. Abscesses must be drained.

- Infections of the oral cavity may respond to penicillin or amoxicillin; however, due to increasing penicillin resistance among anaerobic organisms, combinations of aminopenicillins with a β-lactamase inhibitor (sulbactam, clavulanic acid) may be used as first-line agent. Clindamycin is an alternative in patients allergic to penicillin.

Prevention

- Routine antibiotic prophylaxis for endocarditis is no longer recommended (NICE clinical guideline 64, March 2008).
- Oral hygiene is essential in preventing infections due to viridans streptococci, and particularly important in patients with valvular heart disease and in immunocompromised patients.

What's new?

- Most pharyngitis antibiotic treatment guidelines are recommending a more targeted and restricted use of antibiotics.

What's next?

- A GBS polysaccharide–protein conjugate vaccine is expected to be tested in phase 3 trials (phase 2 trials have been completed).

Further reading

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Chapter 116

Syphilis

Name and nature of organism

- Syphilis is an STI, caused by the spirochaete bacterium *T. pallidum*.
- *T. pallidum* are spiral-shaped, slender, tightly coiled, motile Gram-negative bacteria.
- Other *T. pallidum* subspecies, pathogenic to humans (known as endemic non-venereal treponemal infections), include *Treponema pertenue* (causative agent of yaws), *Treponema endemicum* (bejel) and *Treponema carateum* (pinta).
- These clinical diseases cannot be distinguished using current serological tests.
- *T. pallidum* cannot be grown *in vitro*.
- Humans are the only known natural reservoir for *T. pallidum*.

Epidemiology

- Most cases occur in the highly sexually active age group (young men and women).
- In 2008, ~1.36 million (range 1.16–1.56 million) pregnant women globally were estimated to have probable active syphilis, with ~520 000 adverse outcomes estimated to be caused by maternal syphilis.
- Syphilis is now an uncommon infection in developed countries but remains endemic in many resource-poor countries.
- Although numbers remain small, there has been a resurgence of syphilis in the UK and US in recent years in both heterosexual populations and MSM.
- Diagnoses of 1° and 2° infectious syphilis in UK GUM clinics increased from 342 in 2000 to 2524 in 2008. However, congenital syphilis remains rare, with 37 reported cases in 2005 and nine in 2008, in the UK.

Transmission

- Syphilis is primarily an STI. Other modes of infection include:
  - Passage through the placenta (congenital syphilis). This occurs most often where the mother has untreated or inadequately treated early syphilis (i.e. within the first 4 years after infection). The likelihood of mother-to-baby transmission approaches 100% where the mother has symptomatic early syphilis; overall, it is around 70% in early syphilis, and 10–20% where the mother has late latent syphilis. Congenital disease usually commences *in utero*. Spirochaetes have been detected in the fetus as early as 9–10 weeks of pregnancy

- Mother-to-baby transmission may also occur during delivery by contact of the newborn with infectious genital lesions
- Other close contact (e.g. kissing) with an active lesion (chancre or condyloma)
- Transfusion of contaminated blood (from unscreened donors, mainly in resource-poor countries)
- Direct inoculation.

- The incubation period for 1° syphilis after sexual transmission is usually between 14 and 28 days (range 3–90 days).

Clinical features and sequelae

Syphilis has variable clinical presentations, and it has been known historically as 'the great imitator'.

In the era of pre-penicillin therapy, a famous saying was 'He who knows syphilis knows medicine.' However, today the low incidence of syphilis has led to unfamiliarity with the disease among physicians.

The various clinical syndromes of syphilis include congenital and acquired syphilis, with the latter progressing through four stages—1°, 2°, latent, and tertiary.

Congenital syphilis

- Congenital infection can be manifest as spontaneous abortion, stillbirth, premature birth, neonatal death, IUGR, hydrops fetalis, neonatal disease, or latent infection.
- At least one-third of cases of transplacental transmission will result in spontaneous abortion or intrauterine death.
- About two-thirds of live-born infected infants do not have any abnormal physical findings at birth but present later.
- Congenital syphilis is usually classified as early congenital syphilis, presenting in children <2 years of age, and late congenital syphilis where stigmata of congenital infection develop later in childhood or in adult life.

Early congenital syphilis

- The earliest classic sign is usually rhinitis with nasal discharge ('snuffles') that turns bloody later, soon followed by a diffuse, maculopapular, desquamative rash with extensive sloughing of the epithelium, particularly of the palms, soles, and around the mouth and anus. A vesicular rash and bullae may also develop, containing large numbers of spirochaetes, and are highly infectious.
- Some infants present with non-specific signs, including rash, generalized lymphadenopathy, anaemia, hepatosplenomegaly, thrombocytopenia, and jaundice with hepatitis.
- Osteochondritis/periostitis are common and may present as pseudo-paralysis of one or more limbs. X-ray abnormalities include metaphyseal lesions, periostitis, and ostial lesions which are usually symmetrical and more commonly seen in the long bones. Wimberger's sign (the cat bite) is a classical destruction of the medial part of the proximal tibial metaphysis.

- CNS involvement occurs in at least one-fifth of neonates. The CSF is abnormal in around half of affected babies.
- Necrotizing funisitis is an uncommon sign, seen almost exclusively in preterm infants, caused by inflammation of the umbilical cord.

Late congenital syphilis

- Manifestations include:
  - Hutchinson's triad: interstitial keratitis, Hutchinson's incisors (centrally notched, widely spread, peg-shaped upper central incisors), and VIIIth nerve deafness
  - Characteristic deformities resulting from osteochondritis, perichondritis, and periostitis, including depression of the nasal bridge (saddle nose) and anterior tibial bowing (sabre shin)
  - Recurrent arthropathy and bilateral knee effusions (Clutton's joints), prominent frontal bones, and reduced maxillary bones
  - Neurosyphilis—a common late presentation, but the late development of cardiovascular syphilis is rare.
- The patient is non-infectious during this stage.

Acquired syphilis

Untreated sexually acquired syphilis progresses through four stages: 1°, 2°, latent, and tertiary. 1°, 2°, and early latent phase are the infectious stages of syphilis.

Primary syphilis

The 1° lesion is a painless indurated ulcer or chancre at the site of entry of the infection. Untreated, the chancre heals in 2–6 weeks. The inguinal lymph nodes are moderately enlarged, mobile, discrete, and painless. This stage is often unnoticed, especially in ♀.

Secondary syphilis

Without treatment, spirochaetes later migrate into the bloodstream, and the disease progresses to the 2° stage 6–12 weeks after exposure. Clinical manifestations include fever, malaise, sore throat, headache, a generalized maculopapular rash, and condylomata lata in the genital area. Patients are highly infectious at this stage. Because syphilis is uncommon, the diagnosis may not be considered when patients present to medical services with these symptoms.

Latent syphilis

Untreated, the manifestations of 2° syphilis resolve, and the infection becomes asymptomatic and latent. During this stage, the number of spirochaetes in the blood declines, so that, after 2–4 years, only dormant bacteria remain in deeper organs and tissues.

Tertiary syphilis

Around one-third of untreated patients subsequently develop tertiary syphilis, at least 10–20 years later. Gummas may affect any organ in the body. Other late manifestations include cardiovascular syphilis (especially aortitis) and neurosyphilis.

Diagnosis

General principles

- In 1°, 2°, and early congenital syphilis, examination by dark-field microscopy or immunofluorescence staining of mucocutaneous lesions is the quickest and most direct laboratory method of establishing the diagnosis.
- *T. pallidum* cannot be cultured *in vitro*.
- Molecular methods, such as PCR, can be used to detect *T. pallidum* DNA in clinical material.
- Serological tests are the mainstay of screening and diagnosis. There are two types of serological test: treponemal and non-treponemal. Neither test is specific for *T. pallidum* subspecies *pallidum*. This is rarely a problem in Europe where other treponemal infections do not occur, but this needs to be considered when interpreting serological results from patients from abroad.
- Non-treponemal antibody tests use non-specific antigens. The commonest are the rapid plasma reagin (RPR) and VDRL tests. These tests have a high rate of biological false positives. They become reactive 4–7 days after development of the 1° lesion and are always reactive in 2° syphilis. Non-treponemal tests are mainly used to monitor the response to treatment, because titres decrease after effective treatment. They can be regarded as a sort of 'syphilis ESR' and should not be used to diagnose syphilis without confirmation of seropositivity with a treponemal test.
- Treponemal tests use specific treponemal antigens. These include EIAs for the detection of IgG and/or IgM, the *T. pallidum* haemagglutination assay (TPHA) or *T. pallidum* particle agglutination assay (TPPA), and the fluorescent treponemal antibody-absorbed test (FTA-ABS). With the exception of EIAs for IgM, these tests remain positive indefinitely.
- EIAs are now the most commonly used screening tests for syphilis. EIAs that detect specific anti-treponemal IgM antibodies are useful in diagnosing congenital and early acquired syphilis.

Diagnosis of congenital syphilis

- *T. pallidum* can be demonstrated directly by dark-ground microscopy and/or PCR of exudates from suspicious mucocutaneous lesions or nasal discharge, or placenta if suspected at delivery.
- Serological testing should be performed on the infant's blood (not cord blood).
  - Where screening tests are negative and there are no signs of congenital infection, no further testing is necessary.
  - Infants with a positive screening test must be investigated further to determine whether the infant has been infected or the seropositivity relates to passive transfer of maternal antibodies.
  - A positive IgM test and/or a sustained 4-fold or greater difference of VDRL/RPR titre or TPPA titre above that of the mother is diagnostic of congenital syphilis.
  - Where IgM is negative and the other tests are reactive with titres below those diagnostic of congenital syphilis, previously reactive

tests should be repeated at 3, 6, and 12 months of age, or until all tests become negative. The IgM should be repeated at the age of 3 months in case the infant's response is delayed.
- Further investigations to assess infants with congenital syphilis include: FBC, LFTs, U&Es, CSF examination for cells, protein, and serological tests, X-rays of long bones, and ophthalmic assessment.

Management and treatment

General principles

- Manage with a GUM physician.
- Penicillin remains the drug of choice for treatment of syphilis during pregnancy.
- Recommendations for benzylpenicillin dosage and duration of therapy vary, according to the stage of disease and clinical manifestations.
- Alternative antimicrobial treatment options include azithromycin and ceftriaxone, but these agents have not been proven to be as effective as penicillin in preventing transplacental transmission.
- Consider other STIs.
- Adequate early treatment of a pregnant woman with syphilis usually, but not always, ensures that the fetus will be unaffected.

Management of infants with congenital syphilis

Groups of infants who need full treatment for congenital syphilis

- Infants with proven or probable congenital syphilis.
- Infants born to mothers with syphilis who have had:
  - Treatment only within 4 weeks of delivery
  - Treatment with drugs other than penicillin
  - No treatment or inadequate treatment
  - No documentation of treatment.
- If mothers have been treated adequately with a documented history or a full treatment course of a penicillin-based regimen >4 weeks prior to delivery, and there is no evidence of reinfection or relapse, serological monitoring of the infant alone is recommended.

Treatment regimens

- Benzylpenicillin sodium 12-hourly in the first 7 days of life, and 8-hourly thereafter for 3 days (10 days in total), is the preferred treatment regimen.
- Alternatively, procaine benzylpenicillin daily IM for 10 days.
- If >1 day of treatment is missed, the entire course should be restarted.

Prevention

- All pregnant women are screened for syphilis at the initial antenatal visit. Additionally, for patients at high risk, serological testing should be repeated at 28–32 weeks of gestation and at delivery.
- Acquired syphilis may be prevented by sexual education and by identification and treatment of infected individuals.

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Chapter 117

Tetanus

Name and nature of organism

- *C. tetani* is an anaerobic, spore-forming Gram-positive bacillus.
- Spores are found in soil, house dust, animal and human intestine, and faeces, and remain viable for years.
- Wounds become contaminated with *C. tetani* spores. Spore germination is favoured by anaerobic and acidic conditions, resulting in the release of exotoxin (a neurotoxin—tetanospasmin).

Epidemiology

- Tetanus is rare in Western Europe, and even rarer in children. In the UK, <20 cases of tetanus are reported each year. The main risk groups are the elderly (who may not be fully vaccinated) and injecting drug users. In resource-poor countries, neonates are another important risk group.
- Worldwide, tetanus remains a major public health problem in children and adults due to inadequate immunization coverage, causing 200 000–300 000 deaths each year.
- The mortality rate for untreated tetanus is up to 90%, but, with high-quality intensive care, it is <10%. The mortality rate of those who have received one or two doses of the vaccine, but not a previous complete course, is around half that of the unvaccinated.

Transmission and incubation period

- Tetanus is transmitted by direct inoculation of *C. tetani* spores in soil and animal manure; it is not transmitted from person to person.
- Traumatic wounds (most commonly), burns, ulcers, gangrene, frostbite, and the neonatal umbilical stump are portals of entry.
- Incubation period: 4–21 days, but may range from 1 day to several months.

Clinical features and sequelae

- Tetanus may be generalized (the commonest form) or localized. Complications may be due to direct toxin effect or 2° to spasms.

Generalized tetanus

- Usually commences with muscles spasms, especially of the jaw muscles (trismus or lock jaw).
- As the disease progresses, muscle stiffness and spasms become more generalized.

- Mild stimuli, such as noise, light, and touch, may trigger reflex spasms.
- Other symptoms and signs include facial grimacing (risus sardonicus), dysphagia, restlessness, respiratory difficulty, opisthotonus, and autonomic dysfunction.
- Without supportive care, the disease usually progresses to death.
- Tetanus neonatorum is generalized tetanus in neonates born to unimmunized mothers, caused by unhygienic delivery and/or infection of the umbilical stump. The baby first presents with generalized weakness, apnoea, and poor feeding. This progresses to classic tetanic spasms and opisthotonus. Mortality is very high, as is residual neurological damage in survivors.

Localized tetanus

- This presentation is less common and usually occurs in people who are partially immune.
- Symptoms and signs remain localized to the region of the infection, with weakness of the involved extremity and intense painful spasms in severe cases.
- Cephalic tetanus is a rare form of localized tetanus 2° to craniofacial injuries or infections. The incubation period is usually very short (1–2 days), presenting with cranial nerve palsies.
- Cephalic tetanus is more likely to progress to generalized tetanus.

Diagnosis

- The diagnosis of tetanus is clinical. Because tetanus is rare in the Western world, the first challenge is to suspect the diagnosis, based on the clinical history. It is important to remember that the wound site may not be obvious.
- Detection of *C. tetani*: bacterial culture from the wound site should always be attempted. A PCR method is also available. However, these tests are positive only in a few cases. A negative result certainly does not exclude the diagnosis.
- Detection of *C. tetani* neurotoxin in serum: undertaken only in reference laboratories. Blood must be collected before antitoxin is administered.
- Determination of the tetanus immunity status can also be helpful in investigating patients with suspected tetanus. Absence of detectable antibody or detection of an antibody level below the protective threshold (0.1IU/mL) in a serum sample taken before the administration of immunoglobulins lends support to the clinical diagnosis.

Management and treatment

- Early recognition and treatment can be lifesaving.
- To neutralize unbound toxin, human tetanus immunoglobulin should be given immediately IV (preferably) or IM in multiple sites.
- Toxin production at the site of infection is reduced by thorough wound toilet and antimicrobial therapy, usually IV metronidazole or benzylpenicillin.

- Muscle spasm can be reduced by isolating the patient from noise and bright light stimuli. Sedation with benzodiazepines can decrease rigidity and control spasms. Diazepam alone or anticonvulsants, such as phenobarbital, and chlorpromazine can be used.
- Respiratory failure is managed in a specialist unit by tracheostomy and assisted ventilation after neuromuscular blockade. Paralysing agents, such as pancuronium, can worsen the sympathetic overdrive; magnesium sulfate infusions are used to reduce this.
- After recovery, all patients should receive a course of tetanus vaccination to prevent further recurrence.

Prevention

Tetanus vaccine

- 1° prevention is with tetanus vaccine. This is made from a cell-free purified *C. tetani* toxin that is treated with formaldehyde to turn into toxoid, and adsorbed onto an adjuvant.
- In the UK, it is only available as a component of diphtheria, tetanus, and pertussis (DTP), with or without Hib.
- Individuals who have received five doses at appropriate intervals are considered fully immunized. Routine boosters every 10 years are no longer considered necessary.
  - 1° immunization consists of three doses of tetanus-containing vaccine, with an interval of 1 month between each dose, given at any stage from 2 months up to 10 years of age.
  - A first booster dose is given around 3 years after the 1° course, and a second booster after another 10 years.

Management of wounds

- Thorough cleaning of all wounds is essential.
- The opportunity to check that the injured individual is fully immunized against tetanus should always be taken.
- Tetanus-prone wounds are:
  - Wounds or burns that require surgical intervention that is delayed >6 hours
  - Wounds or burns that show a significant degree of devitalized tissue or a puncture-type injury, particularly where there has been contact with soil or manure
  - Wounds containing foreign bodies
  - Compound fractures
  - Wounds or burns in patients who have systemic sepsis.
- High-risk wounds are wounds where there has been heavy contamination with material likely to contain tetanus spores and/or extensive devitalized tissue.
- The use of active (vaccine) and passive immunization (human tetanus immunoglobulin) depends on the immunization status of the injured person, whether or not the wound is tetanus-prone, and whether or not it is high-risk (Table 117.1).

Table 117.1 Recommended tetanus immunization management for wounds, according to the risk of tetanus

Immunization status	Immunization requirements according to wound assessment		
	Clean	Tetanus-prone	Tetanus-prone and high risk
Fully immunized (has received five doses of vaccine at appropriate intervals)	None required	None required	Human tetanus immunoglobulin
1° immunization complete, boosters incomplete but up-to-date	None required	None required	Human tetanus immunoglobulin
1° immunization incomplete or boosters not up-to-date	Reinforcing dose of vaccine plus further doses, as required, to ensure full immunity	Reinforcing dose of vaccine plus further doses, as required, to ensure full immunity *Plus* Human tetanus immunoglobulin	Reinforcing dose of vaccine plus further doses, as required, to ensure full immunity *Plus* Human tetanus immunoglobulin
Not immunized or immunization status uncertain	Immediate dose of vaccine plus further doses, as required, to ensure full immunity	Immediate dose of vaccine plus further doses, as required, to ensure full immunity *Plus* Human tetanus immunoglobulin	Immediate dose of vaccine plus further doses, as required, to ensure full immunity *Plus* Human tetanus immunoglobulin

What's new?

- Intrathecal route of administration of tetanus immunoglobulin has been shown to be superior to IV route in preventing complications in a meta-analysis. However, this approach should be undertaken only under expert guidance.

What's next?

- Major progress is being made in preventing neonatal tetanus. Globally, the number of cases has decreased by over 90% since the late 1980s. The WHO target year for global elimination of maternal and neonatal tetanus is 2015.

Future research

Long-term follow-up is needed to determine whether the five-dose childhood immunization schedule provides adequate lifelong protection in an increasingly elderly population.

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Tick-borne encephalitis

Name and nature of organism

- The causative agent of TBE is an RNA virus which belongs to the genus *Flavivirus* within the *Flaviviridae* family.
- Antigenic variation of surface protein E allows distinction between European, Central Siberian, and Far Eastern subtypes (prevalent in Eastern Russia) of TBE virus (TBEV).

Epidemiology

- TBE is endemic in Central, Northern, and Eastern Europe and in some areas in Central and Northern Asia (Fig. 118.1).
- Overall incidence of TBE in most endemic areas in European countries is in the range of <1 to 4/100 000. Higher incidence rates (5–20/100 000) have been reported from Czech Republic, Estonia, Latvia, Lithuania, and Slovenia.
- However, there is regional variability of incidence rates within TBEV-endemic countries, including the existence of high-risk areas in countries with an overall low incidence. This is, for example, the case for Black Forest in Germany.
- Year-to-year variability of disease incidence is considerable.
- In accordance with activity levels of ticks, TBE has a strong seasonality and occurs mainly from April to October, with a peak in June and July.
- Incidence is higher in men than in women, and ~2- to 3-fold higher in adults than in children overall.

Transmission and incubation period

- Transmission of TBEV is by the sting (erroneously frequently called a 'bite') of ticks, most commonly *Ixodes ricinus, Ixodes scapularis*, and *Ixodes persulcatus*.
- Rates of TBEV found in these ticks vary extensively by region (<1% in low-endemic areas and up to 5% or more in high-risk areas).
- In contrast to Lyme borreliosis, early removal of feeding ticks from the skin does not prevent TBE, as the virus is transmitted via the tick's saliva as soon as it stings and injects saliva into the human host's skin and subcutaneous layers of the skin.
- Further, although rare, transmission of TBEV by consumption of unpasteurized goat's milk has been reported.

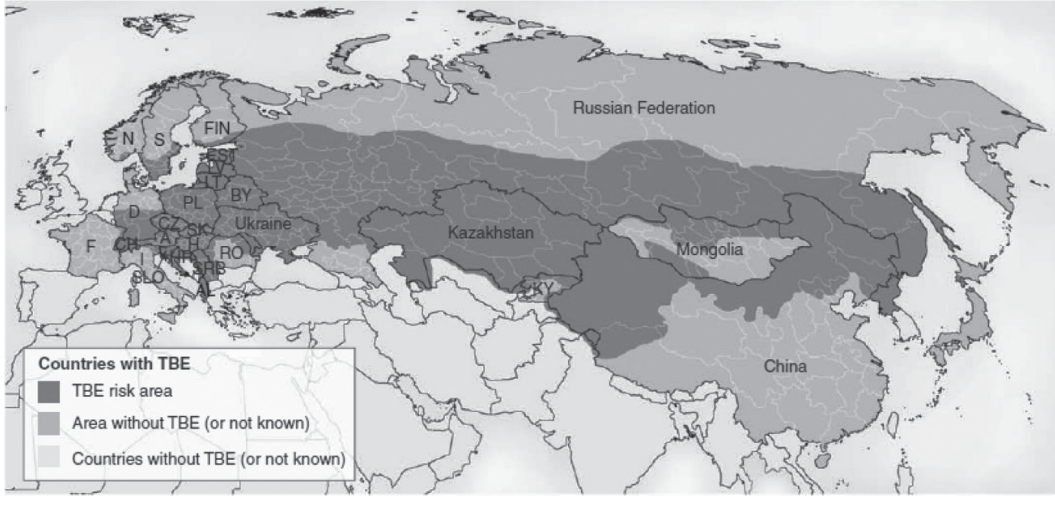

Fig. 118.1 Congenital rubella births (NCRSP) 1971–2013 and rubella-associated terminations* (ONS) 1971–2000.

* Terminations data not published since 2000 because of very low numbers. Reprinted from *Travel Medicine and Infectious Disease*, Vol 8, Eckhardt Petri, Dieter Gniel, and Olaf Zent, Tick-borne encephalitis (TBE) trends in epidemiology and current and future management, 233–245, Copyright 2010, with permission from Elsevier.

- More than 50% of patients with microbiologically confirmed TBE do not recall a tick sting in the preceding weeks. Therefore, a negative history for tick sting does not rule out TBE.
- The incubation period is usually 3–14 days but may be up to 4 weeks.

Clinical features and sequelae

The great majority of TBEV infections are either asymptomatic or present with influenza-like signs and symptoms which persist for a short period of time, usually <5 days. After a symptom-free interval of a few days, 10–15% of infected individuals move on to CNS manifestations, with usually an acute onset. Presenting signs and symptoms are largely age-dependent.

- In children <6 years of age, aseptic meningitis is more frequent than encephalitis or meningo-encephalitis which prevails in older children and adults. Aseptic meningitis typically presents with headache, nausea, and malaise; some children are irritable and/or lethargic; photophobia in aseptic meningitis due to TBEV is not the rule.
- In older children and adolescents, signs of encephalitis, such as impaired consciousness, generalized or focal CNS abnormalities, including seizures, occur. Radiculitis and pareses are rare in children, but frequent in adults.
- Most patients with aseptic meningitis recover completely.
- If meningo-encephalitis occurs, headache and concentration difficulties can persist for several months, frequently leading to social problems and school absence.
- Pareses may persist permanently.
- Death due to TBE occurs but is very rare in children.

Diagnosis

ECDC defines TBE as symptoms of inflammation of the CNS (e.g. meningitis, meningo-encephalitis, encephalomyelitis, encephaloradiculitis, or a combination of these), with laboratory confirmation by at least one of the following five criteria:

1. TBE-specific IgM and IgG antibodies in blood
2. TBE-specific IgM antibodies in CSF
3. Seroconversion or 4-fold increase of TBE-specific antibodies in paired serum samples
4. Detection of TBE viral nucleic acid in a clinical specimen
5. Isolation of TBEV from a clinical specimen.

Lumbar puncture and cerebrospinal fluid tests

- CSF abnormalities do not necessarily correlate with clinical severity.
- Opening pressure, red cells, WCC, glucose, and protein should be measured. These values may be normal in cases of encephalitis, or the protein/WCC may be slightly elevated.
- In patients with aseptic meningitis, a mixture of neutrophils and mononuclear leucocytes in the CSF is commonest.

Brain imaging, electroencephalography

These tests may be performed complementary to laboratory tests, depending on individual CNS manifestations. For details, see Chapter 14 on encephalitis.

Management and treatment

Neither causal treatment nor specific immunoglobulins against TBE are available.

Supportive symptomatic treatment

This is the mainstay of management.

- Neuroprotective measures should be performed, as necessary (see Chapter 14).
- If they occur, seizures should be treated with antiepileptic drugs.
- There is no role for steroids in TBE treatment.

Prevention

Passive immunization by specific IgG anti-TBE antibody formulations, used for PEP until the 1990s, are not available any longer, as they were incriminated to lead to more serious courses of disease by antibody-dependent enhancement of infection.

However, similar types of vaccines by two manufacturers are available in all European countries, and two vaccines by manufacturers in Russia. Here we focus on the two vaccines available all over Europe—Encepur® (Novartis/GSK) and FSME-Immun® (Baxter/Pfizer).

- The vaccines contain inactivated TBEV (aluminum-adjuvanted) which induces a robust immune response against the European TBEV subtype and protective cross-reactive antibodies against the Central Siberian and Far Eastern subtypes.
- Paediatric formulations are available from 1 year of age onwards (0.25mL to be administered IM) until and including 11 years (Encepur®) and 15 years (FSME-Immun®) of age. Beyond these age limits, adult formulations (0.5mL per dose) by both manufacturers are licensed.
- The 1° series consists of three doses (0, 1, 5–12 months).
- Seroconversion, which presumably correlates with protection, is >95% when measured 2–4 weeks after the second dose.
- After the third dose, regular booster doses are recommended, according to licensing by EMA, at 3- (first booster) and 5- (≥ second booster) year intervals if exposure continues.
- Immunization is recommended for residents in, and travellers to, TBE-endemic areas.
- If protection is warranted urgently, rapid immunization schedules can be used: 0, 14 days (FSME-Immun®), followed by a regular third dose 5–12 months later; or 0, 7, 21 days (Encepur®), followed by a fourth dose 12 months later.
- TBE immunizations are well tolerated.

Future research

Surveillance systems for TBE should be harmonized in Europe, based on the case definition proposed by ECDC. A serologic correlate of immunity after TBE immunization should be established in order to better define the optimal interval(s) for vaccine booster doses.

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Chapter 119

Toxocariasis

Name and nature of organism

- Toxocariasis is a zoonotic infection caused by the dog roundworm *T. canis*, or less commonly the cat roundworm *T. cati*.
- Fifty per cent of puppies are infected and produce the highest number of eggs (up to 100 000 eggs/g of faeces). Around 20% of adult dogs are infected, and they produce eggs at lower levels.
- Eggs passed in dog and cat faeces are initially unembryonated and non-infectious; they become infective in the environment 10–21 days after shedding and thereafter can remain viable for years.
- The human is an accidental host. Development stops at the larval stage; migration of larvae to organs and tissues causes the clinical manifestations toxocariasis, visceral larva migrans, or ocular toxocariasis.

Epidemiology

- Toxocariasis occurs worldwide.
- The incidence of symptomatic toxocariasis is unknown; 2–14% of the population in Western world is seropositive, with higher rates in children. However, seropositivity does not mean that clinical illness developed at the time of infection or will develop in the future.
- Only around ten cases of toxocariasis are reported each year in the UK, but this is likely to be an underestimate of the true incidence; the incidence of ocular toxocariasis alone may be up to 6–10 per 100 000 children.
- Risk factors for *Toxocara* seropositivity include contact with puppies, residence in warmer climates, and pica.
- Many studies have shown a high frequency of contamination of children's play areas (especially sandpits) with eggs of *T. canis*.

Transmission and incubation period

- Direct or indirect (via contaminated soil or surfaces) contact with animal faeces containing *Toxocara* eggs.
- Toxocariasis may also rarely be transmitted via handling or ingestion of contaminated undercooked meat.
- After ingestion, embryonated eggs hatch in the intestine; larvae burrow through the intestinal wall and migrate to tissues and organs via the lymphatic and circulatory systems where they induce granulomatous lesions.

- Spread may be to other tissues, particularly the lungs, abdominal organs, and the brain (visceral larva migrans), or to the eyes (ocular larva migrans). Humans tend to get either visceral or ocular larva migrans.
- Incubation period: weeks or months; ocular manifestation may take 4–10 years to develop.

Clinical features and sequelae

Most cases are asymptomatic; when symptoms do occur, they are caused by migration of second-stage larvae. There are two major forms of symptomatic toxocariasis.

- Visceral larva migrans:
  - Commonest in children aged 2–7 years
  - Clinical presentation depends on the organs affected: lungs, liver, and CNS are the commonest body systems affected
  - Non-specific symptoms and signs include fever, fatigue, anorexia, and lymphadenopathy
  - Pulmonary symptoms and signs include cough, dyspnoea, and wheeze
  - Abdominal symptoms and signs include nausea and vomiting, abdominal pain, and hepatosplenomegaly
  - Neurological presentations include headache, seizures, changes in behaviour and sleep pattern, pareses, and transverse myelitis
  - Cardiac manifestations, e.g. myocarditis, pericardial effusion, may rarely occur
  - Most children will have a marked eosinophilia and hypergammaglobulinaemia
  - The term covert toxocariasis is sometimes used to refer to less serious cases of visceral larva migrans
  - An association between visceral toxocariasis and asthma has been proposed, but it is not clear whether *Toxocara* has any pathogenic role.
- Ocular toxocariasis:
  - Usually affects only one eye and presents in older children. (aged 8–16 years)
  - Loss of visual acuity over days or weeks is the commonest symptom
  - Other presentations may include red eye, white pupil, fixed pupil, retinal fibrosis, and retinal detachment
  - Presentations may be confused with retinoblastoma.

Diagnosis

- Demonstration of larvae is difficult, and biopsy of the lesions is seldom justified. Stool examination is of no use.
- Serological diagnosis by ELISA is the test of choice. The sensitivity depends on the worm burden in the patient.
- In ocular toxocariasis, serology is less sensitive; vitreous *Toxocara* antibodies can be measured. It may also be possible to demonstrate larvae in the vitreous and/or aqueous humour, but often the diagnosis is based on clinical findings alone.

Management, treatment, and prevention

- Treatment is indicated for symptomatic cases only.
- Albendazole orally for 5 days is the standard treatment.
- Mebendazole, thiabendazole, and diethylcarbamazine are also effective. Diethylcarbamazine may be the most effective treatment but is less well tolerated—often reserved as a second-line agent.
- Systemic corticosteroid therapy is indicated in ocular toxocariasis and serious visceral larva migrans.
- Regular treatment of dogs and cats (especially young animals) with anthelmintics (deworming) is essential for prevention, together with prompt disposal of animal faeces and avoidance of playing in areas where animals waste is present. Good handwashing, especially before eating and after handling pets, can reduce chances of ingesting *Toxacara* eggs. No vaccine is available.

What's next?

- Because symptomatic toxocariasis is a rare condition, it is unlikely that there will be any evidence-based changes to recommendations for diagnosis or treatment in the near future.
- Further work is required to establish whether there is any benefit in treating asymptomatic patients.

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Chapter 120

Toxoplasmosis

See also Chapters 3, 10, 15, 19, 20, 31, 45.

Name and nature of organism

- *T. gondii* is an obligate intracellular protozoan parasite.
- It exists in three forms (stages)—tachyzoites are seen in acute infection; bradyzoites in cysts are seen in chronic latent infection, and sporozoites are the sexual form in oocysts that occur only in intestines of the cat family.

Epidemiology

- Worldwide seroprevalence of *Toxoplasma* measured by specific anti-*Toxoplasma* IgG antibodies varies between 1% and 100%, depending on environmental and socio-economic conditions.
- The incidence of congenital toxoplasmosis in northern Europe and the US is thought to be ≤1 per 10–100 000 births. A recent systematic review estimated around 200 000 infants worldwide are born annually with congenital toxoplasmosis.
- Congenital infection is associated with maternal 1° infection in pregnancy. Around 50% of women in Western Europe are seropositive by childbearing age, although there are marked differences between individual countries.
- About one-third of infected women may give birth to an infected fetus; first-trimester infection tends to produce more severe disease.
- By adolescence, 10–30% of congenitally infected infants will have developed chorioretinitis.
- Routine antenatal surveillance for *Toxoplasma* infection in pregnancy is undertaken in some European countries with higher seroprevalence, e.g. France, Austria, and Poland.
- Routine antenatal screening is not undertaken in the UK; in a recent surveillance study of symptomatic infants/children, performed from 2002 to 2004, involving paediatricians, ophthalmologists, and the *Toxoplasma* reference laboratory, only 38 children with *Toxoplasma* infection were identified. Twenty-two (58%) were classified as congenital infection (3.4/100 000 live births); two (9%) were stillborn; seven (32%) had intracranial abnormalities and/or developmental delay, five of whom also had chorioretinitis; ten (45%) had chorioretinitis alone. A further 16 children (42%) had been infected after birth and developed chorioretinitis.
- There appears to be considerable regional variation in the disability produced by *Toxoplasma* infection; eye lesions in Brazil, for instance, are more frequent and severe than those in northern Europe. The Brazilian strain of *Toxoplasma* is known to be more pathogenic than the European.

Transmission and incubation period

- Worldwide, many species of mammal are infected.
- Cats are definitive hosts and become infected by feeding on mice containing bradyzoites.
- The parasite replicates in the cat small intestine, and oocysts are then shed 3–30 days after 1° infection.
- The oocysts mature and sporulate outside the cat and may be ingested by intermediate hosts, including cattle, pigs, and sheep. Tissue cysts develop in the organs of these animals.
- Infection in humans results from ingestion of inadequately cooked meat or from contact with infected cat faeces.
- Most infection in early childhood is thought to result from congenital infection; transmission occurs at any stage in pregnancy, but post-natal infection can also occur.
- The incubation period is usually about 7 days but may be between 4 and 21 days.

Clinical features and sequelae

Acquired toxoplasmosis

- This may be asymptomatic or result in a mild infection, with low-grade fever, headache, myalgia, sore throat, and lymphadenopathy.
- Generalized cervical lymphadenopathy may last several weeks.
- In those with immunodeficiency, including HIV infection, encephalitis or pneumonitis may develop.
- In children with AIDS, the commonest presentation is with focal neurological signs, including hemiparesis, speech abnormalities, and convulsions. Cerebral imaging classically shows multiple bilateral ring-enhancing lesions, often at the cortico-medullary junction.

Congenital toxoplasmosis

- Characterized by the classic triad of chorioretinitis, hydrocephalus from aqueductal stenosis, and intracranial calcification.
- Cerebral imaging may show classic parenchymal and periventricular calcification.
- Other features include rash, lymphadenopathy, hepatomegaly, splenomegaly, jaundice, and thrombocytopenia.
- There is high mortality and morbidity in the small number of infants with the classic triad of features and systemic illness.
- Survivors may develop epilepsy and be developmentally delayed.
- In those with chorioretinitis, the macula is often involved. Relapsing disease produces a combination of old scars and active disease. Visual disturbances (often unilateral) usually present later in childhood, thus necessitating careful long-term follow-up.

Diagnosis

- This is complex, and advice should be obtained from an accredited toxoplasmosis reference laboratory.
- In previously well children, a 4-fold rise in IgG, or the presence of specific IgM or IgA, can be diagnostic, although IgM and IgA may persist for many months, thus making it difficult to identify the timing of infection. In immunocompromised children, the presence of specific *T. gondii* IgG demonstrates the possibility of reactivation causing disease.

In pregnancy

- Some countries, such as France, have screening programmes for pregnant women, but their cost-effectiveness and clinical benefits are not entirely clear. Cost efficacy of screening programmes depends on the varying prevalence of infection.
- All pregnant women should be counselled on the prevention of toxoplasmosis.
- The investigation of possible infection during pregnancy has to establish whether this occurred before or after conception.
- IgG assays are used in combination with the IgM EIA. The Sabin–Feldman dye test is used to detect previous infection. An IgG avidity test can also be used to help identify when infection developed, as more recent infection is associated with lower-avidity IgG.

Fetal testing

- With serological evidence of maternal infection, there may be an indication for cordocentesis to obtain specimens for both serology and detection of the parasite using PCR.
- Even with fetal infection, IgM antibodies are rarely detectable.
- Amniocentesis, which provides a lower risk to the fetus, is as sensitive in detecting the presence of *Toxoplasma* infection.

In the newborn

- Testing is done by the collection of paired cord blood, or preferably a neonatal blood sample (to reduce the risk of contamination), and a maternal specimen.
- Comparison is made between neonatal and maternal IgG by immunoblot. In an infant born to a mother with acute toxoplasmosis, the diagnosis can be made by high levels of specific IgG, which continues to persist at high levels in the first year of life. Passive transfer of maternal IgG leads to a rapid decline in these levels.
- Disappearance of IgG in infancy excludes *Toxoplasma* infection, as IgG is detectable for life after infection.
- Detection of neonatal IgM and IgA by EIA and/or immunosorbent agglutination assay (ISAGA) is diagnostic for neonatal infection.
- IgM/IgA may be present in <60% of children with congenital infection in the first month of life, so repeated testing is required.

Management and treatment

- No treatment is usually required in healthy children with acute toxoplasmosis, although lymphadenopathy and other symptoms may persist for up to a year.
- There are no adequate treatment trials in the literature.
- The treatment currently available is, at best, of marginal benefit. Recent cohort data have questioned the efficacy of both antenatal and post-natal therapy.
- In the UK, due to the low prevalence of *Toxoplasma* infection, there are concern about overdiagnosis, overtreatment, and unnecessary terminations of pregnancy. Consequently, toxoplasmosis does not fulfil the criteria to be included in the UK national antenatal screening programme. This is different for other higher-prevalence European countries where routine screening is undertaken.
- If there is evidence of maternal infection, treatment with spiramycin, a macrolide that reduces the risk of maternal transmission to the fetus, should be considered.
- If fetal infection is confirmed, the mother should be treated with pyrimethamine and a sulfonamine (e.g. sulfadiazine) from 30 weeks' gestation until delivery.
- When there is clear evidence of congenital infection in the newborn, pyrimethamine and sulfadiazine are recommended until the age of a year. This may be alternated with spiramycin if there are toxicity problems. Steroids may be used in the presence of ocular infection.
- Pyrimethamine may produce severe neutropenia, and folinic acid can be used to prevent this.
- The outcome for children with congenital infection depends on the severity of cerebral damage *in utero*, along with prompt diagnosis and treatment. Severe hydrocephalus is a poor prognostic sign. In children with less severe disease, prompt treatment can be associated with good neurological and cognitive outcomes. This is a rare disease, and large prospective cohort studies are limited.
- For acquired infection resulting in chorioretinitis, treat with pyrimethamine, sulfadiazine, and steroids. Due to the toxicity of this regimen, newer options being used in small case series include co-trimoxazole, combined with azithromycin, or intravitreal injections of clindamycin and steroids.
- Retinal scars can progress, and long-term ophthalmological review into adult life is critical. Relapses may occur when treatment is stopped at 1 year.
- In immunocompromised children, treatment usually leads to resolution of clinical and radiological abnormalities, but permanent neurological damage sometime occurs. Only correction of the underlying immune deficit prevents further relapses.

Prevention

- There is no vaccine against *Toxoplasma* infection.
- The mainstay of prevention lies in the promotion of excellent hygiene, especially in pregnant women.
- In particular, pregnant women should avoid handling raw meat, ensure vegetables are washed properly before eating, and wash hands thoroughly after any contact with cat litter or soil.

Future research

- There is a need for better investigations to diagnose *Toxoplasma* infection, with a particular emphasis on the timing of infections in pregnant women.
- RCTs of both antenatal and post-natal treatment are required—with safer and more effective therapy.

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Chapter 121

Tuberculosis

See also Chapters 15, 19, 20, 27, 29, 42, 90.

Name and nature of organism

- TB is an infectious disease caused by bacteria belonging to the *M. tuberculosis* complex (includes *M. tuberculosis, M. bovis*, and *Mycobacterium africanum*).
- The genus *Mycobacterium* consists of a diverse group of bacilli that strongly retain specific dyes, despite treatment with acid–alcohol (hence called acid- and alcohol-fast).

Epidemiology

- About 8.6 million new cases of TB disease, and nearly 1.3 million deaths from TB, are estimated to occur around the world every year.
- Most of the estimated cases are in Asia (58%) and Africa (27%), with small proportions of cases in the Eastern Mediterranean Region (8%), the European Region (4%) and the Region of the Americas (3%).
- The emergence and spread of drug resistance poses a major threat to the global efforts for TB control. In 2012, there were a total of 450 000 new cases of MDR-TB.
- In 2011, the burden of childhood TB was estimated by WHO for the first time, and, since then, it is reported annually. In 2012, there were 530 000 cases in children <14 years, leading to about 74 000 deaths among HIV-negative children. These figures may represent an underestimation of the true disease burden because of the difficulty in accurately diagnosing and reporting childhood TB.
- Although TB incidence and prevalence decrease worldwide, progress is slower in some parts of the world due to poor TB control, development of drug resistance, and HIV infection in the population.
- In the EU/EEA, 68 423 TB cases were reported in 2012, which represent a decrease by 6%, compared to 2011. The notification rate was 13.5 per 100 000 population, ranging from 3.4 to 85.2/100 000. During the same year, 2845 TB cases were reported among children, representing 4.2% of all notified TB cases (range 0–7.8%). Notification rate among children under the age of 15 years was 3.6 per 100 000, with a slightly decreasing trend over the last years.
- During 2012, the rate of MDR-TB among newly diagnosed pulmonary TB cases in the EU/EEA was 2.6% (range 0–20.5%), and that among previously treated cases 18.8% (range 0–50%). The proportion of XDR-TB cases among MDR-TB was 13.7%, ranging from 0% to 50%.

- A disproportionately high rate of TB has been noted in recent years in large capital cities of several low-incidence European countries. These high rates are due to an increase of TB among vulnerable groups such as refugees, migrants, prisoners, drug users, or homeless people.
- According to a recent report from ECDC, among the 39 695 paediatric cases reported between 2000 and 2009 in the EU/EEA, 53.4% were pulmonary TB and 27.8% extrapulmonary disease, of which 64.4% concerned intrathoracic or pleural TB. In about 18.4% of cases, the site of disease was unknown. Remarkably, only 42% of the paediatric TB cases were tested by culture, and, of them, 40% were positive.

Transmission and incubation period

- Transmission of *M. tuberculosis* is usually from person to person, through inhalation of aerosolized drops produced by someone with pulmonary TB who is coughing or sneezing.
- The most important factor for contagiousness is the presence of bacilli in the sputum of individuals with pulmonary TB—smear-positive individuals. Most children are usually not infectious, unless they have extensive or cavitating disease. Most non-pulmonary forms of TB are usually non-infectious.
- Following exposure, initial infection in the lung is characterized by the 1° complex (Ghon focus with regional adenitis). In most individuals, the 1° complex resolves spontaneously, with residual scarring or calcification.
- In some individuals, especially infants and children, progressive 1° disease may occur, causing mediastinal lymphadenopathy, invasion and compression of surrounding structures (such as bronchi, pleural and pericardial spaces), or haematogenous extrathoracic spread (CNS disease, bone and joint disease).
- Post-1° or reactivation disease may occur following resolution of the initial 1° complex, usually in adolescent and adults.
- The incubation period from infection to development of a delayed-type hypersensitivity reaction (skin test conversion) is 2–12 weeks. Clinical manifestations of disease after infection usually occur in the first 6 months, although disease can occur many years after infection (post-1° or reactivation disease).
- Due to the paucibacillary nature of most pulmonary childhood TB disease, children with TB who are <10 years are usually (but not always) not infectious.

Clinical features and sequelae

- Children with latent TB infection (LTBI) caused by *M. tuberculosis* are asymptomatic and have a normal physical examination and chest radiography.
- TB disease is characterized by the development of clinical symptoms, signs, and/or radiographic changes.

- A clear decision has to be made whether a child has TB *infection* or *disease*.
- The commonest clinical features include fever, growth delay, weight loss or poor weight gain, chronic cough >3 weeks, and night sweats.
- Clinical examination is often normal, but cachexia, focal chest signs, lymphadenopathy, pleural effusion, and hepatosplenomegaly may occur.
- Radiographic findings include lymphadenopathy (hilar, subcarinal, paratracheal, or mediastinal), atelectasis or infiltrate, pleural effusion, cavitary lesions, or miliary disease. Marked hilar adenopathy with less parenchymal disease may be seen.
- Pleural effusions are mostly seen in older children >6 years old. Pleural tap shows high protein, low sugar, white cells, and usually no organisms, as it represents reactive disease. Pericarditis and an effusion can lead on to a constrictive pericarditis.
- Lymph node disease is common in children, usually supraclavicular or cervical nodes, with slow enlargement of a firm fixed node. Low-grade symptoms of chronic inflammation are common. Neck node disease is the 2° spread from a pulmonary focus, seen on CXR in around a quarter of children.
- TB meningitis is 2° to lymphohaematogenous spread. It occurs in young children from 6 months up to school age. Presentation may be slow or more fulminant. Clinical presentation can be staged into:
  - Stage I: with slow, non-specific headache, drowsiness, and no focal signs
  - Stage II: more rapid disease with meningism, neck stiffness, and focal neurological and cranial nerve signs
  - Stage III: with coma, hemiplegia, and signs of raised ICP.
- Outcome is related to the stage. CSF sugar is low, protein high, with increased lymphocyte count, and TB stains only positive in a minority of cases. CT signs include basal meningeal thickening, hydrocephalus, or, in children with focal disease, a tuberculoma may be seen mimicking malignancy.
- Miliary disease is seen in infants and young children with high fever, cachexia, respiratory distress, widespread micronodular changes on CXR, and hepatosplenomegaly.
- Abdominal TB presents most frequently with weight loss, GI symptoms, lymphadenopathy, and ascites.
- Bone disease includes dactylitis, and focal knee, hip, elbow, or ankle chronic OM. Vertebral disease leads to bone destruction and collapse, with spinal malformation. Local spread is common into soft tissue, causing paraspinal (Pott's disease) or psoas abscess.
- Renal disease is very rare in children due to the long incubation period but may occur in adolescents.
- Severe forms of TB, such as miliary disease or meningitis, are associated with higher mortality and morbidity, often with long-term neurological sequelae.
- Congenital TB is relatively rare and occurs following transmission of TB *in utero* across the placenta.
- Clinical findings in patients with drug-resistant TB disease are indistinguishable from those with drug-susceptible disease.

Diagnosis

- Isolation of *M. tuberculosis* by culture from specimens of gastric aspirates, sputum, bronchial washings, pleural fluid, CSF fluid, urine, or other body fluids or biopsy specimens establishes the diagnosis.
- Microscopic examination of samples using ZN or fluorochrome stains may also be used to identify acid-fast bacilli, although yields are lower than with culture. The use of fluorochrome stains, such as the auramine–rhodamine stain, is now recommended by WHO to increase the sensitivity of microscopy by about 10%. The use of a light-emitting diode (LED) light source for the fluorescence microscope is recommended, because it is cheaper and reliable, and can be battery-operated. Sputum samples are usually obtained from older children and adolescents who are able to produce a sputum sample or by induction with nebulized hypertonic saline.
- In younger children and infants who cannot produce sputum, three consecutive early-morning gastric aspirates are collected. This involves leaving a nasogastric tube in overnight, then aspirating 10–20mL of saline in the morning before feeds.
- The diagnostic yield from three early-morning aspirates remains <50% on culture.
- Recent studies have shown that induced sputum specimens have a higher yield, compared to gastric aspirates, and do not require hospitalization. NPA is also an attractive diagnostic procedure and is minimally invasive. It has been shown to have equal or lower yield, compared to induced sputum or gastric aspirate samples.
- Radiological studies will depend on the site of disease, most commonly a CXR or chest CT scan for pulmonary disease. CT imaging may also be useful for diagnosing CNS disease (TB meningitis or tuberculoma).
- PCR on sputum and other samples appears to have lower sensitivity in children, primarily because of the type of disease seen in children (1° disease, as opposed to post-1°/reactivation disease seen in adults—paucibacillary). The Xpert MTB/RIF is a new molecular rapid test, based on real-time PCR, to detect the presence of *M. tuberculosis* and, at the same time, the presence of resistance to rifampicin (suggesting an MDR strain). It is fully automated and can be performed within <2 hours. Studies conducted in children with pulmonary TB have shown that the test detects almost all smear-positive, and about 53–70% of smear-negative and culture-positive, cases after examination of two samples in most studies. Overall, Xpert detects 2–3 times more cases than those detected by smear microscopy, and the result is available within a very short time. The specificity of the test is very high.
- TST: intradermal injection of two tuberculin units (0.1mL) of purified protein derivative (PPD), followed by measurement of induration (not erythema) 48–72 hours later.
- TST suffers from false positives (previous BCG vaccination, NTM infection) and false negatives (severe disease, malnutrition, immunosuppression).
- IGRAs rely on the measurement of IFN-γ production by lymphocytes following stimulation with antigens specific to *M. tuberculosis* (ESAT-6,

CFP-10). Two IGRAs are commercially available—*Quantiferon* TB-Gold In-Tube assay and T-Spot-TB—and have been introduced in several countries on the basis of limited evidence to either replace TST or performed to exclude false positive TST due to BCG or NTM.

- Similar to the TST, IGRAs are immune-based methods which can only detect the persistence of mycobacteria-specific T-cell responses. Therefore, these tests cannot differentiate between active disease and LTBI. In addition, a negative IGRA or TST result cannot rule out TB infection or disease.
- In a recent meta-analysis of studies conducted in children, it was shown that the sensitivity of TST and IGRAs for the diagnosis of active TB was comparable. The specificity of TST was lower, but with overlapping CIs. The sensitivity of both tests was found lower in low-income countries. In the same study, all three tests correlated equally well with the degree of exposure to TB. The sensitivity of both TST and IGRAs was lower in young and HIV-infected children, although there was not a sufficient number in the group of young children. Almost all studies agree that IGRAs give indeterminate results, more often in young or immunocompromised hosts due to decreased IFN-γ production upon stimulation with the mitogen (PHA) in the control tube.
- The use of IGRAs is currently not recommended by WHO in low- and middle-income countries.
- In high-income countries, IGRAs can be used in severe disease and in immunocompromised children, in combination with the TST, to increase the diagnostic sensitivity. In older BCG-immunized, immunocompetent children with suspected TB, IGRAs can be used to increase the specificity of diagnosis.
- Further long-term follow-up studies are being conducted to determine the predictive role of these assays in the diagnosis of LTBI and TB disease in children.

Management and treatment

- Treatment of LTBI: preferred regimen—3 months of isoniazid and rifampicin (or 6–9 months of isoniazid).
- Treatment of pulmonary disease (including hilar lymphadenopathy) or mild extrapulmonary disease: 2 months of isoniazid plus rifampicin plus pyrazinamide for 2 months, followed by isoniazid plus rifampicin for 4 months (Table 121.1). Ethambutol should be added as a fourth drug during the first 2 months if resistance is suspected. A four-drug initial regimen is also recommended for HIV-positive children.
- Treatment of smear-positive or extensive pulmonary disease, as well as severe extrapulmonary non-CNS disease: 2 months of isoniazid plus rifampicin plus pyrazinamide plus ethambutol, followed by isoniazid plus rifampicin for 4 months.
- Some experts recommend longer duration of therapy (12 months) for osteoarticular disease, especially spinal TB.
- Treatment of CNS TB (including meningitis and tuberculoma): isoniazid plus rifampicin plus pyrazinamide plus ethambutol for 2 months,

Table 121.1 Management and treatment

Hilar adenopathy	2 months of RHZ([a]E), then 4 months of RH
Pulmonary TB	2 months of RHZ([a]E), then 4 months of RH
Extrapulmonary TB	2 months of RHZ([a]E), then 4 months of RH
TB meningitis/tuberculoma	2 months of RHZ([a]E), then 10 months of RH

[a] Where resistance suspected or at increased risk.

E, ethambutol; H, isoniazid; R, rifampicin; Z, pyrazinamide.

followed by isoniazid plus rifampicin for 10 months. Instead of ethambutol, some experts recommend the use of ethionamide (because of better CNS penetration) or an aminoglycoside.

- Corticosteroids are indicated for children with tuberculous meningitis, because they decrease the rates of mortality and long-term neurological impairment.
- Corticosteroids may be considered for children with bronchial obstruction due to enlarged intrathoracic lymph nodes, pericardial and pleural effusions, severe military disease, and endobronchial disease. A dose of prednisolone at 1–2mg/kg/day (maximum 60mg/day) for 4–6 weeks, followed by weaning doses, is usually recommended.
- Most cases of pulmonary TB in children caused by isoniazid-resistant *M. tuberculosis* can be treated with rifampicin, pyrazinamide, and ethambutol.
- Treatment of MDR-TB should include at least four effective agents for at least 12–18 months.
- The treatment of children with drug-resistant TB should only be carried out by, or in conjunction with, specialists with appropriate experience in the management of such cases.

Prevention

- Prompt treatment of infectious cases of TB and contact tracing of household and close contacts of such cases are important preventive measures.
- BCG vaccine is a live attenuated vaccine prepared from a strain of *M. bovis*. It is used in >100 countries globally, as part of routine vaccination programmes of infants, to prevent disseminated and severe forms of TB.
- Two meta-analyses of published clinical trials and case control studies suggest a protective efficacy of 80% against miliary and meningeal TB, and 50% for pulmonary TB.
- BCG vaccination continues to be used in many countries in the world, primarily given to neonates and infants, to prevent severe forms of TB, particularly miliary TB and TB meningitis.

Future research

- New diagnostic methods (including immune-based, molecular, and genome-wide RNA expression assays) for TB disease and LTBI in children.
- Development of vaccines that are more protective than BCG.
- Development of new drugs, particularly for drug-resistant TB, and shorter treatment regimens.

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Chapter 122

Typhoid and paratyphoid—enteric fever

See also Chapters 5, 12, 15, 21, 22, 33, 35, 42, 45.

Name and nature of organism

- *S. enterica* Typhi and *S. enterica* serovar Paratyphi A (rarely Paratyphi B and C) are Gram-negative bacilli causing typhoid and paratyphoid fevers, respectively, collectively known as the enteric fevers.
- Serotypes of *S. enterica* (about 2500) are based on three main surface antigens: O (somatic), H (flagellar), and Vi (capsular). Virulence genes determine invasion and pathogenicity.
- The organisms cause infection exclusively in humans. Human faecal or urinary carriers are the sources of infection. The organisms can persist in food and water contaminated by sewage.

Epidemiology

- Enteric fever is prevalent in low- or middle-income countries in areas where there is inadequate sanitation and poor hygiene.
- More than 25 million new cases are estimated to occur worldwide, with ~200 000 deaths.
- It is commonest in children and young adults (ages 2–35 years).
- The majority of UK infections occur in patients who have travelled to the tropics on holiday or visiting friends and relatives. Occasional cases result from chronic carriers where there is a breakdown in food hygiene. Increasing numbers of reports are being seen—in the UK, now about 500 confirmed cases/year in all ages.
- In comparison, non-typhoidal salmonellas (mainly *S.enterica* Enteritidis and *S.enterica* Typhimurium) affect 2500 children/year in the UK.
- Typhoid fever cases are estimated to outnumber paratyphoid cases worldwide by 10:1, although, in some areas of Asia, particularly China and the Indian subcontinent, paratyphoid has recently become as common as typhoid.
- Paratyphoid fever can be as severe as typhoid fever.

Transmission and incubation period

- The disease is spread by the faecal–oral route, usually by ingestion of food or water contaminated with faeces and/or urine from an infected person excreting the bacteria. Uncooked or undercooked foods are common routes of infection.

- Average incubation period of 1–3 weeks, but may be longer, depending on the size of the infecting inoculum. The risk of developing disease is associated with higher ingested dose, reduced gastric acid, young infants, and the immunocompromised. The evidence that typhoid is more severe in HIV infection is scanty (as opposed to non-typhoidal salmonellosis).
- Chronic carriers continue to excrete for years. Food handlers who are asymptomatic chronic carriers (e.g. the cook Typhoid Mary) can be important sources of transmission. Consider the source of a child's exposure to typhoid, including the occupation of their parents and carers.

Clinical features and complications

Enteric fever is a systemic bacterial disease with a wide range of clinical presentations. Classic symptoms include, in the first 2 weeks, a gradually more severe illness:

- Continued high-spiking fever which may persist for several weeks
- Malaise, headache, dry cough
- Diarrhoea ± blood and/or mucus—later constipation.

Physical findings can include:

- Splenomegaly, hepatomegaly
- Relative bradycardia—not usually seen in children
- Rose-coloured spots (2–4mm pink blanching papules) on the trunk.

The most important acute complications usually occur after 2–3 weeks of illness and are:

- GI haemorrhage
- Intestinal perforation
- Encephalopathy and shock
- Myocarditis
- Septicaemia—especially in children aged <2 years or the immunocompromised.

Many other focal complications have been described but are relatively rare, including:

- Cholecystitis, hepatitis
- Osteomyelitis, septic arthritis (especially in children with sickle-cell disease)
- Pneumonia
- Meningitis (rare and usually in infants), brain abscesses
- Psychotic states
- Glomerulonephritis.

Some patients initially present with the disease complication (e.g. an acute abdomen due to intestinal perforation, or encephalopathy/confusion).

The disease may also be complicated by relapse (recurrence of the illness 1–2 weeks after recovery from the first episode) and by chronic faecal or urinary carriage (defined by persistent excretion of the organism in faeces or urine for >1 year).

Diagnosis

Confirmation of the diagnosis requires isolation of the organisms from a normally sterile site. This is much more difficult if the child has already received oral antibiotics, which is often the case.

The diagnosis may have to be on clinical probability alone in a child with a prolonged swinging fever, who has recently returned from a typhoid-endemic area and does not have either malaria or any other common focal infection (e.g. UTI, otitis media, etc.).

Blood culture

Blood culture is the usual method of isolation.

- Positive in 40–80% of cases, often early in the disease.
- Sensitivity affected by prior antibiotic use, stage of illness, level of bacteraemia, and volume of blood taken.

Bone marrow culture

Bone marrow culture is more sensitive than blood culture and remains positive later in the disease process.

- Positive in 80–90% of cases.
- May remain positive for several days after antibiotics started.
- Of less use practically in children.

Stool and urine cultures

- Worth doing, although may reflect chronic bacterial carriage, not acute infection.
- Important in follow-up to exclude faecal and urinary carriage.

Serology

- The Widal test detects agglutinating antibodies to *S. enterica* Typhi O and H antigens. Used extensively in resource-limited countries but is an unreliable diagnostic test.
- RDTs detecting IgM antibodies are available in endemic areas. Examples include Typhidot-M and TUBEX. Inadequate sensitivity and specificity remain a problem.

Nucleic acid amplification tests

- Nested and real-time PCRs have been used in research studies.

Other laboratory findings in typhoid

- A mild normochromic anaemia, mild thrombocytopenia, and an increased ESR are common.
- Most patients have a total WBC within the normal range or mild leucocytosis. Very high leucocytosis may suggest either perforation or another diagnosis (e.g. appendicitis, ulcerative colitis).
- The liver enzymes (ALT and AST) are usually elevated, 2–3 times above normal.
- Laboratory evidence of mild DIC is common, but rarely of clinical significance.

Management and treatment

- Prompt treatment with appropriate antibiotics, as well as full supportive care, reduces the mortality to <1%. Widespread use of antibiotics has led to an increase in MDR, especially in South East Asia and the Indian subcontinent.
- Fluoroquinolones, such as ciprofloxacin, have been the first-line treatment for many years. However, isolates with decreased or intermediate susceptibility to ciprofloxacin are now very common in Asia. The laboratory may report these as ciprofloxacin-susceptible, but patients infected with these isolates with decreased susceptibility frequently do not respond to ciprofloxacin. Resistance to nalidixic acid is a surrogate laboratory marker of decreased susceptibility. Alternatively, the laboratory can measure the ciprofloxacin MIC.
- Resistance may also be an emerging problem with azithromycin. The laboratory should check for this by performing an azithromycin MIC.
- Resistance to ceftriaxone currently remains rare.
- In an ill child with suspected enteric fever, start with IV ceftriaxone, while awaiting culture and sensitivity results. Treatment courses can be completed with high-dose oral azithromycin (or ciprofloxacin if susceptible), once resolution of fever has occurred.
- Delay in the resolution of fever for 2–3 days after starting IV antibiotics is common in typhoid fever, even if the infection is fully susceptible. There is often a period of concern where the antibiotics have been started and the fever persists for a few days before slowly settling. It is reasonable to wait this out if the child remains clinically stable.
- Prolonged treatment courses are required to prevent relapse. The usual treatment duration is 10–14 days, but focal disease, such as OM, requires 4–6 weeks.

Severe typhoid

Typhoid gastrointestinal perforation

- Nasogastric suction, administration of fluids to correct hypotension, and prompt surgery.
- Simple closure of perforations is adequate, but experienced surgeons use procedures to bypass the worst affected sections of the ileum in order to reduce post-operative morbidity. Closure of perforations should be accompanied by vigorous peritoneal toilet.
- Metronidazole or clindamycin should be added to the therapy of ceftriaxone or fluoroquinolone-treated patients.
- Altered conscious level and shock—dexamethasone may be used.
- In one study in Indonesia, dexamethasone, 3mg/kg infused IV over half an hour, followed by eight doses of 1mg/kg 6-hourly, resulted in a 10% case fatality, compared to 55.6% in controls.

Prevention

- Improvements to public health and sanitation in endemic areas are crucial.
- Eradication of carriage in long-term carriers may be necessary, especially if they are food handlers. Eradication requires prolonged high-dose antibiotics to which the bacteria are susceptible.
- Notification to the public health authorities is mandatory.
- Vaccination is important in endemic areas and for travellers.

Vi polysaccharide vaccine

- IM injection.
- Provides cover for 3 years.
- Not considered suitable or effective for children <2 years.

Live attenuated vaccine (Ty21)

- Oral vaccine.
- Three doses of a single capsule every alternate day.
- Provides 12 months' protection.
- Not considered suitable or effective for children <6 years.

Future research

- Development and evaluation of cheap and simple RDTs suitable for use in resource-limited settings.
- Optimizing antimicrobial regimens for treating typhoid in the face of changing patterns of resistance.
- Development of new Typhi vaccines and a Paratyphi A vaccine.

What's new?

- Studies of typhoid and paratyphoid in a human challenge model.
- The emergence of paratyphoid fever as a major problem in China and the Indian subcontinent.
- Re-recognition of typhoid as a significant problem in sub-Saharan Africa with several recent large outbreaks.

What's next?

- New typhoid vaccines (Vi capsular vaccine; single-dose oral vaccine) and paratyphoid vaccines.
- New point-of-care diagnostics.
- Continued microbiological surveillance of antimicrobial resistance in *Salmonella* infections.

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Chapter 123

Typhus

See also Chapters 15, 33, 34, 41, 42.

Introduction

- The genus *Rickettsia* is included in the bacterial tribe *Rickettsiae*, family *Rickettsiaceae*, and order *Rickettsiales*.
- 'Typhus', which is derived from the Greek word '*typos*', represents 'fever with stupor'.
- Typhus is a group of infectious bacterial diseases of the *Rickettsia* genus. It comprises two main Gram-negative obligate intracellular bacteria: *Rickettsia typhi* (causes murine or endemic typhus) and *Rickettsia prowazekii* (causes epidemic typhus).

Endemic or murine typhus (flea-borne typhus, *Rickettsia typhi*)

Name and nature of organism

- A rickettsial disease caused by the organism *R. typhi*, and less commonly by *Rickettsia felis*.

Epidemiology

- Flea-borne rickettsioses are widely distributed, especially throughout the tropics and subtropics and in port cities and coastal regions. In Europe, it is prevalent in Portugal, Spain (included the Canary Islands), and Greece.
- Most cases occur in summer and autumn. It is also reported among travellers returning from Asia, Africa, and Southern Europe, and it has also been reported from Hawaii, California, and Texas.

Transmission and incubation period

- Reservoirs: wild rats, mice, and other rodents. It is maintained in nature by the rodent–flea cycle.
- *R. typhi* infects gut epithelial cells of the flea and is excreted in its faeces, as it feeds on the reservoir (the rodent). The rodent is infected and carries *R. typhi* without ill effect.
- Infected rat fleas (*Xenopsylla cheopis*), and probably cat fleas (*Ctenocephalides felis*), transmit the agents to humans via their faeces. Distribution is sporadic, but worldwide incubation period ranges from 6 to 18 days (mean 10 days).

Clinical features and sequelae

- Endemic typhus is milder than epidemic typhus, causing shaking chills, headache, fever, and rash.
- The patient's temperature increases steadily over the first few days and may become intermittent when the rash appears, with the morning temperature tending to be normal.
- Children may have a fever as high as 41°C (106°F). Fever usually lasts ~12 days, then gradually returns to normal.
- The rash and other manifestations are similar to those of epidemic typhus, but less severe. The early rash is sparse and discrete.
- A mild to moderate elevation of serum AST level is present in ~90% of patients.
- Mortality is low, although higher in elderly patients.

Diagnosis

- Consider this diagnosis in patients with fever and/or rash and a history of cat contact or flea bite.
- The gold standard of diagnosis of murine typhus is IFA; a 4-fold increase in titre between the acute and convalescent phase sera is considered to be diagnostic.
- Murine typhus can be identified by immunohistology of a skin biopsy, PCR with the use of peripheral blood, buffy coat, and/or plasma specimens, or serum ELISA.

Management and treatment

- 1° treatment is doxycycline, while the patient improves and becomes afebrile, continued for at least 7 days, or 2–4 days after defervescence, to preclude relapses. The risk of dental staining by doxycycline is zero when a short course of therapy is given (5–10 days).
- Patients can also be treated with IV or IM doxycycline. In pregnant women and children <8 years of age, whose disease course is mild, macrolides (clarithromycin or azithromycin) may be used.
- Chloramphenicol is the second-line treatment.

Prevention

- Incidence can be decreased by reducing rat numbers, and thus rat fleas.
- No effective vaccine exists.

Epidemic typhus (louse-borne typhus, *Rickettsia prowazekii*)

Name and nature of organism

- A rickettsial disease caused by the organism *R. prowazekii*, a small Gram-negative intracellular bacterium.

Epidemiology

- In Europe, this rickettsiosis is a long-known infectious disease and remains important in some communities.

- The Plague of Athens is the oldest recorded epidemic which occurred around 429 BC. Outbreaks have often been associated with periods of war, poverty, and natural disasters, especially during the colder months when louse-infested clothing is not laundered.
- It reappeared in Europe during the Napoleonic Wars and, more recently, during the world wars. Following improvements in hygiene, outbreaks have largely been controlled.

Transmission and incubation period

- Transmitted by body lice (*Pediculus humanus corporis*) when louse faeces are scratched or rubbed into bites or other wounds.
- Humans may occasionally contract epidemic typhus after contact with southern flying squirrels in the US (flying squirrel disease).
- *R. prowazekii* is a potential category B bioterrorism agent, because it is stable in dried louse faeces and can be transmitted by aerosols.
- The natural reservoirs are humans and wild rodents.
- Incubation period ranges from 7 to 14 days.

Clinical features and sequelae

- Patients usually have 1–3 days of malaise before an abrupt onset of severe headache and fever. Prolonged high fever up to 40°C persists, with slight morning remission, for about 2 weeks.
- Intractable headache accompanied by CNS manifestations (e.g. delirium, coma, and seizures) in 80% of cases.
- Maculopapular rash, which appears on the fourth to sixth days, rapidly covers the body, usually involving the axillae and upper trunk, but not the palms, soles, or face. Eschars are absent. In severe cases, the rash becomes petechial or haemorrhagic.
- Splenomegaly is sometimes present. Hypotension occurs in most seriously ill patients.
- *Brill–Zinsser disease* is a mild form of relapsing epidemic typhus that occurs in convalescent patients with subclinical infection.
- Fatal outcome is observed in up to 40% of untreated cases.
- Fatalities are rare in children <10 years, but mortality increases with age and may reach 60% in untreated patients >50 years old. However, it is ~4% if effective antibiotics are given.
- Poor prognostic signs are vascular collapse, renal insufficiency, encephalitic signs, ecchymosis with gangrene, and pneumonia.

Diagnosis

- Diagnosis of epidemic typhus is based on the detection of specific antibodies in sera. Plate microagglutination is a sensitive test.
- Indirect immunofluorescence test is the current reference method. An IgG titre of 1:128 or an IgM titre of 1:32 confirms the diagnosis.
- Louse infestation is usually obvious and strongly suggests typhus if the history (e.g. living in, or visiting, an endemic area) suggests possible exposure.
- Culture (shell vial assay) is now used to isolate from clinical samples (blood or skin biopsy), using L929 fibroblast cell monolayers, and identification of rickettsial isolates may be done by microscopic examination after Gimenez staining or by immunofluorescence. PCR is an RDT but is expensive and not yet widely available.

Management and treatment

- 1° treatment is doxycycline, while the patient improves and becomes afebrile, continued for at least 7 days, or 2–4 days after defervescence, to preclude relapses. Patients can also be treated with IV or IM doxycycline. In pregnant women and children <8 years of age, whose disease course is mild, macrolides (clarithromycin or azithromycin) may be administered.
- Chloramphenicol for 7 days is the second-line treatment.

Prevention

- Louse control is highly effective for prevention. Delousing methods consist of removing and destroying all lice by bathing the patient and changing and boiling infested clothes.
- Lice may be eliminated by an insecticide (10% DDT, 1% malathion, or 1% permethrin)—also an effective method.

Future research

- Mouse models may be useful for studying and assessing new therapeutic molecules and vaccine candidates.

Scrub typhus (tsutsugamushi disease, *Orientia tsutsugamushi*—formerly called *Rickettsia tsutsugamushi*)

Name and nature of organism

- An acute febrile, potential fatal zoonotic disease, caused by the intracellular Gram-negative bacterium *Orientia tsutsugamushi* (formerly called *Rickettsia tsutsugamushi*).
- *O. tsutsugamushi* is a very tiny (0.5 × 1.2–3 micrometres (μm) in size) organism without peptidoglycan and LPS in its cell wall.
- More than 30 antigenically distinct serotypes are present in the endemic area.

Epidemiology

- One of the important travel-related diseases.
- First described in China in AD 313. The '*tsutsugamushi*' is derived from two Japanese words '*tsutsuga*' (something tiny and dangerous) and '*mushi*' (a live organism, bug).
- ~1 billion people are at risk of this disease, and 1 million cases are reported annually (between 25% and 50% of cases are children in endemic areas).
- Distributed widely in the Western Pacific area and Asia (known as the 'Tsutsugamushi triangle'), covering from Northern Japan and South Korea, as far south as Northern Australia, and to the west as far as Afghanistan and Pakistan.
- Significantly commoner in men than women, and similarly boys are more often infected than girls among school-aged children.
- Children (incidental hosts) are infected mainly in summer.

Transmission and incubation period

- *O. tsutsugamushi* is transmitted by the bite of trombiculid mite larvae (chiggers) to vertebrate animals.
- Rodents are the main recipients of transmission by infected chigger bites; however, humans (local residents, farmers, outdoor workers, soldiers, and travellers) are opportunistic hosts.
- About 20 species of the trombiculid mite (*Leptotrombidium* spp.) are the 1° vectors and reservoirs of *O. tsutsugamushi*. It is tiny (0.2–0.4mm).
- The incubation period is about 5–21 days (with a mean of around 10–12 days) after the initial chigger bite.

Clinical features and sequelae

- The commonest symptom is abrupt fever of unknown origin.
- The other characteristic feature is one or more typical eschars, which can be accompanied by regional or generalized lymphadenopathy that may be tender, seen in 60–70% of patients.
- An eschar is a non-painful ulcer covered by a centrally depressed dark scab and surrounded by a red areola (Figure 123.1). The dark scab may be absent when scratched off (Figure 123.2 a and b). Eschars are more commonly found in scrub typhus than murine typhus.
- Major clinical manifestations of paediatric scrub typhus are fever and chills, cough, anorexia, eschar, and lymphadenopathy.
- Other symptoms and signs include headache, maculopapular rash, GI symptoms (abdominal pain, vomiting, diarrhoea, and anorexia), neck stiffness, hepatosplenomegaly, pitting oedema, oliguria, jaundice, and seizures. Hearing loss and epididymo-orchitis are very rarely seen.
- Children with mild cough may have evidence of interstitial pneumonitis on CXR.
- Typical eschar location varies between adults and children—mainly within 30cm below the umbilicus on the anterior trunk and on the lower extremities in adults, and mainly in the axillary and genital regions (moist and warm areas of the body) in children.
- Maculopapular skin rash appears after the onset of fever, lasts for 5–8 days, and is transient, pale, and easy to miss.
- Seizure with mental change or delirium is reported, particularly in children with CNS involvement, including meningomyelitis and encephalitis (reported in about 13% patients).
- Serious complications of scrub typhus may involve the liver, lungs, heart, brain, or kidneys. The commonest complications are hepatic dysfunction (over 90%) and pneumonitis (over 50%). Typical pathology is a focal or diffuse vasculitis, with destruction of endothelial cells and perivascular infiltration of leucocytes.
- Multi-organ dysfunction, such as fulminant hepatic failure, pericardial effusion, myocarditis, severe pneumonitis with progressive ARDS, thrombocytopenia, DIC, acute kidney injury, and cardiogenic and septic shock are the most serious complications of scrub typhus.
- Most children respond well to adequate antibiotic treatment and recover completely. However, relapses may occur and are associated with a short duration of therapy.

- Mortality rates vary widely, ranging from 1% to 60% in adults and <5% in Taiwanese children. Factors determining the outcome include appropriate timely antibiotic treatment, prior status of the patient, and the strain of *O. tsutsugamushi*.

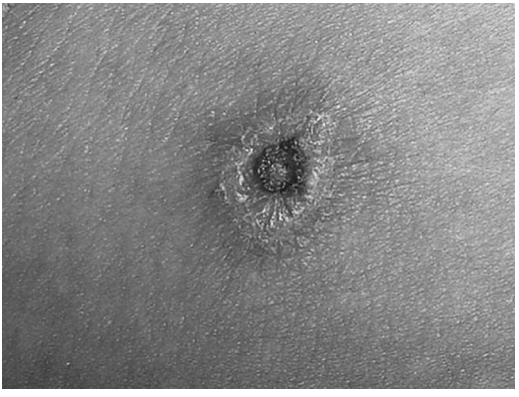

Fig. 123.1 An eschar is a non-painful ulcer covered by a centrally depressed dark scab and surrounded by a red areola. Please see colour plate section.

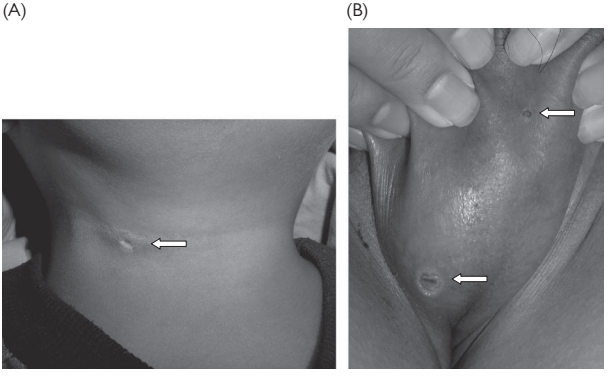

Fig. 123.2 The dark crust scratched off from eschars on neck (A) and scrotum (B). Please see colour plate section.

Diagnosis

- Clinical and laboratory features are non-specific; the diagnosis of scrub typhus is difficult to make. Physicians should maintain a high index of suspicion, especially in children with a fever of obscure cause, with hepatic dysfunction or pneumonitis in endemic areas.
- The key to diagnosing scrub typhus is finding a typical eschar. Although not present in all cases, it can be found in about 50–67% of children with scrub typhus after careful examination.
- Patients respond promptly to antibiotic treatment, with rapid improvement, becoming afebrile within an average of 1.5 days (range 1–5 days). Serological tests, based on a 4-fold antibody rise for *O. tsutsugamushi* measured in acute and convalescent paired sera, are the most reliable tool for diagnosis. Tests include IFAs, ELISA, immunochromatographic test, and immunoperoxidase assays. PCR, especially real-time quantitative PCR, test for *O. tsutsugamushi* in blood, eschar, and lymph node biopsies, and loop amplification (*groEL*) can be helpful.
- Non-specific laboratory values: raised CRP (>96% of children), elevation of liver enzyme levels (90–100% children), with or without hypoalbuminaemia, renal function impairment (<30%), and elevation of PCT may also help in diagnosis.
- CXR abnormalities seen in scrub typhus include diffuse, bilateral, reticulonodular opacities, cardiomegaly, and massive consolidation (rare).
- Abdominal ultrasound may show pictures of acute cholecystitis (double wall of gall bladder, hydrops of gall bladder), hyperechogenicity of the liver parenchyma, and hepatosplenomegaly.

Management and treatment

- β-lactam antibiotics are ineffective treatment for scrub typhus, since *O. tsutsugamushi* does not have peptidoglycan in its cell wall and is an intracellular obligate infection. A few studies report that aminoglycosides, such as gentamicin, are ineffective in human and mice scrub typhus infection.
- Empirical antimicrobial therapy should be started early and should not await confirmatory testing.
- Doxycycline and chloramphenicol are the drugs of choice for childhood scrub typhus. However, doxycycline-resistant *O. tsutsugamushi* has been reported in northern Thailand. Rifampin may be effective in drug-resistant areas.
- One week of oral doxycycline or newer macrolide antibiotics (roxithromycin, azithromycin) is recommended for mild and uncomplicated paediatric scrub typhus.
- Most severely ill children respond well to doxycycline for 7–10 days or until afebrile for ≥3 days, with supportive therapy during hospitalization.

Prevention

- Application of insect repellents (dibutyl phthalate, benzyl benzoate, and diethyltoluamide) to the skin and clothes to prevent chigger bites.
- Avoid sitting in overgrown grass and brush in endemic areas. Wear long pants, sleeves, socks, or other suitable covering garments.
- Rodent control and public health education (via media to local residents and travellers).
- No effective vaccine is available. High antigenic variation makes this difficult.

Boutonneuse fever—Mediterranean spotted fever

This tick-borne disease is caused by *Rickettsia conorrii* and is seen across the Mediterranean basin, including Portugal, and into Africa and Asia. The disease is transmitted by the dog tick. The illness causes a high fever around a week after the tick bite, with the classic spotted rash being seen a few days after the fever starts. Boutonneuse fever is generally a milder disease, though severe complications can occur. The management is similar to scrub typhus.

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Chapter 124

Yellow fever

See also Chapters 18, 41.

Name and nature of organism

- A systemic viral (haemorrhagic) arthropod-borne disease with sudden onset and a broad clinical spectrum.
- Yellow fever virus is a member of the family *Flaviviridae*, genus *Flavivirus*.
- The prototype member of the genus *Flavivirus*, yellow fever virus is a small, single-stranded, positive-sense RNA virus with a lipid envelope.
- At least seven genotypes have been distinguished in specific geographical regions; however, there is a single serotype.

Epidemiology

- Yellow fever probably originated in Africa 3000 years ago. It was transported to the Americas during the seventeenth century on slave ships and to Europe via the maritime trade route.
- Widespread epidemics occurred in North America and Europe up to the late nineteenth century.
- Yellow fever now is a risk only in the tropical regions of sub-Saharan Africa, South America, Trinidad in the Caribbean, and Panama.
- In recent years, there have been 50–2500 cases of yellow fever reported in endemic countries. However, the number of cases and deaths is likely to be grossly under-reported. It has been estimated that, for every symptomatic case, there are seven subclinical infections.
- The majority of cases and deaths occur in sub-Saharan Africa where there are 31 countries with a risk of yellow fever transmission. In Africa, in 2013, it was estimated that 130 000 cases with fever and jaundice occurred, with 78 000 deaths. In South and Central America, and the Caribbean, there are 12 countries at risk.
- The epidemiology of yellow fever is dynamic, and the virus may emerge in areas previously considered free of the disease.
- Between 1970 and 2013, there were nine fatal cases of yellow fever in unvaccinated travellers who returned to their country of origin.

Transmission and incubation period

- Yellow fever is a zoonotic infection. Non-human primates are the main reservoir. This means that it will not be possible to eradicate yellow fever.
- Yellow fever virus is transmitted by mosquito species most active during the daytime.

- In Africa, *Aedes* spp. mosquitoes transmit infection. In sylvatic (jungle) areas of South America, *Haemagogus* spp. transmit infection, with *Aedes aegypti* as the predominant species in urban outbreaks.
- Transmission occurs year-round. In Africa, the risk of transmission is highest during the rainy season in areas of habitation that border the jungle and forests (intermediate cycle). In South American forests, transmission in the monkey population increases intermittently, resulting in waves of disease activity. Humans living in, or visiting, these areas are at risk of infection (sylvatic cycle).
- Transmission occurs in urban environments (urban cycle) where breeding conditions are favourable for *A. aegypti* (water storage containers and collections of rainwater).
- The incubation period after an infective bite is 3–6 days.

Clinical features and sequelae

- Infection can be subclinical, a mild febrile infection, or a severe illness with jaundice, haemorrhage, multi-organ failure, and death.
- Onset of symptoms is abrupt.
- During the first 3–4 days (viraemic stage), symptoms include fever, headache, prostration, myalgia, photophobia, anorexia, irritability, epigastric tenderness, nausea, and hepatomegaly.
- Bradycardia relative to fever (Faget's sign) can be present. Fever can be as high as 40°C (105°F).
- There is leucopenia with relative neutropenia.
- After a brief period of remission (up to 24 hours), about 15% progress to more serious disease. Symptoms include return of fever, jaundice with elevation of liver enzymes, nausea, vomiting, and oliguria.
- Complications are haemorrhage (e.g. DIC, melaena, petechiae, epistaxis), myocardial damage and arrhythmias, profound hypotension and shock, encephalopathy, coma, and renal and liver failure.
- Five to 10 days after the onset of symptoms, the patient recovers, or death occurs as a result of multi-organ failure (case fatality rate 20–50%).

Diagnosis

- Clinical symptoms with appropriate exposure history (differential diagnoses include other VHFs, leptospirosis, louse-borne relapsing fever, viral hepatitis, Q fever, Rift Valley fever, typhoid, and malaria).
- Detection of virus or viral antigen in blood or body tissue:
  - Viral culture, RT-PCR
  - Post-mortem diagnosis by immunocytochemical staining for yellow fever antigen in the liver, heart, or kidney.
- Detection of yellow fever antibody in sera: IgM (presumptive diagnosis on a single sample, confirmed by rise in titres in acute and convalescent samples; can cross-react with other flaviviruses); plaque reduction neutralizing test (PRNT, more specific for yellow fever).
- Yellow fever is a notifiable infectious disease globally under International Health Regulations (2005).

Management and treatment

- There is no specific antiviral treatment.
- Intensive supportive care with management of complications is necessary for severe cases. In high-income countries, all cases or suspected cases of yellow fever should be managed in a specialist unit for infectious or tropical diseases, with appropriate infection control measures.

Prevention

- Prevention is by vaccination, mosquito bite avoidance, and vector control.
- Vector control (using insecticides and larvicides) in the urban environment can interrupt the mosquito breeding cycle and transmission of the virus.
- Vaccination is included as routine immunization in many endemic countries where there is a risk of yellow fever transmission.
- Vaccination should be given to:
  - Children aged ≥9 months and adults who plan to visit yellow fever risk areas
  - Laboratory workers handling infected material.
- Vaccination should be given at least 10 days before travel to allow protective immunity to develop. Protective levels of neutralizing antibody are seen in about 90% of vaccinees within 10 days of vaccination, and in up to 99% of vaccinees within 30 days.
- In most individuals, a single dose of yellow fever vaccine is sufficient to confer lifelong immunity against yellow fever disease.
- Risk groups that may benefit from booster doses of vaccine are those who were immunized <2 years of age, during pregnancy, and while immunosuppressed or HIV-infected.
- An interval of 28 days between yellow fever and MMR vaccines should be observed; co-administration of these two vaccines could lead to suboptimal antibody responses to yellow fever, mumps, or rubella.
- The administration of yellow fever vaccine is regulated under the WHO International Health Regulations (2005) that stipulate that 'State parties shall designate specific yellow fever vaccination centres within their territories in order to assure the quality and safety of the procedures and materials employed.'
- Vaccination is a requirement for entry into some countries under International Health Regulations (see National Travel Health Network and Centre, Country Information pages, available at: http://www.nathnac.org>). Vaccination must be recorded in an International Certificate of Vaccination or Prophylaxis (ICVP).
- The ICVP becomes valid 10 days after administration of yellow fever vaccine in first-time vaccines, and immediately if re-immunized. The current interval for revaccination under International Health Regulations is 10 years. Although a single dose of vaccine confers lifetime protection in most individuals, it may take a period of time before the WHO member states (countries) adopt this and extend the interval for yellow

fever vaccination validity. Latest WHO guidance should be consulted (available at: http://www.who.int/ith/en/>).

- In the UK, vaccination is with yellow fever 17D (204 strain) live-attenuated vaccine that contains no antibiotics or preservatives (alternative, but similar, vaccines are in production globally). It is supplied in a lyophilized preparation with a diluent and must be reconstituted immediately before use.
- 17D vaccine is manufactured in chick embryo cell culture; the vaccine contains very small amounts of egg protein.
- There are specific contraindications and precautions associated with yellow fever vaccine. A careful risk assessment should be made before administration, and specialist advice sought as appropriate.
- 17D vaccine has been used for >70 years and has a well-documented history of tolerability and safety. However, rare severe and fatal adverse reactions to the vaccine have been reported:
  - Anaphylaxis is rare (0.8–1.8 cases per 100 000 doses)
  - Yellow fever vaccine-associated neurologic disease (VAND) (0.4–0.8 cases per 100 000 doses):
    - —First-time recipients of vaccine only
    - —Onset 3–28 days after vaccination (median 14 days)
    - —Direct viral invasion of the CNS, or an autoimmune reaction to the virus, e.g. Guillain-Barré syndrome
    - —Fever, focal neurological dysfunction, convulsions, paresis
    - —Nearly all patients recover
  - Yellow fever vaccine-associated viscerotropic disease (VAVD) (~0.3–0.4 cases per 100 000 doses; rates have varied between those who have received the vaccine in endemic versus non-endemic settings, with rates in endemic settings usually lower):
    - —First-time recipients of vaccine only
    - —Onset 1–8 days post-vaccination (median 3 days)
    - —Fever, malaise, headache, *progressing to*
    - —Hepatitis, hypotension, respiratory failure, renal failure, coagulopathy
    - —Case fatality rate is ~60%.
- Risk for either VAND or VAVD increases for first-time vaccinees aged ≥60 years (1.4 and 1.8 cases per 100 000 doses, respectively).
- Risk of severe adverse neurological events is increased for infants aged <9 months, with the risk being inversely proportional to age. The vaccine should never be given to infants aged <6 months because of the risk of post-vaccination encephalitis. Infants aged 6–9 months should only be immunized if the risk of yellow fever during travel is unavoidable.
- Transmission of the vaccine virus through breastfeeding has been reported in three infants aged <1 month. Vaccination of pregnant and breastfeeding women should be avoided, where possible. However, where the risk of disease exposure is high, women should be offered vaccination.
- Mosquito avoidance measures include clothing that covers exposed skin and application of *N,N*-diethylmetatoluamide (DEET) or picaridin-containing insect repellents.

What's new and what's next?

- Dynamic epidemiology of yellow fever risk requiring ongoing surveillance.
- Investigation of mechanisms of severe adverse events following yellow fever vaccination.
- Evaluation of the safety, immunogenicity, and need for booster doses of live attenuated 17D yellow fever vaccine in specific risk groups.
- Evaluation of the safety, tolerability, and immunogenicity of inactivated yellow fever vaccine, as well as other vaccine types.
- Implementation of the recommendation of lifelong immunity following yellow fever vaccine by WHO member states under International Health Regulations.

Further reading

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Chapter 125

Yersiniosis

See also Chapters 12, 15, 22, 69.

Name and nature of organism

- *Y. enterocolitica* and *Yersinia pseudotuberculosis* are short pleomorphic Gram-negative rods or coccobacilli, which often exhibit bipolar staining.
- Grow on simple laboratory media, including those containing bile salts (e.g. MacConkey agar).

Epidemiology

- *Y. enterocolitica* and *Y. pseudotuberculosis* are zoonotic infections.
- Main reservoir is the GI tract of a wide range of animals, including pigs, cattle, cats, dogs, rodents, rabbits, and birds. Animals tend to be chronic carriers and excrete large numbers of organisms, which may contaminate water or dairy products.
- *Y. enterocolitica* causes the majority of cases of yersiniosis. Six different biotypes (1A, 2–5) and >57 serotypes have been described, of which 11 have been associated with human infection. In Europe, most infections are due to biotype 4, serotype O-3, whereas, in the US (where yersiniosis is less common), serotype O-8 predominates.
- Pigs are considered the main reservoir of human pathogenic strains, with the organisms being carried in tonsils and also excreted in faeces.
- Approximately two-thirds of cases of yersiniosis occur in infants and young children, with more cases occurring in ♂ than ♀.
- Most cases occur in autumn or winter.
- Yersiniosis is commoner in Scandinavia and northern Europe, though cases have been reported worldwide. Third commonest zoonosis in humans in the EU. Low number of cases in the UK (0.09/100 000), compared to Finland (9.78/100 000), in 2010.
- Patients with iron overload, e.g. haemochromatosis, thalassaemia, or conditions requiring repeated blood transfusions, are at increased risk of infection from these siderophilic organisms, and, in these patients, the infection tends to be more severe.

Transmission and incubation period

- Infection follows ingestion of inadequately cooked meat (especially pork) or other food contaminated with *Yersinia* spp. (e.g. unpasteurized milk or milk products).
- Infection may also occur after contact with infected pets.

- Ability of *Y. enterocolitica* to grow at +4°C means refrigerated meat can be a source of infection. Infections have occurred following transfusion of blood stored for >3 weeks at +4°C.
- In Northern Europe, most cases are sporadic.
- In US, food-borne outbreaks associated with contaminated chocolate, improperly pasteurized dairy products, tofu, lettuce, and carrots have been described.
- Incubation period: *Y .enterocolitica* 3–10 days (median 4 days), *Y. pseudotuberculosis* 7–21 days.

Clinical features and sequelae

Although both organisms cause a similar spectrum of infections, the majority of *Y. enterocolitica* infections present as acute enteritis or acute terminal ileitis, whereas *Y. pseudotuberculosis* is more commonly associated with mesenteric adenitis or acute pseudo-appendicitis.

- Children ≤4 years of age typically present with thin, watery diarrhoea, which may contain blood and mucus, mimicking shigellosis. Right iliac fossa pain, mimicking acute appendicitis, commoner in children aged 5–14 years.
- Necrotizing enterocolitis has been described in young infants.
- Mesenteric adenitis, acute pseudo-appendicitis, or terminal ileitis are characterized by abdominal pain in the right lower quadrant and low-grade fever. In some cases, the pain may be so severe, acute appendicitis is suspected. Intussusception may occur.
- The majority of cases of enteritis and mesenteric adenitis are self-limiting, with recovery after 1–3 weeks (median 10 days).
- Post-infectious complications include a reactive arthritis (especially in HLA-B27-positive individuals) tending to affect the wrists, knees, and ankles, developing 1 month after the initial diarrhoea, and generally resolving within 1–6 months, and erythema nodosum which usually resolves spontaneously within 1 month.
- Bacteraemia may occur in otherwise healthy children, as well as in those with underlying co-morbidities. Children with conditions associated with iron overload, including haemolytic anaemias, thalassaemia, sickle-cell anaemia, and those with diabetes mellitus and immunosuppression (including HIV) are at risk. Infants <3 months of age are also at increased risk of developing bacteraemia.
- A range of extra-intestinal complications of *Yersinia* spp. bacteraemia have been reported. These include hepatic and splenic abscess, pneumonia, empyema, septic arthritis, meningitis, endocarditis, mycotic aneurysms, and acute interstitial nephritis.
- A clone of *Y. pseudotuberculosis*, which produces a superantigenic exotoxin, has been associated with a toxic shock-like syndrome resembling Izumi fever, an illness that occurs epidemically in Japan, or Kawasaki disease. Symptoms and clinical findings include fever, rash, diarrhoea, vomiting, desquamation, a strawberry tongue, abdominal pain resembling acute appendicitis, arthralgia, lymphadenopathy, hepatosplenomegaly, and conjunctivitis.

Diagnosis

- *Y. enterocolitica* can be isolated from stool cultures on a selective medium such as CIN (cefsulodin–irgasan–novobiocin) agar. A cold-enrichment technique of incubation at +4°C for up to 3 weeks may be necessary to recover the organisms. Clinicians should inform the laboratory if they suspect a yersinial infection to ensure selective media and isolation techniques are used.
- *Y. pseudotuberculosis* is rarely isolated from stool culture but may be recovered from mesenteric lymph node culture.
- Blood cultures should be taken.
- *Yersinia* spp. can be identified by MALDI-TOF. Strains can be typed by pulsed-field gel electrophoresis (PFGE) or multilocus variable-number tandem-repeat analysis (MLVA).
- Serological tests, including agglutination tests and ELISA, may be used. False positive results from cross-reacting antibodies to salmonellae, *E. coli*, and *Brucella* spp. occur.

Management and treatment

- The majority of cases of *Yersinia* enteritis and mesenteric adenitis are generally self-limiting and do not require antimicrobial therapy. However, antimicrobials should be administered to ill children and immunocompromised patients.
- Septicaemia, extra-intestinal foci of infection, and enteritis in immunocompromised patients should be treated with antimicrobials.
- *Y. enterocolitica* is generally resistant to penicillin, ampicillin, and first-generation cephalosporins.
- Fluoroquinolones, co-trimoxazole, and aminoglycosides have all been used successfully to treat *Y. enterocolitica* infections.
- *Y. pseudotuberculosis* is usually susceptible to penicillin and ampicillin.

Prevention

- Good hygienic practices should be observed at all stages of the production and preparation of food.
- All meat, especially pork, must be thoroughly cooked before consumption.
- Vegetables and salads should be washed before consumption.
- Use separate chopping boards for raw meat and other foods.
- Avoid storing raw meat at +4°C for prolonged periods.
- Children visiting farms and handling animals should wash their hands thoroughly before eating.
- There are no vaccines.

Future research

- Further studies of the natural history and epidemiology of *Y. enterocolitica* and *Y. pseudotuberculosis*.

Further reading

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Chapter 126

Kingella kingae

Name and nature of organism

K. kingae is a β-haemolytic facultative anaerobic bacterium of the *Neisseriaceae* family that appears as pairs or short chains of plump Gram-negative coccobacilli with tapered ends.

K. kingae is part of the normal respiratory flora and is carried asymptomatically in the oropharynx. The carriage rate is nil in the first 6 months of life, gradually increasing to 10% at the age of 12 months, remains stable between 10% and 12% in the second year of life, and diminishes afterward. Carriage of the organism is substantially increased among young attendees to childcare facilities.

Carriage of *K. kingae* in young children is characterized by frequent turnover of colonizing strains that differ in their virulence and tissue tropism. Some strains are seldom, if ever, isolated from patients with clinical disease, while others are common causes of invasive infection and are significantly associated with bacteraemia, septic arthritis (SA), osteomyelitis (OM), or endocarditis.

Epidemiology

Because the importance of *K. kingae* as a paediatric pathogen has been recognized only in recent years, information on the epidemiology of infections caused by the organism is limited. Although an annual incidence of culture-proven *K. kingae* infections of 9.4 per 100 000 children younger than 4 years was found in southern Israel, because of the fastidious nature of the bacterium, this figure should be considered a minimal estimate, and many cases probably remain undiagnosed. The calculated risk of young Swiss carriers to develop *K. kingae* OM or SA was found to be <1% per year.

K. kingae infections are rare below the age of 6 months; the attack rate peaks between 6 and 12 months of age, gradually decreasing thereafter. Over 95% of patients are younger than 4 years, paralleling the age-related prevalence of the organism in the pharynx. Occurrence of the disease in older children and adults is exceptional and is usually associated with underlying conditions such as cardiac valve pathology, immunodeficiency, malignancies, or SLE. A ♂:♀ ratio of 1.3 has been reported, and the majority of clinical infections are detected between July and December.

Transmission and incubation

Like other upper respiratory commensals, *K. kingae* is transmitted from child to child by direct contact or through fomites among youngsters with poor hygienic habits that share toys coated with respiratory secretions or saliva. The incubation period of invasive *K. kingae* infections has not been established precisely. Of note, in clusters of disease detected in childcare centres, all cases occurred within a 1-month period.

Pathogenesis

All *K. kingae* isolates produce a potent repeats-in-toxin (RTX) that exerts cytotoxic activity against macrophage-like cells, leucocytes, synoviocytes, and respiratory epithelial cells, promoting colonization of the pharyngeal mucosa and ensuring survival of the organism in the bloodstream and invasion of deep body tissues. Blood and pharyngeal isolates of children with invasive *K. kingae* disease demonstrate genomic identity, indicating that the oropharynx is likely to be the site from which virulent organisms enter the bloodstream and disseminate. Preceding or concomitant viral respiratory infections and primary herpetic gingivostomatitis are frequently detected in children with invasive *K. kingae* disease, suggesting that, by damaging the respiratory epithelium, viral diseases facilitate bloodstream invasion.

Clinical features and sequelae

The clinical presentation of children with invasive *K. kingae* infections, other than endocarditis, is usually mild, requiring a high index of suspicion, and is characterized by:

- Good general condition
- Normal body temperature or low-grade fever in half of patients
- Lack of leucocytosis (<15 × 10^9 WBC/L) in 60% of patients
- Frequently normal CRP and ESR levels.

With the exception of patients with endocarditis who develop embolic phenomena, a single focus of infection is usually detected.

The clinical spectrum of *K. kingae* disease comprises:

- Skeletal system infections: in 53% of patients, including:
  - Arthritis: 77%
  - OM: 17%
  - Spondylodiscitis: 5%
  - Tenosynovitis: 1%
- Bacteraemia with no focus: 44%
- Endocarditis: 2–3%
- Lower respiratory tract infections, ocular infections, meningitis, and other infections: <1%.

Skeletal system infections

Use of improved culture methods and nucleic acid amplification assays has revealed that *K. kingae* is a common cause of joint, bone, and intervertebral disc infections in children aged 6 months to 4 years.

Septic arthritis

- Onset of the disease is acute, and most patients seek medical attention within 2–3 days after onset of symptoms.
- Low-grade fever, $<15 \times 10^9$ WBC/L, and normal or mildly elevated acute-phase reactants are common.
- However, it is disputed whether clinical features and/or laboratory test results may reliably differentiate between *K. kingae* arthritis and joint infections caused by traditional pathogens.
- The WBC count in the synovial fluid shows $<50 \times 10^9$ WBC/L in one-quarter of patients, and the Gram stain is rarely positive.
- Because of mild inflammatory response, young patients with *K. kingae* infections of the hip may be misdiagnosed as suffering from transient synovitis.
- The large weight-bearing joints (knee, ankle, or hip joints) are involved in 78% of patients.
- The wrist, shoulder, or elbow in 27%.
- The metacarpophalangeal, tarsal, sternoclavicular, and sacroiliac joints, which are rarely affected by other bacterial pathogens, are over-represented in *K. kingae* arthritis.
- Polyarticular involvement occurs in 6% of patients.

Osteomyelitis

- Onset of *K. kingae* OM is generally more insidious than that observed in SA, and most children are diagnosed after >1 week of evolution.
- *K. kingae* infections affect the tubular bones of the arms and legs in two-thirds of cases.
- Involvement of the pelvis, tarsal bones, sternum, or clavicle is remarkably frequent.
- The epiphysis of long bones, which is rarely invaded by pyogenic organisms, is not uncommonly involved in *K. kingae* OM.
- Despite the frequent diagnostic delay and severe radiological picture noted in some cases, no evolution to chronicity or significant residual orthopaedic disabilities have been reported.

Spondilodiscitis

K. kingae is detected in over a quarter of children younger than 5 years with haematogenous spondylodiscitis, whereas occurrence of the disease in older children and adults is exceptional. Because intervertebral disc biopsies and aspirations are rarely performed in children, it is presumed that many cases remain undiagnosed. The following characterize *K. kingae* spondylodiscitis:

- The disease usually affects a single intervertebral disc
- Anatomic involvement, in decreasing order of frequency: lumbar > thoracolumbar > thoracic > lumbosacral > cervical spaces
- Clinical presentation: limping, abdominal or low back pain, refusal to sit or walk, or neurological symptoms
- Narrowing of the intervertebral space on X-ray or MRI imaging
- Intravertebral and spinal subdural abscesses (detectable on MRI)
- If adequately treated, the disease usually runs a benign clinical course, leaving no permanent neurologic sequelae
- Residual narrowing of the intervertebral space (rare).

Abortive infections

Although bone and joint infections are not considered self-limited diseases, transient involvement of the skeletal system during an episode of *K. kingae* bacteremia may occur. Children with this condition present with limping or refusal to walk or weight-bear, but without objective signs of osteoarthritis, and, by the time blood cultures became positive, patients are already afebrile, and the skeletal complaints had resolved without antimicrobial therapy, suggesting an abortive clinical course. Despite this favourable experience, caution is recommended, and adequate antibiotics should be administered to all patients in whom *K. kingae* is recovered from a normally sterile site or body fluid.

Other skeletal infections

Soft tissue infections, including cellulitis, tenosynovitis, and dactylitis, bursitis, subcutaneous and presternal abscesses, have also been reported.

Bacteraemia

K. kingae bacteraemia,[1] without evidence of endocarditis or development of a focal infection, has been diagnosed mostly in children. A maculopapular rash, resembling disseminated meningococcal or gonococcal infection or frank Henoch–Schönlein purpura, has been described in a few bacteraemic patients.

Mild to moderate fever is usually recorded, and the mean WBC count frequently shows $<15 \times 10^9$/L. Therefore, current guidelines for managing young febrile children with no apparent focus, which rely on body temperature and the presence of leucocytosis for obtaining blood cultures, may miss the diagnosis.

Endocarditis

K. kingae stands for the 'K' of the HACEK acronym that denotes a group of fastidious oral and upper respiratory tract organisms that is collectively responsible for up to 6% of cases of bacterial endocarditis. The following features characterize *K. kingae* endocarditis:[2]

- Commoner in older children and adults
- Native and prosthetic valve involvement has been reported with similar frequency
- The left side of the heart is usually involved, and the mitral valve is the most commonly affected
- Cardiac malformations and rheumatic fever are the usual predisposing factors, but many paediatric patients had no antecedent valvular disease
- Blood WBC, CRP, and ESR are significantly increased in *K. kingae* endocarditis, compared to other infections
- However, no laboratory result reliably diagnoses or excludes endocardial invasion by the organism in bacteraemic children.

Despite the benign course observed in other invasive *K. kingae* infections and the remarkable susceptibility of the bacterium to antibiotics, a variety of severe and life-threatening complications have been frequently reported, as follows:

- Mycotic aneurysms
- Embolism to peripheral arteries

- Cerebrovascular accidents
- Meningitis
- Mitral valve rupture, perforation, or insufficiency
- Paravalvular abscesses
- Cardiogenic shock
- Pulmonary infarction.

Early surgical interventions have been necessary for life-threatening complications unresponsive to medical therapy.

- Overall mortality rate: 16%.

Because of the potential severity of *K. kingae* endocarditis, routine echocardiographic evaluation of all patients from whom the organism is isolated from a normally sterile site is strongly recommended.

Laboratory diagnosis

Culture detection of *Kingella kingae*

The recovery of *K. kingae* from clinical specimens seeded onto routine solid culture media is suboptimal but can be significantly improved by inoculating synovial fluid specimens into aerobic blood culture vials of a variety of automated blood culture systems. When vials detected as positive by the blood culture instrument are subcultured onto blood agar or chocolate agar plates, *K. kingae* grows readily, indicating that dilution of a purulent aspirate in a large volume of nutrient broth decreases the concentration of inhibitory factors, improving the recovery of this fastidious organism. In studies conducted in Israel and France, in which blood culture vials were routinely inoculated with synovial fluid exudates from young children with arthritis, *K. kingae* was isolated in almost half of the patients with bacteriologically proven disease.

Detection by nucleic acid amplification assays

In recent years, the use of conventional and real-time PCR has enabled the identification of the aetiologic agents of SA and OM within 24 hours and improved the detection of difficult-to-culture pathogens. Use of *K. kingae*-specific probes targeting the *cpn60* or *rtx* genes enables the detection of as few as 30 CFUs of *K. kingae* per mL of synovial fluid, is superior to the blood culture vial technique for detecting the organism, reducing the fraction of culture-negative infections, and convincingly demonstrates that the bacterium is the leading bacterial aetiology of suppurative arthritis and OM in children aged 6–48 months.

Antibiotic susceptibility

- *K. kingae* is usually susceptible to the usual antibiotics that are empirically administered to young children with suspected invasive bacterial diseases.
- Production of β-lactamase, a TEM-1 enzyme encoded in a plasmid and more rarely in the chromosome, is limited to a few *K. kingae* clones.
- Our current knowledge on the prevalence of β-lactamase production by *K. kingae* is limited and fragmentary.

- Wide differences in the local prevalence of β-lactamase has been found (50% among invasive Icelandic isolates, and rare to exceptional in France and Spain).
- As a measure of caution, all *K. kingae* isolates from normally sterile body fluids should be routinely tested for β-lactamase production.
- With rare exceptions, *K. kingae* is also susceptible to aminoglycosides, macrolides, TMP-SMX, fluoroquinolones, rifampicin, tetracycline, and chloramphenicol.
- *K. kingae* exhibits decreased susceptibility to oxacillin (MIC_{50}: 3 micrograms/mL, and MIC_{90}: 6 micrograms/mL); 40% of isolates are resistant to clindamycin, and all strains are highly resistant to glycopeptide antibiotic drugs that are empirically administered to children with skeletal system infections in regions where community-associated MRSA is prevalent.

Treatment

Because of the lack of specific guidelines for treating *K. kingae* disease, patients have been administered a variety of antibiotic regimens, according to protocols developed for infections caused by traditional bacterial pathogens. Children with *K. kingae* arthritis have been administered 2–3 weeks of antibiotics. Recent evidence suggests that a total 10-day course of sequential parenteral and oral antibiotic drugs may suffice for uncomplicated suppurative arthritis, but experience with this novel approach in the treatment of *K. kingae* joint infections is still limited. Children with *K. kingae* OM have been treated from 3 to 6 weeks, and those with spondylodiscitis from 3 to 12 weeks.

Children with *K. kingae* bacteraemia have been generally administered initial β-lactam antibiotics by the IV route, followed by oral therapy once the clinical condition improved and endocarditis has been ruled out. Total duration of therapy has ranged from 1 to 2 weeks. Patients with *K. kingae* endocarditis are usually administered IV β-lactam antibiotics alone or in combination with an aminoglycoside for 4–7 weeks.

Prevention

There is usually no indication to eradicate *K. kingae* colonization from asymptomatic carriers. However, when data of six clusters of invasive disease detected in day-care centres are pooled, a total of 18 of 122 (14.8%) classmates developed a documented or presumptive *K. kingae* infection, and a large proportion of attendees carried the infecting strain, indicating that the organism exhibited an unusual colonization ability, remarkable transmissibility, and high virulence. Rifampicin (20mg/kg twice daily for 2 days), alone or in combination with amoxicillin (80mg/kg/per day) in two divided doses for 2 or 4 days, was administered in an attempt to prevent further cases of the disease. Although, in most cases, the effectiveness of these regimens was limited and only partial eradication of the causative

strain from the facility was achieved, no further cases of the disease were detected after administration of antibiotic prophylaxis.

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Morbidity and mortality from infection

Introduction

- Globally, the number of deaths in children younger than 5 years had halved from 12.6 million (90 deaths per 1000 live births) in 1990 to 6.6 million (48 deaths per 1000 live births) in 2012. It is estimated that the lives of 90 million children have been saved since 1990.
- Every region has at least halved its under-5 mortality rate, with the exception of West and Central Africa and sub-Saharan Africa as a whole.
- Across Europe overall, child mortality rates are substantially worse in Central Europe (average mortality rate 6.7 deaths per 1000 births) and Eastern Europe (average mortality rate 9.7 deaths per 1000 births). In Western Europe, the UK has one of the highest mortality rates in children <5 years (4.9/1000 live births), with an estimated 3800 deaths among <5 year olds in 2013, but lower than the US (8/1000 live births).
- Infections are a significant and potentially preventable cause of death, particularly in young children.
- In England and Wales, there are around 650 000 births annually, with ~3000 stillbirths, ~2000 neonatal deaths (<28 days), ~3000 infant deaths (<1 year), and ~4500 childhood (0–15 years) deaths a year (Fig. A1.1).
- In the UK, the recent Confidential Enquiry into Maternal and Child Health (CEMACH, available at: <www.cmace.org.uk>) reported infection to be the 'largest single cause of death in children dying of an acute physical illness … despite comprehensive and expanding immunization programmes, antibiotic availability, training in resuscitation and life support'.

Childhood deaths

- In the UK, the CEMACH report estimated that infection was relevant in at least 20% of the childhood deaths they reviewed, and this was supported by a recent analysis of childhood death certificates.
- Among infection-related deaths, the median age was 1 year, and half of all children who died had an underlying medical condition recorded on their death certificate.
- The contribution of infection to childhood deaths was highest in the 1–4 year age group (27% of all deaths), followed by <1 year olds (21%) and 5–14 year olds (12%).

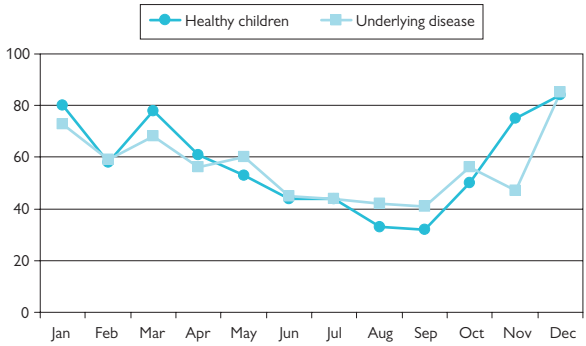

Fig. A1.1 Number of infection-related deaths by month of death among previously healthy children and those with underlying disease, England and Wales 2003–05.
(Source data from Ladhani S, Pebody RG, Ramsay ME, Lamagni TL, Johnson AP, Sharland M. Continuing impact of infectious diseases on childhood deaths in England and Wales, 2003–2005. *Pediatr Infect Dis J* 2010;**29**: 310–13.)

- The proportion of children who died of an infection and had an underlying medical condition recorded on their death certificate increased with age.
- Underlying medical conditions varied with age—prematurity and associated problems were commonest in infants (<1 year olds), cerebral palsy and its complications in 1–4 year olds, and malignancy in 5–14 year olds.
- Girls who died were more likely to have an underlying medical condition than boys.
- Septicaemia was recorded in half of all infection-related deaths, followed by respiratory tract infections (30%) and infections of the CNS (15%).
- Previously healthy children were more likely to die of meningitis or encephalitis, while those with underlying medical conditions were more likely to die of septicaemia.
- Among previously healthy children, respiratory tract infections were most prevalent in infant deaths, septicaemia in 1–4 year olds, and meningitis or encephalitis in 5–14 year olds.
- Where a pathogen was specified on the death certificate, 60% were bacterial, 30% viral, 8% fungal, and 2% other infections (Table A1.1)
- In previously healthy children, meningococci were the most commonly reported organisms (28%), followed by pneumococci (18%) and other streptococci (13%).
- In children with underlying medical conditions, Gram-negative bacilli accounted for over half of all bacterial infections, while enterococci and staphylococcal infections contributed a further 20% of deaths.
- Viral infections contributed equally to deaths among previously healthy children and those with underlying medical conditions (20%)—over half the deaths attributed to viral infections were caused by four viruses: RSV (16%), adenovirus (12%), influenza (12%), and CMV (10%).

Table A1.1 Pathogens noted on death certificates in previously healthy children and those with an underlying medical condition (excluding deaths in the neonatal period, <28 days after birth) in England and Wales between 2003 and 2005

	Previously healthy (*n* = 681)		Underlying conditions (*n* = 676)		All cases (*n* = 1357)	
Bacterial (total)	**339**		**155**		**494**	
Meningococcal	133	39.2%	5	3.2%	138	27.9%
Pneumococcal	72	21.2%	17	11%	89	18%
Other streptococci	51	15%	11	7.1%	62	12.6%
Unspecified Gram-negative	6	1.8%	36	23.2%	42	8.5%
Staphylococcal	15	4.4%	23	14.8%	38	7.7%
Klebsiella	1	0.3%	16	10.3%	17	3.4%
E. coli	4	1.2%	12	7.7%	16	3.2%
Pseudomonas	5	1.5%	9	5.8%	14	2.8%
Unspecified Gram-positive	2	0.6%	1	0.6%	3	0.6%
Other/not specified	50	14.7%	25	16.2%	75	15.2%
Viral (total)	**122**		**134**		**256**	
Respiratory syncytial virus	8	6.6%	34	25.4%	42	16.4%
Adenovirus	11	9%	21	15.7%	32	12.5%
Influenza	18	14.8%	12	9%	30	11.7%
Cytomegalovirus	17	13.9%	10	7.5%	27	10.5%
Varicella	8	6.6%	11	8.2%	19	7.4%
Other/not specified	60	49.2%	46	34.3%	106	41.4%
Fungal (total)	**5**		**64**		**69**	
Candida	3	60%	23	35.9%	**26**	37.7%
Aspergillus	0	0%	22	34.4%	**22**	31.9%
Pneumocystis	0	0%	6	9.4%	**6**	8.7%
Other/not specified	2	40%	13	20.3%	**15**	21.7%
Tuberculosis	**12**		**4**		**16**	
Other	**3**		**2**		**5**	
Not specified	**203**		**317**		**520**	

Neonatal deaths

- Globally, neonatal mortality is of particular concern, since the interventions needed to address it are different from those needed for older children.
- The neonatal mortality rate has fallen from 33 deaths per 1000 live births in 1990 (4.6 million deaths) to 21 deaths per 1000 live births in 2012 (2.9 million deaths). The decline was observed in all regions worldwide, but with lesser drops in South Asia (39%) and sub-Saharan Africa (28%).
- The contribution of neonatal deaths to childhood mortality rates, however, has increased from 37% in 1990 to 44% in 2012.
- In England and Wales, the neonatal death rate (defined as deaths among infants under 28 days of age) has remained constant at 3.4–3.9 per 1000 live births over the past decade, which is significantly lower than the global neonatal mortality rate of 30 per 1000 live births.
- Worldwide, the largest cause of neonatal mortality is infection, accounting for 36% of deaths, but, in England and Wales, as in the rest of the developed world, the most significant cause of neonatal mortality is prematurity and its complications, with infection playing a smaller role.
- In England and Wales, analysis of death certificate data estimated that at least 11% of neonatal deaths were infection-related, which is similar to the 10% estimated by the 2007 CEMACH report.
- Overall, 36% of the neonatal infection-related deaths occurred in term neonates, 17% in preterm neonates (28–36 weeks), and 47% in extremely preterms (<28 weeks' gestation).
- Fifty-seven per cent of all, and 49% of term, neonatal infection-related deaths had an underlying medical condition recorded on their death certificate, mainly respiratory in premature and extremely premature neonates and cardiac, respiratory, and birth asphyxia in term neonates.
- Septicaemia was the commonest clinical presentation (50%), followed by pneumonia (15%) and meningitis (5%).
- A pathogen was recorded on the death certificate of only 44% of neonatal deaths—of these, 80% were bacterial, 10% were fungal, and 9% were viral (Table A1.2).
- GBS were recorded in a third of neonatal deaths where a bacterial infection was specified, and in 11% of all infection-related neonatal deaths. A similar number and proportion of deaths were additionally recorded to be due to unspecified streptococci.
- Among preterm and extremely preterm deaths, Gram-negative pathogens (particularly *E. coli*), staphylococci (mainly CoNS), and fungi (mostly *Candida* spp.) predominated.
- Deaths caused by viral infections were rare, except for HSV which almost exclusively affected healthy term neonates.

Table A1.2 Pathogens reported on the death certificates of neonates who died in England and Wales between 2003 and 2005

	Healthy term neonates (>36 weeks' gestation)		Preterm neonates (28–36 weeks' gestation)		Extremely preterm neonates (<28 weeks' gestation)	
Bacterial (total)	**111**		**42**		**120**	
Gram-positive	**81**	**73.0%**	**18**	**42.9%**	**58**	**48.3%**
Unspecified Streptococci	75	67.6%	11	26.2%	23	19.2%
Group B *Streptococcus*	58	52.3%	10	23.8%	19	15.8%
Pneumococcus	4	3.6%	1	2.4%	0	0%
Other streptococci	13	11.7%	0	0%	4	1.6%
Unspecified Staphylococci	6	5.4%	6	14.3%	29	24.2%
Coagulase-negative staphylococci	0	0.0%	2	4.8%	11	9.2%
S. aureus	1	0.9%	1	2.4%	3	2.5%
MRSA	2	1.8%	1	2.4%	1	0.8%
Unspecified *Staphylococcus* spp.	3	2.7%	2	4.8%	14	11.7%
Other/unspecified Gram-positive	0	0.0%	1	2.4%	6	10.3%
Gram-negative	**27**	**24.3%**	**24**	**57.1%**	**60**	**50.0%**
E. coli	10	9.0%	9	37.5%	18	30.0%
Pseudomonas spp.	6	5.4%	3	12.5%	10	16.7%
Klebsiella spp.	2	1.8%	1	4.2%	5	8.3%
Other/unspecified Gram-negative	9	8.1%	11	45.8%	27	45.0%
Unspecified bacteria	**3**	**2.7%**	**0**	**0%**	**2**	**1.7%**
Viral (total)	**23**		**3**		**3**	
Herpes simplex	13	56.5%	1	33.3%	0	0%
Coxsackie	3	13.0%	0	0%	0	0%
Respiratory syncytial virus	1	4.3%	0	0%	1	33.3%
Other/unspecified viral	6	26.1%	2	66.6%	2	66.6%
Fungal (total)	**2**		**4**		**31**	
Candida spp.	2	100.0%	2	50%	19	61.3%
Aspergillus spp.	0	0.0%	0	0%	1	3.2%
Other/unspecified fungal	0	0.0%	2	50%	11	35.5%

Source data from Ladhani S, Pebody RG, Ramsay ME, Lamagni TL, Johnson AP, Sharland M. Continuing impact of infectious diseases on childhood deaths in England and Wales, 2003–2005. *Pediatr Infect Dis J* 2010;**29**: 310–13.

Conclusions

- Infections contribute to around 10% of neonatal, and 20% of childhood, deaths in England and Wales.
- Around half the neonates and children who die have other underlying co-morbidities.
- GBS contribute significantly to neonatal deaths, while meningococci and pneumococci remain important causes of death among previously healthy infants and young children—these infection-related deaths may be preventable through routine infant immunization in the near future.
- Among children with underlying medical conditions, as well as preterm and extremely preterm neonates, Gram-negative bacteria and fungi contribute significantly to death—this group of children share similar risk factors, such as recurrent and prolonged hospitalizations, exposure to multiple antibiotics and immunosuppressive medications, and insertion of indwelling vascular catheters.

What's new?

- The introduction of a maternal pertussis immunization programme in the UK was highly effective in preventing disease and pertussis-related deaths in infants in the first 3 months of life.
- A protein-based broad-spectrum meningococcal vaccine (Bexsero®, Novartis Vaccines) was licensed in Europe in early 2013. It is estimated that this vaccine could protect against 78% (range 73–87%) of meningococcal group B (MenB) strains causing invasive disease in Europe and should also protect against invasive disease caused by other meningococcal groups.
- A conjugate vaccine against the commonest serotypes causing invasive GBS disease in neonates is currently undergoing large-scale clinical trials. Vaccinating pregnant women has the potential to significantly reduce the burden of invasive GBS disease in pregnant women, neonates, and young infants.

What's next?

- Further studies are needed to identify modifiable risk factors for death in children with co-morbidities, e.g. delays in health-seeking behaviour, inappropriate empiric antimicrobial therapy, and early need for intensive care support. The UK is the first country to introduce this vaccine into the national infant immunization programme in September 2015.
- The introduction of new vaccines to prevent serious bacterial infections into national immunization programmes could lead to significant reduction in infection-related deaths, especially in healthy infants and children, but will need careful monitoring in the coming years.

Further reading

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Appendix 2

Guidance on infection control in school and other childcare settings

Prevention of the spread of infections is best ensured by: routine immunization, high standards of personal hygiene and practice, particularly handwashing, and maintaining a clean environment. Once infection has occurred, it may be necessary to exclude children from contact with others so as to prevent further cases. Advice on exclusion periods often varies across Europe. Table A2.1 is based on unpublished work carried out for ECDC.

In England, it is advised to discuss community infection control with the local health protection unit (HPU).

Table A2.1 Guidance on infection control in school and other childcare settings

Illness	Recommended period to be kept away from school, nursery, or childminders	Comments
Diarrhoea and vomiting		
Diarrhoea and/or vomiting	48 hours from last episode of diarrhoea or vomiting	Exclusion from swimming pools should be for 2 weeks following last episode of diarrhoea
E. coli 0157 VTEC	Symptomatic cases should be excluded, until they have had normal stools for 48 hours. Children <5 years may need to be excluded until they have had two consecutive negative faecal samples	Exclusion from swimming pools should be for 2 weeks following last episode of diarrhoea
Shigella (dysentery)	Symptomatic cases should be excluded. Children <5 years should be excluded for a further 48 hours. Always consult with your HPU	Exclusion from swimming pools should be for 2 weeks following last episode of diarrhoea
Typhoidal (and paratyphoidal) (enteric fever)	Symptomatic cases should be excluded. Children <5 years should be excluded until three negative stools have been collected. Always consult with HPU	Exclusion from swimming pools should be for 2 weeks following last episode of diarrhoea
Respiratory infections		
Influenza	Until recovered	
Tuberculosis[a]	Always inform HPU if smear-positive for at least 2 weeks after starting treatment	Not usually spread from children. Requires prolonged close contact
Whooping cough[a] (pertussis)	5 days from commencing appropriate antibiotic treatment or 21 days from onset of illness if no antibiotic treatment	Preventable by vaccination. After treatment, non-infectious coughing may continue for many weeks
Rashes/skin		
Athlete's foot	None	Athlete's foot is not a serious condition. Treatment is recommended
Chickenpox	5 days after last lesion has crusted over	Contacts who are immunosuppressed or pregnant should seek urgent advice

(*Continued*)

Table A2.1 (*Contd.*)

Illness	Recommended period to be kept away from school, nursery, or childminders	Comments
Cold sores (herpes simplex)	None	Avoid kissing and contact with the sores. Cold sores are generally a mild self-limiting disease
German measles (rubella)[a]	6 days from onset of rash	Preventable by immunization (MMR × 2 doses). Pregnant ♀ staff in contact with rubella in the period 7 days before to 6 days after the development of the rash should consult their GP or obstetrician
Hand, foot, and mouth disease	None	Contact HPU if a large number of children are affected. Exclusion may be considered in some circumstances
Impetigo	Children should be excluded from school until all the sores have crusted over or for 48 hours after starting antibiotic treatment	Antibiotic treatment by mouth may speed healing and reduce infectious period
Measles[a]	4 days from onset of rash	Preventable by vaccination (MMR × 2 doses.) Contacts who are immunosuppressed or pregnant should seek advice
Molluscum contagiosum	None	A self-limiting condition
Ringworm	Exclusion is not necessary, but treatment should be commenced as soon as possible	Different treatments are required for the different forms of the disease; not all are available from a pharmacist. Also check/treat symptomatic pets
Roseola (infantum)	None	None
Scabies	Child can return after treatment	Two treatments, 1 week apart, for cases. Contacts should have one treatment; include the entire household and any other very close contacts. If further information is required, contact your local HPU
Scarlet fever[a]	24 hours after commencing antibiotics	Antibiotic treatment recommended for the affected child

(*Continued*)

Table A2.1 (*Contd.*)

Illness	Recommended period to be kept away from school, nursery, or childminders	Comments
Slapped cheek/fifth disease. Parvovirus B19	None	Pregnant contacts and carers of children with sickle-cell disease should seek advice from their GP or obstetrician
Warts and verrucae	None	Verrucae should be covered in swimming pools, gymnasiums, and changing rooms
Other infections		
Conjunctivitis	None	If an outbreak/cluster occurs, consult HPU
Diphtheria[a]	Exclusion is important	Preventable by vaccination. HPU will organize any contact tracing
Glandular fever	None	About 50% of children get the disease before they are 5, and many adults also acquire the disease without being aware of it
Head lice	None	Treatment is recommended only in cases where live lice have definitely been seen. Close contacts should be checked and treated if live lice are found. Regular detection (combing) should be carried out by parents
Hepatitis A[a]	Exclusion may be necessary. Always consult with HPU	Good personal and environmental hygiene will minimize any possible danger of spread of hepatitis A
Hepatitis B[a] and C[a]	None	
HIV/AIDS	None	HIV is not infectious through casual contact. There have been no recorded cases of spread within a school or nursery
Meningococcal meningitis[a]/ septicaemia	Until recovered	Meningococcal C meningitis is preventable by vaccination. There is no reason to exclude siblings and other close contacts of a case. The HPU will give advice on any action needed and identify contacts requiring antibiotics

(*Continued*)

Table A2.1 (*Contd.*)

Illness	Recommended period to be kept away from school, nursery, or childminders	Comments
Meningitis[a] due to other bacteria	Until recovered	Hib meningitis and pneumococcal meningitis are preventable by vaccination. There is no reason to exclude siblings and other close contacts of a case. Always contact the HPU who will give advice on any action needed and identify contacts requiring antibiotics
Meningitis viral[a]	None	Milder illness than bacterial meningitis. There is reason to exclude siblings and other close contacts of a case. Contact tracing is not required
MRSA	Contact precautions, consider isolation	Good hygiene, in particular handwashing and environmental cleaning, is important to minimize any danger of spread. If further information is required, contact your local HPU
Mumps[a]	5 days from onset of swollen glands	Preventable by vaccination. (MMR × 2 doses)
Threadworms	None	Treatment is recommended for the child and household contacts
Tonsillitis	None	There are many causes, but most cases are due to viruses and do not need an antibiotic

[a] *Denotes a notifiable disease in England*. It is a statutory requirement that doctors report a notifiable disease to the proper office of their local authority. In addition, organizations may be required via locally agreed arrangements to inform their local HPU.

Outbreaks: if a school, nursery, or childminder suspects an outbreak of infectious disease, they should inform their HPU. Advice can also be sought from the school health service.

HPU, health protection unit; VTEC, verotoxigenic *Escherichia coli*.

Source data from HPA guidance. (Guidance on infection control in schools and other childcare settings). <http://www.hpa.org.uk/web/HPAwebfile/HPAweb_C/1194947358374> (accessed October 2010), and unpublished work from the European Centre for Disease Control and Prevention.

Appendix 3

Variation in immunization schedules in Europe

Introduction

All European countries have immunization programmes with recommendations for the general population (routine or universal immunization) and additional recommendations for certain risk groups with specific indications. These recommendations are usually established by independent experts, forming a National Immunisation Technical Advisory Group (NITAG). After licensing (centralized via EMA for EU member states) of specific vaccines, NITAGs deal with specific aspects of the vaccine(s) and the disease(s) it is supposed to prevent in a standardized fashion. Most frequently, the concept of *Grading of Recommendations Assessment, Development, and Evaluation* (*GRADE*) is applied. At the end of this evaluation process, vaccination is either recommended or not, and country-specific issues on age groups, vaccination schedules, and catch-up strategies for age groups not primarily targeted are published. Finally, issues on funding and implementation are considered. Today, country-specific circumstances make immunization programmes in each European country unique, and no two countries have identical immunization recommendations. A harmonized European immunization schedule would have benefits and disadvantages; however, it is not currently a realistic goal.

- ECDC has a useful interactive website which allows users to review all EU countries' immunization schedules individually in an overview or specifically for the respective target disease (available at: <http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx>). For Switzerland, see <http://www.ekif.ch>.
- For country-specific immunization recommendations (and statistics on vaccination coverage) worldwide, see <http://apps.who.int/immunization_monitoring/globalsummary>.

Here we briefly summarize the general characteristics of variations in routine immunization schedules in European countries by diseases or disease complexes and frequently used vaccine combinations. It should be noted that, where a vaccine is not routinely recommended, it may be available in the private market—in some countries, the coverage in the population through private purchase can be significant.

Bacille Calmette-Guérin

- The majority (three-quarters) of European countries have a policy of offering BCG.
- There is variation regarding target groups, with more countries offering it to all babies (routine) and slightly fewer offering it only to babies born into high-risk groups (selective) or not at all (e.g. Germany).
- There is consistency regarding the number of doses (one) and the timing of BCG, with nearly all countries recommending vaccine at birth or in the first month of life.

Diphtheria, tetanus, pertussis-based combination vaccines

- All European countries recommend a 1° series against diphtheria, tetanus, and pertussis (DTP), starting in infants, either at 2 or 3 months of age (where 2 months of age is defined as the day 2 months after the date of birth). With the exception of Poland, which still uses pertussis whole-cell vaccines (wP), all countries use acellular component pertussis vaccines (aP).
- Depending on the country's individual recommendations, multicomponent DTP combination vaccines, with additional Hib, IPV, and HBV surface antigen, are available.
- The 1° series comprises either two or three doses in the first year of life and a further (also designated as first booster) dose at, shortly before, or after the child's first birthday ('3 + 1' or '2 + 1' schedules).
- Further doses, if recommended, are usually given with reduced diphtheria and pertussis (less so for tetanus) antigen contents, for which the acronym 'Tdap' (where the 'a' stands for acellular) is used most frequently. Timing and numbers of recommended booster doses vary substantially by country (Fig. A3.1)
- Similarly, the timing and number of booster doses for diphtheria, tetanus, Hib, and IPV vary from country to country
- Hib immunization is recommended only for children up to 5 years of age (see Chapter 69).

For Footnotes, see <http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx>.

Hepatitis B vaccines

- HBV vaccines are available as monocomponent or multicomponent vaccines (e.g. as bivalent with hepatitis A or multivalent with D/T/aP/IPV/Hib).
- Many (but not all) European countries recommend HBV vaccines for routine infant immunization with two or three doses, followed by a booster dose in the second year of life or for (pre-) adolescents.
- Few countries have recommendations restricted to high-risk groups such as health-care personnel.

Human papillomavirus vaccines

- Two HPV vaccines are currently available, with recommended schedules of three doses given at 0, 1, and 6 months or 0, 2, and 6 months, depending on the product. There are emerging data to support two-dose schedules, and some countries already recommend this schedule for girls <15 years of age (e.g. Switzerland).
- The majority of European countries currently recommend routine HPV vaccines for adolescent ♀, with the majority focusing on 12- to 13-year-old girls, but with eligibility ranging from 9 to 26 years in different countries.
- Several European countries are currently considering introducing recommendations for HPV vaccination for boys, too (already introduced in Austria).

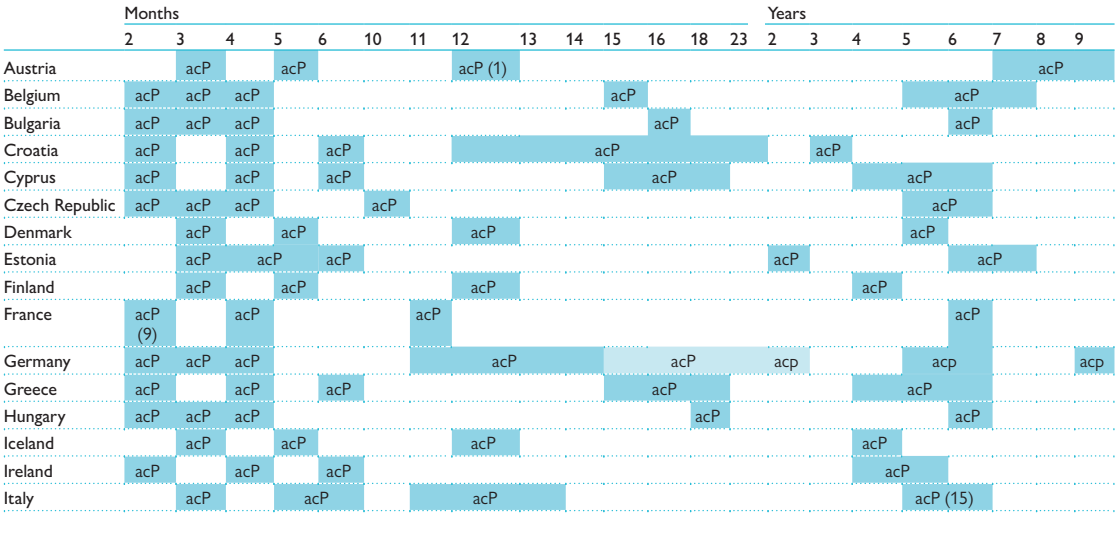
Influenza vaccines

- Many influenza vaccines are available but are either trivalent inactivated vaccines (TIV, injected) or live-attenuated vaccine (LAIV, intranasal). Quadrivalent vaccines (containing antigens of two types of influenza A and two types of influenza B virus strains) have recently become available.
- A minority of European countries recommend routine influenza vaccines for all healthy children (from 6 months of age), with only one (the UK) specifically recommending LAIV (from 2 years of age).
- All other countries recommend LAIV or TIV for specific risk groups only.

Measles, mumps, rubella combination vaccines

- All European countries recommend a two-dose MMR immunization schedule, with the first dose given anywhere between age 11 months (in outbreak or epidemic situation, based on local recommendations, this is permitted as early as 6 months of age) or 15 months.
- Timing of the second dose (which mainly is intended as a second chance to develop a protective immune response for those who did not respond to one or more of the three attenuated vaccine viruses after the first dose) varies from as early as 4 weeks after the first dose (recommended when the risk of disease exposure, based on local or national epidemiology, is high) to as late as 12 years of age.
- All countries recommend catch-up immunization for incompletely immunized older children and adolescents, or even (young) adults.

Recommended immunisations for pertussis



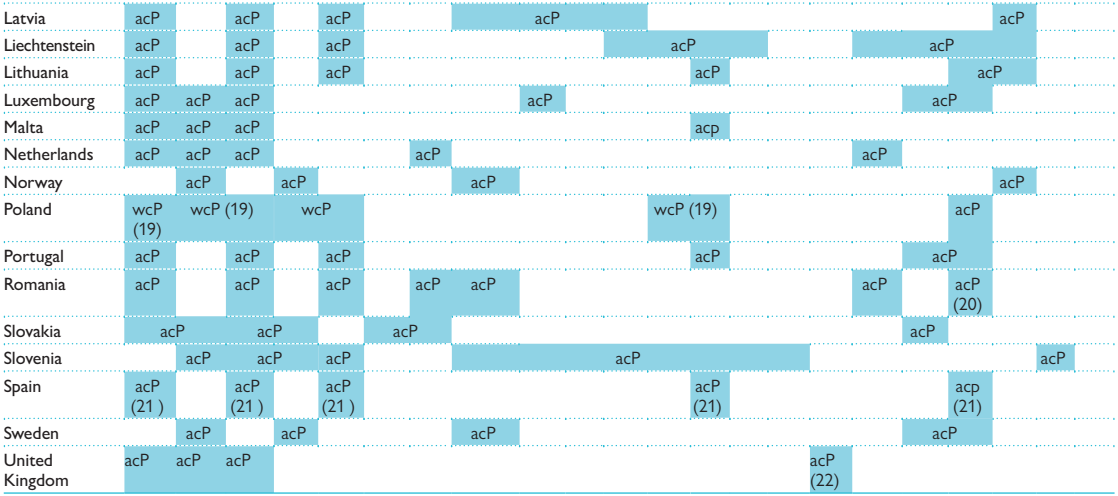


Fig. A3.1 Recommended immunizations for pertussis in EU countries.

Footnotes:

1: Earliest 6 month after the second dose

2: For children who received ony dTIPV previously

3: dTaP-IPV every 10 years between 18 and 60 years of age.

4: dTaP-IPV every 5 years from 65 years of age

5: One dose of dTTpa for all adults, with emphasis on cocoon vaccinationVaccination of expectant mothers during every pregnancy with a pertussis-containing vaccine in week 24 to week 32 of pregnancy

6: One dose of dTTpa for all adults, with emphasis on cocoon vaccination

7: Recommeded only. One of the booster doses should include pertussis (Td-acp).

8: only to children born in the period 1990-1995 and previously vaccinated at the age 12 years by sixth dose of dT vaccine.

9: or 8 weeks of age

10: For those who did not receive a dose of pertussis containing vaccine during the past 5 years, a booster with a quadrivalent vaccine (dTacP-IPV) is recommended at the time of the Td-IPV booster at 25 years.For those aged 25 years and above that did not receive a booster dose, catch-up with a dTacP-IPV vaccine can be proposed until 39 years of age. Recommendation to have an interval of 10 years in adults between a documented pertussis and pertussis re-vaccination.

11: Only one of the Td 10-yearly booster doses should be with a Tdacp vaccine in adults. Subsequent booster doses are to be done with Td vaccines..

12: Td booster every 10 year. One of the booster dose should be with Tdacp or Tdacp-IPV. Td from 65 years of age

13: Booster dose

14: Tdacp - Vaccination for pregnant women between 27-36 weeks gestation (introduced in September 2013). If the recipient does not have a medical card, they must pay administration cost of the vaccination out-of-pocket.

15: After seven years, a low-dose pertussis-containing dT vaccine should be used

16: To be given ten years after completing primary vaccination with DTaP-containing vaccines

17: Boosters at the age of 25-29, 45, 65, then every 10 years. First booster preferably before having first child, in order to protect the newborn against pertussis.

18: Subsequent Tdacp-IPV booster every 10 years

19: An acellular pertussis component (aP) combination vaccine should be used for children with contraindications to vaccination with the whole cell pertussis vaccine and in children born before 37th week of pregnancy or born with birth weight less than 2500 g

20: DTacP-IPV at 6 years to begin in 2015

21: For more detail on review and recommendation for pertussis vaccination in Spain, please refer to http://msc.es/profesionales/saludPublica/prevPromocion/vacunaciones/docs/TosFerina.pdf

22: Either DTacP-IPV or dTacP-IPV can be given depending on availability

23: Specific programme to vaccinate expectant mothers with a pertussis-containing vaccine from 28 weeks of pregnancy. for more information, refer to http://immunisation.dh.gov.uk/pertussis-pregnant/

- General recommendation for Austria
- Recommendation for specific groups only for Austria
- Catch-up (e.g. if previous dosed missed) for Austria

Meningococcal vaccines

- Meningococcal polysaccharide and polysaccharide–protein conjugate vaccines against one or more serogroups (A, C, Y, W) are available for routine immunization. A multicomponent outer membrane protein-based vaccine directed against serogroup B strains (but likely to cover other serogroups too) has also recently been licensed in Europe, and was introduced in the national immunization programme in the UK in October 2015 for infants.
- Many European countries (but not all) have incorporated MenC (monocomponent group C polysaccharide–protein conjugate) into their routine schedules, often with one or two infant doses and a booster in the second year of life or, more simply, with a single dose in the second year of life.
- In recognition of the peak incidence seen in adolescence, several countries have now added a routine dose in this age group and/or included a 'catch-up' dose for those not previously immunized.
- Only two countries (Austria, Greece) recommend a quadrivalent conjugate vaccine, rather than MenC (both as an adolescent booster).

Pneumococcal vaccines

- Both pneumococcal polysaccharide and polysaccharide–protein conjugate vaccines (PCV) are available, with two different conjugate vaccines currently licensed and used in Europe (10-valent or 13-valent).
- Nearly all European countries use PCVs for routine infant immunization, with two or three doses given in infants, followed by a booster dose in the second year of life. There is variation as to which of the PCVs is currently used.

Poliomyelitis vaccines

- In Europe, IPVs are exclusively used (except for OPV as a booster dose in Poland), whereas oral, live-attenuated vaccines (OPV) are used in some other parts of the world (Asia, Africa).
- Poliomyelitis vaccines are available as monocomponent or multicomponent vaccines (multivalent with D/T/aP/IPV/HepB or reduced antigen d/T/aP).
- All European countries recommend IPV for routine infant immunization with two or three doses, followed by a booster dose in the second year of life. One or more further booster dose(s) (up to a total of five) are recommended throughout childhood in most European countries. Further booster doses are recommended, usually at 10-year intervals, for risk groups and/or for outbreak control (check the WHO website for specifics).

Rotavirus vaccines

- Two (live attenuated, oral) rotavirus vaccines are currently available; one requires two, and the other three, doses, and all schedules have to be completed as early as possible (28 and 32 weeks of age, respectively, at the latest) in order to avoid doses being given around the peak age for intussusception.
- Approximately one-third of European countries currently recommend rotavirus vaccines for routine use in infants.

Varicella vaccines

- Two live attenuated vaccines are available (monocomponent or in combination with MMR), with two-dose schedules generally recommended for both.
- A minority of countries currently recommend vaccines for routine use, generally beginning in the second year of life.
- Several countries reserve vaccination only for older children and adolescents who are susceptible (based variably on the absence of a history of disease or of vaccination or of serological evidence of immunity), while several countries recommend it only for risk groups (which may include conditions where a family member is at risk, i.e. for indirect protection).

Further reading

Brighton Collaboration. Available at: <http://www.brightoncollaboration.org>.
European Centre for Disease Prevention and Control. *Immunisation*. Available at: <http://www.ecdc.europa.eu/en/healthtopics/immunisation/Pages/index.aspx>.

Appendix 4

Blue book antimicrobial dosing guide

This guidance aims to provide a simple reference for prescribing the antimicrobials discussed in the main text of the *Blue Book*. It is not a formulary of all available antimicrobials and does not aim to replace country-specific formularies. The general aim has been to simplify prescribing by using weight-based dosing (where possible), rather than age bands or surface area. Doses are given as single individual doses, followed by how often they are to be given, rather than total daily doses. The guide does not include side effects, drug interactions, and dosing in renal or hepatic impairment. Neonatal dosing is usually based on post-menstrual age (PMA), which is defined as the gestational age added to the chronological age (e.g. a baby born at 26 weeks' gestation, i.e. 4 weeks old, has a PMA of 30 weeks).

Dosing guidance reflects, where possible, the licensed dose given in the manufacturer's Summary of Product Characteristics. Some of the guidance here involves the use of unlicensed medicines or of licensed medicines for unlicensed use (off-label use), and the drug and dose are then used at the responsibility of the prescriber. Dosing guidance varies considerably across Europe, and clinicians need to be aware that this variation often reflects the very limited evidence base for specific doses, particularly in neonates. Dosing of antibiotics may also vary, depending on antimicrobial resistance patterns across Europe.

Helpful leaflets for parents and children on some antibiotics can also be found at <http://www.medicinesforchildren.org.uk>.

For this new edition of the *Blue Book*, we have also attempted to provide a summary of the level of pharmacological evidence (based on a formal systematic review) for current dosing recommendations. The aim of this guidance is to alert clinicians to the strength of the evidence behind the dosing recommendation. The idea behind this approach is to alert prescribers to where there is good, reasonable, or very limited evidence for the doses given, if the clinician notes unexpected clinical failure or toxicity.

We have included an assessment of the strength of the evidence for the dose, using a simple visual scale in the form of facial symbols alongside each drug regimen, as shown below.

☺	1a Systematic review of PK/(PD) studies including meta-analysis of raw data based on prospective data warehousing and common definitions of PK/PD variables
☺	1b Systematic review of PK/(PD) studies including meta-analysis of raw data without prospective data warehousing
😐	2a Multiple pooled individual PK/(PD) studies (non-systematic search strategy and/or analysis)
😐	2b Individual PK/(PD) studies with external data collection and validation
😐	2c Individual PK/(PD) studies with recommendations based on modelling and simulation or bridging methodologies
☹	3 Individual PK/(PD) studies without modelling and simulation
☹	4 Case study/case series with descriptive PK or based on therapeutic drug monitoring
☹	5 Expert opinion based on physiology, first principles, and *in vitro* and animal studies

The editors are especially grateful to Dr Steve Tomlin, Dr Jodi Lestner, Professor Irja Lutsar, and many others for their very considerable help with the production of this dosing guide.

Drug	Route	Neonatal dose	Paediatric dose	Comments
Abacavir	**By mouth**	No dosing information	≥3 months: 8mg/kg/dose (max 300mg) given twice daily OR 16mg/kg (max 600mg) once daily 😐 14–21kg: 150mg twice daily OR 300mg/dose given once daily 😐 21–30kg: 150mg in the morning and 300mg in the evening OR 450mg/dose given once daily ☹ >30kg: 300mg twice daily OR 600mg/dose given once daily ☹	a. HLA-B*5701 test before starting abacavir (ABC), as, if positive, there is an increased risk of hypersensitivity reactions and should not be used. HSR usually within first 6 weeks of therapy—requires careful evaluation. If proven, ABC not to be given again (rare in patients of Afro-Caribbean descent)
Abacavir + lamivudine (Kivexa®)	By mouth Tablets—one tablet contains abacavir 600mg + lamivudine 300mg	No dosing information	≥40kg: one tablet given once daily ☹	a. HLA-B*5701 test before starting b. Tablets can be cut
Aciclovir	By mouth	No dosing information	1 month to 18 years: 10mg/kg/dose (max 400mg) given four times daily ☹ Double dose for varicella-zoster, immuno-compromised, and CNS involvement ☹	a. Doses highly dependent upon indication b. Maintain adequate hydration c. Dose adjustments required in renal failure d. Use ideal body weight for dose calculation
	Intravenous Infusion: give over 60min	0–28 days: 20mg/kg given 8-hourly ☺	1–3 months: 20mg/kg/dose given 8-hourly 😐 3 months to 12 years: 10mg/kg/dose given 8-hourly ☹ 12–18 years: 5mg/kg/dose given 8-hourly ☹ Double dose for varicella-zoster, immuno-compromised, and CNS involvement	

Albendazole	By mouth	No dosing information	2–18 years Threadworm, hookworm, large roundworm and tapeworm: 400mg single dose, repeated in 2–3 weeks for threadworms and tapeworms ☹ Whipworms and *Strongyloides*: 400mg/dose given once daily for 3 days. Repeat after 3 weeks, if necessary ☹ Trichinosis and cutaneous larva migrans: 400mg/dose given once daily for 5 days. ☹ Neurocysticercosis: 7.5mg/kg/dose (max 400mg) given twice daily for 14–28 days. ☹ Hydatid disease: 7.5mg/kg/dose (max 400mg) given twice daily for 28 days, followed by a 14-day break, and then repeat for up to 2–3 cycles ☹ Toxicariasis: 10mg/kg/dose (max 400mg) given twice daily for 5 days ☹	
Amantadine	By mouth	No dosing information	1–18 years: 2–2.5mg/kg/dose (max 100mg) given twice daily 😐	a. No longer recommended by NICE
Amikacin	Intravenous	PMA ≤28 weeks: 15mg/kg/dose given 36-hourly 😐 PMA >28 weeks: 15mg/kg/dose given 24-hourly 😐	1 month to 18 years: 15mg/kg/dose given 24-hourly 😐	a. Pre-dose ('trough') plasma concentration should <5mg/L b. Neonates, infants, and those with renal impairment should have renal, auditory, and vestibular function monitored

(*Continued*)

Drug	Route	Neonatal dose	Paediatric dose	Comments
Amoxicillin	By mouth	Under 7 days: 30–60mg/kg/dose given twice daily ☹ 7–28 days: 30–60mg/kg/dose given three times daily ☹	1 month to 18 years: 15–30mg/kg/dose given three times daily (max 500mg/dose) ☹	
	Intravenous injection	As for oral ☹	1 month to 18 years: 30–60mg/kg/dose given 8-hourly ☹	
Amphotericin (Fungizone®) Prescribe as brand, i.e. Fungizone®	Intravenous Infusion over 2–6 hours	0–28 days: 1–1.5mg/kg/dose given 24-hourly 😐	1 month to 18 years: 1–1.5mg/kg/dose given 24-hourly 😐	a. Avoid other nephrotoxic drugs, if possible. Saline pre-treatment reduces toxicity
Amphotericin complex (Amphocil®) Prescribe as brand, i.e. Amphocil®	Intravenous Infusion at 1–2mg/kg/hour	No dosing information	1 month to 18 years: 3mg/kg/dose given 24-hourly. Max dose 6mg/kg/dose given 24-hourly. 😐	a. Avoid other nephrotoxic drugs, if possible
Amphotericin lipid complex (Abelcet®) Prescribe as brand, i.e. Abelcet®	Intravenous Infusion at 2.5mg/kg/hour	No dosing information	1 month to 18 years: 5mg/kg/dose given 24-hourly ☹	a. Avoid other nephrotoxic drugs, if possible

Amphotericin liposomal (AmBisome®) Prescribe as brand, i.e. AmBisome®	Intravenous Infusion over 30–60min	0–28 days: 3mg/kg/dose given 24-hourly. Usual max dose of 5mg/kg/dose given 24-hourly ☹	1 month to 18 years: 3mg/kg/dose given 24-hourly. Usual max dose 5mg/kg/dose given 24-hourly ☹	a. Avoid other nephrotoxic drugs, if possible
Ampicillin	By mouth	Under 7 days: 30–60mg/kg/dose given twice daily ☹ 7–21 days: 30–60mg/kg/dose given three times daily ☹ 21–28 days: 30–60mg/kg/dose given four times daily ☹	1 month to 18 years: 15–30mg/kg/dose (max 500mg) given four times daily ☹	a. Oral—to be taken on an empty stomach
	Intravenous injection	Under 7 days: 30–60mg/kg/dose given 12-hourly ☹ 7–21 days: 30–60mg/kg/dose given 8-hourly ☹ 21–28 days: 30–60mg/kg/dose given 6-hourly ☹	1 month to 18 years: 25mg/kg/dose (max 1g) given 6-hourly; may be doubled in severe infection ☹ For *Listeria* meningitis, increase the IV dose to 100mg/kg/dose (max 2g) given 4-hourly ☹	

(*Continued*)

Drug	Route	Neonatal dose	Paediatric dose	Comments
Artemether with lumefantrine (Riamet®)	By mouth Tablets	No dosing information	Body weight 5–15kg: one tablet initially, followed by five further doses of one tablet given at 8, 24, 36, 48, and 60 hours after first dose ☺ Body weight 15–25kg: two tablets initially, followed by five further doses of two tablets given at 8, 24, 36, 48, and 60 hours ☺ Body weight 25–35kg: three tablets initially, followed by five further doses of three tablets given at 8, 24, 36, 48, and 60 hours ☹ Child 12–18 years and body weight over 35kg: four tablets initially, followed by five further doses of four tablets given at 8, 24, 36, 48, and 60 hours ☹	a. Total of six tablets over 60 hours
Atazanavir	By mouth	No dosing information	15–20kg: 150mg once daily, with ritonavir 80–100mg once daily ☺ 20–40kg: 200mg once daily, with ritonavir 100mg once daily ☺ >40kg: 300mg once daily, with ritonavir 100mg once daily ☺	a. Give with food b. Avoid indigestion remedies and gastric acid suppressant c. Always check potential drug interactions between antiretrovirals and other medicines—see <http://www.hiv-druginteractions.org>

Atripla® Tenofovir + emtricitabine + efavirenz	By mouth Tablets—one tablet contains tenofovir 300mg + emtricitabine 200mg + efavirenz 600mg	No dosing information	12–18 years: individual tenofovir, emtricitabine, and efavirenz—max dose as for adults, one tablet once daily	a. Give on empty stomach (2 hours after food) b. Do not cut c. Always check potential drug interactions between antiretrovirals and other medicines—see J <http://www.hiv-druginteractions.org>
Atovaquone	By mouth	No dosing information	1–3 months: 15mg/kg/dose given twice daily ☹ 2–24 months: 22.5mg/kg/dose given twice daily ☹ >24 months: 15mg/kg/dose given twice daily 😐	a. Give with food
Atovaquone/ proguanil	By mouth Tablets: PAEDIATRIC tablet proguanil 25mg + atovaquone 62.5mg STANDARD tablet proguanil 100mg + atovaquone 250mg	No dosing information	Treatment of malaria 5–9kg: two paediatric tablets given once daily for 3 days 😐 9–11kg: three paediatric tablets given once daily for 3 days 😐 11–21kg: one standard tablet given once daily for 3 days 😐 21–31kg: two standard tablets given once daily for 3 days 😐 31–40kg: three standard tablets given once daily for 3 days 😐 >40kg: four standard tablets given once daily for 3 days 😐	a. Reduce dose in renal impairment

(*Continued*)

Drug	Route	Neonatal dose	Paediatric dose	Comments
Azithromycin	By mouth	No dosing information	<15kg: 10mg/kg/dose given once daily (max 500mg/dose) for 3 days ☺ 15–25kg: 200mg once daily for 3 days ☺ 26–35kg: 300mg once daily for 3 days ☺ 36–45kg: 400mg once daily for 3 days ☺ >45kg: 500mg once daily for 3 days ☺ Uncomplicated genital chlamydial infection and non-gonococcal urethritis 12–18 years: 1g as a single dose ☹ Lyme disease, mild to moderate typhoid 6 months to 18 years: 10–15mg/kg/dose given once daily (max 500mg/dose) for 7–10 days ☺	
Aztreonam	Intravenous	0–7 days: 30mg/kg/dose given 12-hourly ☹ 7–28 days: 30mg/kg/dose given 6- to 8-hourly ☹	1 month to 2 years: 30mg/kg/dose given 6- to 8-hourly ☹ 2–18 years: 30mg/kg/dose given 8-hourly (increase to 50mg/kg/dose 6-hourly in severe infection and cystic fibrosis. Max 2g/dose) ☹	
Benzathine benzylpenicillin	Intramuscular	>1200g: 50 000U/kg/dose given once per week ☹	1 month to 18 years: 50 000U/kg/dose given once per week ☹	

Benzylpenicillin	Intravenous injection or infusion	Under 7 days: 25mg/kg/dose given 12-hourly ☹ 7–28 days: 25mg/kg/dose given 8-hourly ☹ Double dose in severe infections ☹ Neonatal meningitis—75mg/kg/dose given 8-hourly ☹	1 month to 18 years: 25mg/kg/dose given 6-hourly Double dose in severe infection to 50mg/kg/dose up to 4- to 6-hourly ☹	a. Give doses of >50mg/kg over longer administration times
Carbenicillin	By mouth	No dosing information	1 month to 18 years: 7.5–12.5mg/kg/dose given four times daily (max 750mg/dose given four times daily) ☹	
Caspofungin	Intravenous Infusion over 60min	0–28 days: 25mg/m^2/dose given 24-hourly 😐	1–3 months: 25mg/m^2/dose given 24-hourly 😐 3–12 months: 50mg/m^2/dose given 24-hourly 😐 1–18 years: 70mg/m^2 on day 1, followed by 50mg/m^2/dose given 24-hourly on subsequent days 😐 Max dose 70mg/dose	a. Incompatible with glucose solutions
Cefaclor	By mouth	7–28 days: 15mg/kg/dose given twice daily ☹	1 month to 18 years: 7–14mg/kg/dose given three times daily ☹	

(*Continued*)

Drug	Route	Neonatal dose	Paediatric dose	Comments
Cefadroxil	By mouth	No dosing information	1 month to 18 years: 12.5–25mg/kg/dose given twice daily ☹ (max 1g/dose)	
Cefalexin	By mouth	<7 days: 25mg/kg/dose given twice daily 😐 7–21 days: 25mg/kg/dose given three times daily 😐 21–28 days: 25mg/kg/dose given four times daily 😐 Max dose of 125mg/dose	1 month to 18 years: 12.5–25mg/kg/dose given twice daily (max 1.5g) given four times daily ☹	
Cefixime	By mouth	No dosing information	6 months to 18 years: 5–8mg/kg/dose given once daily ☹ (max 400mg/dose)	
Cefotaxime	Intravenous injection or infusion	<7 days: 25–50mg/kg/dose given 12-hourly 7–21 days: 25–50mg/kg/dose given 8-hourly 21–28 days: 25–50mg/kg/dose given 6-hourly 😐	1 month to 18 years: 50mg/kg/dose given 6- to 8-hourly 😐 (max 4g/dose given 8-hourly) Gonorrhoea in 12–18 years: 500mg as single dose ☹	

Cefradine	By mouth	No dosing information	7–18 years: 12.5–25mg/kg/dose given 6- to 12-hourly ☹ (max 1g/dose given four times daily)	
Ceftazidime	Intravenous injection or infusion	Under 7 days: 25–50mg/kg/dose given 24-hourly ☹ 7–21 days: 25–50mg/kg/dose given 12-hourly 😐 21–28 days: 25–50mg/kg/dose given 8-hourly ☹	1 month to 18 years: 25–50mg/kg/dose (max 2g/dose) 😐	
Ceftriaxone	Intravenous or intramuscular injection or infusion	0–28 days: 25–50mg/kg/dose given once daily 😐	1 month to 18 years: 50–80mg/kg/dose given once daily (max 80mg/kg daily or 4g daily) 😐 Meningitis—80mg/kg/dose given once daily	a. Ceftriaxone is not recommended in premature neonates b. Doses over 50mg/kg must be infused over 60min c. Do not give with calcium-containing salts as risk of precipitation

(*Continued*)

Drug	Route	Neonatal dose	Paediatric dose	Comments
Cefuroxime	By mouth	No dosing information	3 months to 18 years: 10–15mg/kg/dose given twice daily (max 500mg/dose given twice daily) 😐	a. Oral—to be taken with food
	Intravenous injection or infusion	Under 7 days: 25–50mg/kg/dose given 12-hourly ☹ 7–21 days: 25–50mg/kg/dose given 8-hourly ☹ 21–28 days: 25–50mg/kg/dose given 6-hourly ☹	1 month to 18 years: 20–60mg/kg/dose given 6- to 8-hourly (max 1.6g/dose) 😐	
Cidofovir	Intravenous	No dosing information	1 month to 18 years: 5mg/kg/dose given once a week ☹	a. With probenicid and hydration
Ciprofloxacin	By mouth	0–28 days: 10–15mg/kg/dose given twice daily ☹	1 month to 18 years: 15mg/kg/dose given 12-hourly (max 750mg/dose) 😐	a. Oral—not to be used with preparations containing zinc, iron, milk, or indigestion remedies b. Use with caution in children with epilepsy, G6PD deficiency, myasthenia gravis
	Intravenous Infusion over 60min	Birth to 28 days: 6–10mg/kg/dose given 12-hourly ☹	1 month to 18 years: 10mg/kg/dose 8- to 12-hourly (max 400mg/dose) 😐	

Chloramphenicol	Intravenous	0–14 days: 12.5mg/kg/dose given 12-hourly ☹ 14–28 days: 12.5mg/kg/dose given 6- to 8-hourly ☹	1 month to 18 years: 12.5–25mg/kg/dose given 6-hourly ☹	a. Plasma chloramphenicol levels should be monitored when using double doses. Assess neonates for grey baby syndrome
Chloroquine	By mouth	No dosing information	1 month to 18 years: 10mg/kg loading dose (max 620mg), then 6–8 hours later give a single dose of 5mg/kg (max 310mg), then 5mg/kg/dose (max 310mg) given once daily for 2 days ☺	a. Doses are expressed as chloroquine base
Clarithromycin	By mouth	Birth to 28 days: 7.5mg/kg/dose given twice daily ☹	1 month to 18 years: 7.5–15mg/kg/dose (max 500mg) given twice daily ☹	
	Intravenous	Birth to 28 days: 7.5mg/kg/dose given 12-hourly ☹	1 month to 18 years: 7.5mg/kg/dose (max 500mg) given 12-hourly ☹	
Clindamycin	By mouth	0–14 days: 3–6mg/kg three times daily ☹ 14–28 days: 3–6mg/kg four times daily ☹	1 month to 18 years: 6mg/kg/dose given four times daily (body weight under 10kg, minimum dose 37.5mg three times daily) ☹	
	Intravenous Infusion	No dosing information	1 month to 18 years: 6–10mg/kg/dose given 6-hourly (max 1.2g/dose) ☹	

(*Continued*)

Drug	Route	Neonatal dose	Paediatric dose	Comments
Co-amoxiclav	By mouth Expressed as amoxicillin/clavulanic acid	0–28 days: 0.25mL/kg of 125/31 suspension three times daily ☹	1 month to 6 years: 0.25–0.5mL/kg/dose of 125/31 suspension three times daily ☹ 6–12 years: 0.15–0.3mL/kg/dose of 250/62 suspension three times daily ☹ 12–18 years: one 250/62 strength tablet three times daily; increased in severe infections to one 500/125 strength tablet three times daily ☹	
	By mouth Augmentin® Duo Suspension		2 months to 18 years: 0.15–0.2mL/kg/dose of 400/57 suspension given twice daily ☹	
	Intravenous Expressed as amoxicillin/clavulanic acid combined Injection	0–28 days: 30mg/kg/dose given 12-hourly ☹	1–3 months: 30mg/kg/dose given 8-hourly. ☹ 3 months to 18 years: 30mg/kg/dose given 6- to 8-hourly (max 1.2g/dose) 😐	
Colchicine	By mouth	No dosing information	1 month to 18 years: 20–30 micrograms/kg/dose (max 2mg/dose) given once daily ☹	a. Avoid in patients with blood dyscrasias b. Use in caution in patients with reduced renal function to avoid neuromuscular toxicity and bone marrow dysplasia

Colistin	Intravenous Injection	No dosing information	1 month to 18 years: Body weight under 60kg: 25 000 units/kg/dose given 8-hourly ☹ Body weight over 60kg: 2 million units/dose given 8-hourly ☹	
	Nebulized	No dosing information	1 month to 2 years: 500 000–1 million units/dose given 12-hourly; increased to 1 million units 8-hourly for isolates of *P. aeruginosa* ☹ 2–18 years: 1–2 million units/dose given 12-hourly; increased to 2 million units 8-hourly for respiratory isolates of *P. aeruginosa* ☹	
Co-trimoxazole	By mouth	No dosing information	6 weeks to 18 years: 24mg/kg/dose (max 960mg) given twice daily ☹ Treatment of *Pneumocystis jirovecii* (*P. carinii*) pneumonia (PCP) 6 weeks to 18 years: 60mg/kg/dose given twice daily ☹ Prophylaxis of *Pneumocystis jirovecii* (*P. carinii*) 6 weeks to 18 years: 30mg/kg/dose given once daily ☹	a. 480mg of co-trimoxazole consists of sulfamethoxazole 400mg and trimethoprim 80mg b. Monitor blood counts on prolonged treatment, and discontinue if blood disorders or rash develop
	Intravenous Infuse over 60–90min	No dosing information	Treatment of *Pneumocystis jirovecii* (*P. carinii*) infections: same as oral dose above ☹	

(*Continued*)

Drug	Route	Neonatal dose	Paediatric dose	Comments
Cycloserine	By mouth	No dosing information	2–18 years: 5mg/kg/dose given twice daily (max 250mg) ☹	a. Adjust dose, based on blood concentration and response b. Peak concentration (at 3–4 hours post-dose) should not exceed 30mg/L
Dapsone	By mouth	No dosing information	1 month to 18 years: 2.5mg/kg/dose (max 100mg) given once daily ☺	a. Possible haemolysis in G6PD deficient patients b. Avoid in acute porphyria
Darunavir	By mouth	No dosing information	20–30kg: 375mg/dose given twice daily, with ritonavir 50mg/dose given twice daily 😐 30–40kg: 450mg/dose given twice daily, with ritonavir 60mg/dose given twice daily 😐 >40kg: 600mg/dose given twice daily, with ritonavir 100mg/dose given twice daily 😐	
Didanosine	By mouth	No dosing information	1–3 months: 50–100mg/m^2 /dose given 12-hourly 😐 >3 months: 200mg/m^2/dose given once daily 😐 (max <60kg = 250mg given once daily; max >60kg = 400mg given once daily)	a. Give on empty stomach (2 hours after, and 1 hour before, food or milk) b. Caps can be opened and sprinkled on a spoonful of food, e.g. yoghurt, but decrease in AUC c. Do not co-administer with tenofovir

Diethylcarbamazine	By mouth	No dosing information	1 month to 18 years: 0.3mg/kg/dose given three times daily Increase dose gradually over 3 days to 2mg/kg/dose given three times daily (<10 years maintenance dose of 1mg/kg/dose given three times daily)	a. Febrile reactions are possible in heavy infections b. Encephalopathy is possible in loa loa infection
Diloxanide	By mouth	No dosing information	1 month to 18 years: 7mg/kg/dose (max 500mg/dose) given three times daily ☹	a. Treat for 10 days, and repeat course if necessary
Doxycycline	By mouth	No dosing information	12–18 years: 200mg loading dose, then 100mg/dose given twice daily ☹	a. Antacids and products containing aluminium, calcium, iron, magnesium, and zinc salts, and milk may reduce the absorption of demeclocycline b. Do not give to children under 12 years or pregnant or breastfeeding women, as deposits in growing bones and teeth

(*Continued*)

Drug	Route	Neonatal dose	Paediatric dose	Comments
Efavirenz	By mouth	No dosing information	Children >3 months— capsules (or liquid) dosing 3.5–5kg: 100mg given once daily (capsules) ☺ 5–7.5kg: 150mg given once daily (capsules) ☺ 7.5–15kg: 200mg given once daily (liquid 270mg) ☺ 15–20kg: 250mg given once daily (liquid 300mg) ☺ 20–25kg: 300mg given once daily (liquid 360mg) ☺ 25–32.5kg: 350mg given once daily (liquid 450mg) ☺ 32.5–40kg: 400mg given once daily (liquid 510mg) ☺ >40kg: 600mg given once daily (liquid 720mg) ☺	a. Preferably given before bedtime b. Liquid is not bioequivalent to tablets or capsules c. Always check potential drug interactions between antiretrovirals and other medicines—see <http://www.hiv-druginteractions.org> d. There is no PK data on the liquid in children <13kg—use the capsules.

Emtricitabine	By mouth	No dosing information	≥4 months: 6mg/kg/dose given once daily of the oral solution (max dose 240mg once daily) 😐 ≥33kg: 200mg given once daily as capsule; 240mg once daily of the oral solution 😐	a. Can be administered with food b. Liquid is not bioequivalent to tablets or capsules
Enfuvirtide	Subcutaneous injection	No dosing information	6–18 years: 2mg/kg/dose given 12-hourly (max dose 90mg/dose) ☹	
Ertapenem	Intravenous Infusion	No dosing information	3 months to 13 years: 15mg/kg given 12-hourly (max 1g daily) 😐 13–18 years: 1g once daily ☹	a. Incompatible with glucose solutions
Erythromycin	By mouth	0–28 days: 12.5mg/kg/dose given four times daily ☹	1 month to 18 years: 12.5–25mg/kg/dose (max 1g) given four times daily ☹	a. Check for drug interactions b. Use with caution in impaired liver function and severe renal impairment c. Intravenous doses to be diluted to 1–5mg/mL with sodium chloride 0.9% and infused over 20–60min. Concentrations of up to 10mg/mL may be used via central administration. Do not dilute with glucose solutions, unless buffered with sodium bicarbonate
	Intravenous Infusion	0-28 days: 10–12.5mg/kg/dose given 6-hourly ☹	1 month to 18 years: 12.5mg/kg/dose (max 1g) given 6-hourly ☹	

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Drug	Route	Neonatal dose	Paediatric dose	Comments
Ethambutol	By mouth	0–28 days: 20mg/kg/dose given once daily for 2 months during the initial phase of TB treatment (used in combination with other antibiotics) ☹	1 month to 18 years: 20mg/kg/dose given once daily (for 2-month initial phase) 😐 OR 30mg/kg/dose given three times a week ☹ (for 2-month initial phase)	a. Toxic effects, including visual disturbances commoner where excessive dosage is used or if renal function impaired
Ethionamide	By mouth	No dosing information	Treatment of TB 1 month to 18 years: 15–20mg/kg/dose (max 1g) given once daily 😐 Leprosy 1 month to 18 years: 5–8mg/kg/dose (max 375mg) given once daily ☹	a. Administer with food to reduce GI distress b. Neurotoxic effects may be relieved by administration of pyridoxine
Etravirine	By mouth Tablets	No dosing information	Adult: 200mg/dose given twice daily 😐	a. Take with food (AUC decreased by 50% if taken on empty stomach) b. Tablet disperses in water c. Always check potential drug interactions between antiretrovirals and other medicines—see <http://www.hiv-druginteractions.org>
Famciclovir	By mouth	No dosing information	6–18 years: 10–15mg/kg/dose (max 250mg) given three times daily ☺	

Flucloxacillin	By mouth	Under 7 days: 25mg/kg/dose given twice daily ☹ 7–21 days: 25mg/kg/dose given three times daily ☹ 21–28 days: 25mg/kg/dose given four times daily ☹	1 month to 18 years: 25mg/kg/dose (max 500mg) given four times daily 😐	a. Very rarely, cholestatic jaundice and hepatitis may occur up to several weeks after treatment with flucloxacillin has stopped. Risk is increased with prolonged courses b. Rash, fever, neutropenia occur with higher doses and prolonged treatment
	Intravenous Infection: vials (intravenous or injection or infusion)	As above Severe infection: use 50mg/kg/dose ☹	1 month to 18 years: 25–50mg/kg/dose (max 2g) given 6-hourly 😐	
Fluconazole	By mouth	Under 14 days: 6–12mg/kg/dose given every 72 hours 😐 14–28 days: 6–12mg/kg/dose given every 48 hours 😐	1 month to 18 years: 6–12mg/kg/dose (max 400mg) given every 24 hours 😐	a. Caution when used alongside hepatotoxic drugs—increased risk of hepatotoxicity
	Intravenous Infuse over 10–30min	Under 14 days: 6–12mg/kg/dose given every 72 hours 😐 14–28 days: 6–12mg/kg every 48 hours 😐	1 month to 18 years: 6–12mg/kg/dose (max 400mg) given every 24 hours 😐	

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Drug	Route	Neonatal dose	Paediatric dose	Comments
Flucytosine	Intravenous Infuse over 20–40min	0–28 days: 50mg/kg/dose given 12-hourly ☹	Systemic yeast and fungal infections 1 month to 18 years: 50mg/kg/dose given 6-hourly ☹ Cryptococcal meningitis 1 month to 18 years: 25mg/kg/dose given 6-hourly for 2 weeks 😐	a. Monitor renal and liver function and blood counts
Fosamprenavir	By mouth	No dosing information	25–32kg: 18mg/kg/dose given with ritonavir 3mg/kg per dose given twice daily 😐 33–38kg: (tablet or oral suspension) 18mg/kg/dose given with ritonavir 100mg per dose given twice daily 😐 ≥39kg: (tablet or oral suspension) 700mg given with ritonavir 100mg per dose given twice daily 😐	a. Give with or after food to aid palatability of liquid
Foscarnet	Intravenous Infuse over at least 60min	No dosing information	1 month to 18 years: 60mg/kg/dose given 8-hourly for 2–3 weeks, then 60mg/kg/dose given once daily as maintenance (increase maintenance to 90–120mg/kg/dose given once daily, if tolerated) ☹	a. Repeat induction regimen for CMV retinitis if retinitis progresses while on maintenance dose b. Monitor electrolytes, especially calcium and magnesium c. Monitor renal function regularly, and adjust dose in renal impairment

Fusidic acid	By mouth Suspension	0–28 days: 15mg/kg/dose given three times daily ☹	1 month to 18 years: 15mg/kg/dose (max 750mg) given three times daily ☹	
	By mouth (as sodium fusidate) Tablets	No dosing information	12–18 years: 500mg to 1g/dose given three times daily ☹	
	Intravenous (as sodium fusidate)	0–28 days: 10mg/kg/dose given 12-hourly ☹	1 month to 18 years: 6–7mg/kg/dose (max 500mg) given 8-hourly ☹	
Ganciclovir	Intravenous Infuse over 60min	Congenital CMV 0–28 days: 6mg/kg/dose given 12-hourly ☹	1 month to 18 years: 5mg/kg/dose given 12-hourly ☹	
Gentamicin	Intravenous Injection over 3–30min	<32 weeks corrected gestation: 5mg/kg/dose given 36-hourly ☺ >32 weeks corrected gestation: 5mg/kg/dose given 24-hourly 😐	1 month to 18 years: 7mg/kg/dose given once daily 😐	a. Intravenous administration—pre-dose (trough) plasma concentrations should be: <1mg/L for children >1 month; <2mg/L for neonates b. Neonates, infants, and those with renal impairment should have renal, auditory, and vestibular function monitored, together with serum gentamicin concentrations
Griseofulvin	By mouth	No dosing information	1 month to 18 years: 10–20mg/kg/dose (max 500mg) given once daily ☹	a. Avoid in acute porphyria, patients with severe liver disease, and those with systemic lupus erythematosus

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Drug	Route	Neonatal dose	Paediatric dose	Comments
Halofantrine	By mouth	No dosing information	1 month to 18 years: 10mg/kg/dose (max 500mg) given every 6 hours (three doses) ☹	
Imipenem	Intravenous Infuse over 20–60min	<7 days: 15mg/kg/dose given 12-hourly ☺ 7–21 days: 15mg/kg/dose given 8-hourly ☺ 21–28 days: 15mg/kg/dose given 6-hourly ☺ Where *Pseudomonas* suspected: 25mg/kg/dose given 8-hourly ☺	1–3 months: 20mg/kg/dose given 8-hourly ☹ 3 months to 18 years: 15mg/kg/dose (max 500mg) given 6-hourly ☹ In children >12 years, the dose may be doubled in severe infection to 1g ☹ Where *Pseudomonas* suspected, 25mg/kg given 6-hourly ☹	a. Avoid in CNS disorders (e.g. epilepsy) b. Avoid in patients taking MAOIs
Isoniazid	By mouth Tablet Liquid: extemporaneous liquid formulations may be available	0–28 days: 10mg/kg/dose given once daily 😐	Treatment of TN 1 month to 18 years: 10mg/kg/dose (max 300mg) given once daily 😐 OR 15mg/kg/dose (max 900mg) given three times a week ☹	a. Increased risk of side effects in patients with slow acetylator status b. Possible peripheral neuritis with high doses and in breastfed infants—consider pyridoxine prophylaxis
	Intravenous	0–28 days: 10mg/kg/dose given 24-hourly 😐	1 month to 18 years: 10mg/kg/dose (max 300mg) given 24-hourly 😐	c. Seek immediate medical attention if symptoms of liver toxicity such as persistent nausea, vomiting, malaise, or jaundice develop

Itraconazole	By mouth	No dosing information	1 month to 18 years: 2.5–5mg/kg/dose (max 200mg) given once daily 😐	a. Capsules have extremely poor bioavailability; use liquid in preference as oral preparation b. Avoid in hepatic impairment, if possible, and discontinue if signs of hepatitis develop
	Intravenous Infuse over 60min	No dosing information	1 month to 18 years: 2.5mg/kg/dose (max 200mg) given 12-hourly for 2 days, then 2.5mg/kg/dose (max 200mg) given 24-hourly for max of 12 days 😐	
Ivermectin	By mouth	No dosing information	*Strongyloides stercoralis* 5–18 years: 200 micrograms/kg/dose given once daily for 2 days ☹ Onchocerciasis 5–18 years: 150 micrograms/kg/dose given as a single dose Repeat every 6–12 months for 10 years ☹	a. Do not eat food 2 hours either side of the dose b. Avoid in CNS disorders (e.g epilepsy) c. Monitor for ophthalmic and other hypersensitivity reactions when onchocerciasis is being treated
Ketoconazole	By mouth	No dosing information	Body weight 15–30kg: 100mg/dose given once daily ☹ Body weight over 30kg: 200mg/dose given once daily (increase to 400mg, if necessary) ☹	a. Risk of hepatotoxicty increased if used for >10 days. Monitor liver function pre-treatment, and at weeks 2 and 4 of treatment, then monthly
Lamivudine	By mouth	0–28 days: 2mg/kg/dose given twice daily 😐	1 month to 18 years: 4mg/kg/dose (max 150mg) given twice daily 😊 >3 years: Can be given as 8mg/kg/dose (max 300mg) given once daily 😐	

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Drug	Route	Neonatal dose	Paediatric dose	Comments
Levamisole	By mouth	No dosing information	1 month to 18 years: 2.5mg/kg/dose (max 150mg) given as a single dose for roundworm or hookworm ☹	a. For hookworm, the dose can be repeated after 7 days, if necessary
Linezolid	By mouth	<7 days: 10mg/kg/dose given twice daily (increase to three times daily if poor response) ☹ 7–28 days: 10mg/kg/dose given three times daily ☹	1 month to 12 years: 10mg/kg/dose (max 600mg) given three times daily ☹ 12–18 years: 600mg/dose given twice daily ☹	a. FBC should be monitored weekly for patients receiving treatment for >10 days, who have pre-existing myelosuppression, severe renal impairment, or receiving concomitant drugs that have adverse effects on blood count, haemoglobin, or platelet function
	Intravenous Infusion over 30–120min	<7 days: 10mg/kg/dose given 12-hourly (increase to 8-hourly if poor response) 😐 7–28 days: 10mg/kg/dose given 8-hourly 😐	1 month to 12 years: 10mg/kg/dose (max 600mg) given 8-hourly 😐 12–18 years: 600mg/dose given 12-hourly ☹	b. Visual function should be monitored regularly if treatment is required for longer than 28 days
Lopinavir (LPV/r)	By mouth	14–28 days: 300mg/m^2/dose given twice daily ☹	1–6 months: 300mg/m^2/dose given twice daily 😐 ≥6 months: 250–300mg/m^2/dose (max 400mg) given twice daily 😐	a. Liquid—give with or after food

Maraviroc	By mouth Tablets	No dosing information	No dosing information ☹ Adult: 300mg/dose given 12-hourly ☺	a. Profile assay for co-receptor tropism b. Pharmacy advice on dosing with potentially interacting drugs c. Always check potential drug interactions between antiretrovirals and antiretrovirals and other medicines—see 🖱 <http://www.hiv-druginteractions.org>
Mebendazole	By mouth	No dosing information	Threadworms 6 months to 18 years: 100mg given as a single dose ☹ Whipworms, roundworms, and hookworms 1–18 years: 100mg/dose given twice daily for 3 days ☹	a. For threadworms, the dose can be repeated after 2 weeks, if necessary.

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Drug	Route	Neonatal dose	Paediatric dose	Comments
Mefloquine	By mouth	No dosing information	Treatment (rarely used) 3 months to 18 years: 15mg/kg/dose (max 750mg) given as a single dose, then 10mg/kg/dose (max 500mg) given as a single dose 6–8 hours later ☹ Prophylaxis (started 2–3 weeks before entering endemic area, and continued for 4 weeks after leaving) 5–18kg: 62.5mg once weekly ☹ 16–25kg: 125mg once weekly ☹ 25–45kg: 187.5mg once weekly ☹ >45kg: 250mg once weekly ☹	a. Prophylaxis can be taken for up to 1 year b. Avoid in patients with cardiac conductive disorders, epilepsy, and children under 3 months (5kg)
Meropenem	Intravenous Infuse over 15–30min	Under 7 days: 40mg/kg/dose given 12-hourly 😐 7–28 days: 40mg/kg/dose given 8-hourly 😐	1 month to 12 years: 10–40mg/kg/dose (max 500mg) given 8-hourly ☺	a. Avoid if history of immediate hypersensitivity to β-lactam antibacterials
Metronidazole	By mouth	0–28 days: 7.5mg/kg/dose given 12-hourly 😐	1 month to 18 years: 7.5mg/kg/dose (max 400mg) given three times daily ☹	a. Take tablets with or after food, but suspension should be taken on an empty stomach b. Disulfiram-like reaction with alcohol
	Intravenous Infuse over 20–30min	Same as oral	Same as oral	

Micafungin	Intravenous Infusion over 60min	Treatment 0–28 days: 2–4mg/kg/dose given 24-hourly ☹ Prophylaxis 0–28 days: 1mg/kg/dose given 24-hourly ☹	Treatment 1 month to 18 years: 2–4mg/kg/dose (max 100mg) given 24-hourly ☹ Prophylaxis 1 month to 18 years: 1mg/kg/dose (max 50mg) given 24-hourly ☹	a. Monitor liver function, and discontinue if significant and persistent abnormalities
Miconazole	By mouth Oral gel	0–28 days: 1mL applied topically to mouth 2–4 times daily ☹	1 month to 2years: 2.5mL smeared around mouth twice daily after food ☹ 2–6 years: 5mL twice daily after food ☹ 6–12 years: 5mL four times daily after food ☹ 12–18 years: 5–10mL four times daily after food (retain near lesions before swallowing) ☹	a. Antacids and products containing aluminium, calcium, iron, magnesium, and zinc salts, and milk may reduce the absorption of demeclocycline b. Do not give to children under 12 years, or pregnant or breastfeeding women, as deposits in growing bones and teeth
Minocycline	By mouth	No dosing information	Child 12–18 years: 100mg/dose given twice daily ☹	a. Antacids and products containing aluminium, calcium, iron, magnesium, and zinc salts, and milk may reduce the absorption of demeclocycline b. Do not give to children under 12 years, or pregnant or breastfeeding women, as deposits in growing bones and teeth

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Drug	Route	Neonatal dose	Paediatric dose	Comments
Nalidixic acid	By mouth	No dosing information	3 months to 12 years: 12.5mg/kg/dose given four times daily for 7 days, reduced to 7.5mg/kg/dose given four times daily in prolonged therapy 12–18 years: 900mg/dose given four times daily for 7 days, reduced in chronic infections to 600mg/dose given four times daily	
Nevirapine	By mouth	Post-exposure prophylaxis for baby born to HIV-positive mother Refer to <http://www.bhiva.org> 0–14 days: 2mg/kg/dose given once daily for first week, then 4mg/kg/dose given once daily for second week, then stop ☺ (If mother has received >3 days of nevirapine therapy immediately before delivery, dose in neonate 4mg/kg/dose given once daily for 2 weeks, then stop) ☹	>14 days: 150–200mg/m^2/dose given once daily for 2 weeks, then 150–200mg/m^2/dose given twice daily (max dose 200mg/dose twice daily) ☺ >12 years: 200mg/dose given once daily for 14 days, then increase to 200mg/dose given twice daily if no rash or LFT abnormalities ☹	a. Always check potential drug interactions between antiretrovirals and other medicines—see <http://www.hiv-druginteractions.org>

Niclosamide	By mouth	No dosing information	Pork, beef, fish tapeworms 1 month to 2 years: 500mg given as a single dose ☹ 2–7 years: 1g given as a single dose ☹ 7–18 years: 2g given as a single dose ☹ Dwarf tapeworm 1 month to 2 years: 500mg given on day 1, then 250mg given daily for 6 days ☹ 2–7 years: 1g given on day 1, then 500mg given daily for 6 days ☹ 7–18 years: 2g given on day 1, then 1g given daily for 6 days ☹	
Nitrofurantoin	By mouth	No dosing information	Treatment 3 months to 18 years: 1mg/kg/dose (max 100mg) given four times daily ☹ Prophylaxis 3 months to 18 years: 1mg/kg/ dose (max 100mg) given once daily ☹	a. Contraindicated in G6PD deficiency
Nystatin	By mouth 100 000U/mL	0–28 days: 1mL given four times daily ☹	1 month to 12 years: 1mL given four times daily (immunocompromised children may require higher doses, e.g. 5mL four times daily) ☹ 12–18 years: 5mL given four times daily (doubled in severe infections) ☹	a. Give after feeds

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Drug	Route	Neonatal dose	Paediatric dose	Comments
Oseltamivir	By mouth	0–28 days: 2mg/kg twice daily 😐	1–3 months: 2.5mg/kg/dose given twice daily 😐 3 months to 1 year: 3mg/kg/dose given twice daily 😐 6–12 months: 3mg/kg/dose given twice daily ☹ 1–13 years: Under 15kg: 30mg/dose given twice daily ☹ 15–23kg: 45mg/dose given twice daily ☹ 23–40kg: 60mg/dose given twice daily ☹ Over 40kg: 75mg/dose given twice daily ☹ 13–18 years: 75mg/dose given twice daily ☹ * Treatment is for 5 days. Prophylaxis can be given for 10 days using the above doses once daily	a. If suspension not available, capsules can be opened, and the contents mixed with a small amount of food, just before administration
Oxytetracycline	By mouth	No dosing information	12–18 years: 250–500mg/dose given four times daily	a. Antacids and products containing aluminium, calcium, iron, magnesium, and zinc salts, and milk may reduce the absorption of demeclocycline b. Do not give to children under 12 years, or pregnant or breastfeeding women, as deposits in growing bones and teeth

Palivizumab	Intramuscular	0–28 days: 15mg/kg/dose given once a month during season of RSV risk ☺	1 month to 2 years: 15mg/kg/dose given once a month as prophylaxis only during season of RSV risk ☺	a. Divide injection volumes over 1mL between two or more sites
Paromomycin	By mouth	No dosing information	2–18 years: 8–12mg/kg/dose given three times daily for 5–10 days ☹	
Pentamidine	Intravenous Infuse over 60min Intramuscular	No dosing information	1 month to 18 years: 4mg/kg/dose given 24-hourly ☹	a. Risk of severe hypotension following administration b. Avoid concomitant use of other nephrotoxic drugs c. Use a nebulized bronchodilator before nebulizing pentamidine
	Nebulized	No dosing information	1 month to 18 years Treatment 600mg/dose given daily for 3 weeks ☹ Prophylaxis 300mg/dose given 4-weekly ☹	
Phenoxymethyl-penicillin (penicillin V)	By mouth	No dosing information ☹	1 month to 18 years: 15mg/kg/dose (max 1g) given four times daily ☹	
Piperacillin with tazobactam	Intravenous Injection or infusion Dose expressed as combination of piperacillin and tazobactam combined	0–28 days: 90mg/kg/dose given 8-hourly ☹	Dose expressed as combination of piperacillin and tazobactam combined 1 month to 18 years: 90mg/kg/dose (max 4.5g) given 6- to 8-hourly ☹	

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Drug	Route	Neonatal dose	Paediatric dose	Comments
Piperazine	By mouth Oral powder	No dosing information	3 months to 1 year: one level 2.5mL spoonful given as a single dose ☹ 1–6 years: one level 5mL spoonful given as a single dose ☹ 6–18 years: contents of one sachet given as a single dose ☹	a. For threadworms, repeat the dose after 14 days b. Take the dose in the morning
Pivmecillinam	By mouth	No dosing information	Acute uncomplicated cystitis Over 40kg: initially 400mg as single dose, then 200mg/dose given three times daily for 3 days ☹ Chronic or recurrent bacteriuria <40kg: 5–10mg/kg/dose given four times daily ☹ >40kg: 400mg/dose given 3–4 times daily ☹	
Posaconazole	By mouth or intravenously	No dosing information	>12 years: 200mg/dose given four times daily 😐	
Praziquantel	By mouth	No dosing information	Over 4 years: 20mg/kg, followed after 4–6 hours by a further dose of 20mg/kg (20mg/kg three times daily for 1 day for *S. japonicum* infections) ☹	a. Take doses after light breakfast

Primaquine	By mouth	No dosing information	*P. ovale* treatment 6 months to 18 years: 250 micrograms/kg/dose (= 0.25mg/kg/dose) (max 15mg) given once daily ☹ *P. vivax* treatment 6 months to 18 years: 500 micrograms/kg/dose (= 0.5mg/kg/dose) (max 30mg) given once daily ☹	a. Treat for 14 days b. For roundworms, repeat the dose at monthly intervals for up to 3 months
Procaine penicillin	Intramuscular injection	50 000 units/kg given once daily ☹	50 000 units/kg given once daily (max 4.8 million units per day) ☹	
Proguanil with atovaquone	By mouth Paediatric and standard tablets	No dosing information ☹	Treatment of malaria 5–8kg: two 'paediatric tablets' given once daily ☹ 9–10kg: three 'paediatric tablets' given once daily ☹ 11–20kg: one 'standard tablets' given once daily ☹ 21–30kg: two 'standard tablets' given once daily ☹ 31–40kg: three 'standard tablets' given once daily Treat for 3 days ☹	a. Four paediatric tablets are equivalent to one standard tablet

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Drug	Route	Neonatal dose	Paediatric dose	Comments
Pyrazinamide	By mouth Tablet Liquid: extemporaneous liquid formulations may be available	Congenital TB 0–28 days: 35mg/kg/dose given once daily ☹	1 month to 18 years: 35mg/kg/dose (max 2g) given once daily ☹ OR 50mg/kg/dose (max 2g if <50kg or 2.5g if >50kg) given three times a week ☹	a. Seek immediate medical attention if symptoms, such as persistent nausea, vomiting, malaise, or jaundice, develop
Pyrimethamine	By mouth	Congenital toxoplasmosis 0–28 days: 1mg/kg/dose given twice daily for 2 days, then 1mg/kg/dose given once daily for 6 months, then 1mg/kg/dose given three times a week for 6 months ☹	Ocular toxoplasmosis, toxoplasmosis in immunocompromised patient 1 month to 18 years: 2mg/kg/dose once daily for 2 days, then 1mg/kg/dose given once daily for 6 weeks 😐	a. Taken in combination with sulfadiazine and folinic acid b. Check blood counts regularly
Quinine	By mouth	No dosing information	1 month to 18 years: 10mg/kg/dose (max 600mg) given three times daily ☹	
	Intravenous Infusion over 4 hours	0–28 days: 20mg/kg loading dose, then 8 hours later 10mg/kg/dose 8-hourly ☹	1 month to 18 years: 20mg/kg (max 1.4g) loading dose, then 8 hours later 10mg/kg/dose (max 700mg) given 8-hourly ☹	
Raltegravir	By mouth	No dosing information	16–18 years: 400mg/dose given twice daily 😐	a. Avoid indigestion remedies

Ribavirin	By mouth	No dosing information	Chronic hepatitis C 3–18 years: 7.5mg/kg/dose (max 600mg) given twice daily ☹	a. Contraindicated in women who are, or may become, pregnant b. Monitor FBC, platelets, electrolytes, creatinine, LFTs before and during treatment
	Intravenous Injection bolus	0–28 days: 33mg/kg single dose, then 16mg/kg/dose given 6-hourly for 4 days, then 8mg/kg/dose given 8-hourly for 3 days ☹	Life-threatening viral infection in immunocompromised children 1 month to 18 years: 33mg/kg single dose, then 16mg/kg/dose given 6-hourly for 4 days, then 8mg/kg/dose given 8-hourly for 3 days ☹	
Rifabutin	By mouth	No dosing information ☹	1–18 years: 5–7.5mg/kg/dose given once daily ☹	a. May colour body secretions red
Rifampicin	By mouth	0–28 days: 5–10mg/kg/dose given twice daily ☹ Suspected congenital TB 0–28 days: rifampicin 10mg/kg/dose given once daily for 6 months (used in combination with other antibiotics) ☹	Staphylococcal infection 1 month to 18 years: 10mg/kg/dose (max 600mg) given twice daily 😐 Treatment of TB 1 month to 18 years: 15mg/kg/dose (max 600mg) given once daily 😐 OR 15mg/kg/dose (max 900mg) given three times a week ☹	a. May colour urine red b. May colour contact lenses red c. Monitor liver function tests and blood counts in hepatic disorders, and on prolonged therapy
Rimantidine	By mouth	No dosing information	1 month to 18 years: 2.5mg/kg/dose (max 100mg) given twice daily ☹	a. Not active against influenza B

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Drug	Route	Neonatal dose	Paediatric dose	Comments
Ritonavir	By mouth Tablets Liquid	No dosing information	For boosting other PIs, see specific drug. Not recommended as a single PI	a. With or after food b. Can mask bitter taste with chocolate milk c. Always check potential drug interactions between antiretrovirals and other medicines—see <http://www.hiv-druginteractions.org>
Saquinavir	By mouth Tablets	No dosing information	No dosing information; seek specialist advice ☹	
Sodium stibogluconate	Intravenous Injection over 5min	No dosing information	1 month to 18 years: 20mg/kg/dose (max 850mg) given 24-hourly for at least 20 days ☹	
Spiramycin	By mouth	Chemoprophylaxis of congenital toxoplasmosis 0–28 days: 50mg/kg/dose given twice daily ☹	Toxoplasmosis in pregnancy 12–18 years: 1.5g/dose given twice daily until delivery ☹	a. 3000U = 1mg of spiramycin b. May prolong QT interval
Stavudine	By mouth	≤13 days: 0.5mg/kg/dose given twice daily ☹ 14–28 days: 1mg/kg/dose given twice daily ☹	<30kg: 1mg/kg/dose given twice daily ☹ 30–60kg: 30mg/dose given twice daily ☹ >60kg: 40mg/dose given twice daily ☹	a. Do not co-administer with zidovudine b. High risk of lipodystrophy

Streptomycin	Intramuscular Deep intramuscular injection	No dosing information	TB 1 month to 8 years: 15mg/kg/dose (max 1g) given 24-hourly ☹ Adjunct to doxycycline in brucellosis 1 month to 18 years: 5–10mg/kg/dose given 6-hourly ☹	a. Aim for 1 hour peak concentration of 15–40mg/L and pre-dose (trough) level of <5mg/L (<1mg/L in renal impairment) b. Change the injection site for each dose
Sulfadiazine	By mouth	Congenital toxoplasmosis 0–28 days: 50mg/kg/dose given twice daily for 12 months ☹	Toxoplasmosis 12–18 years: 50mg/kg/dose (max 1g) given twice daily for 12 months ☹	a. To be given in combination with pyrimethamine and folinic acid
Sulfadoxine/pyrimethamine (Fansidar®)	By mouth	No dosing information	Treatment of *P. falciparum* (adjunct to wuinine) 2 months to 4 years: half tablet as single dose ☹ 5–6 years: one tablet as single dose ☹ 7–9 years: one and a half tablets as single dose ☹ 10–14 years: two tablets as single dose ☹ 14–18 years: three tablets as single dose ☹	a. Avoid excessive exposure to the sun
Teicoplanin	Intravenous Injection—bolus or infusion	0–28 days: 16mg/kg for one dose, followed 24 hours later by 8mg/kg/dose once daily 😐	1 month to 18 years: 10mg/kg/dose given 12-hourly for three doses, then 10mg/kg/dose (max 200mg) given once daily 😐	a. By intravenous infusion only in neonates

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Drug	Route	Neonatal dose	Paediatric dose	Comments
Tenofovir	By mouth	No dosing information	2–8 years: 8mg/kg/dose given once daily 😐 >8 years: 210mg/m²/dose (max 300mg) given once daily 😐	a. Do not co-administer with didanosine
Terbinafine	By mouth	No dosing information	1–18 years: 6mg/kg/dose (max 250mg) given once daily 😐	a. Oral treatment is usually 4 weeks for tinea capitis; 2–6 weeks for tinea pedis; 2–4 weeks for tinea cruris; 4 weeks for tinea corporis; 6 weeks to 3 months for nail infections
Tetracycline	By mouth	No dosing information	12–18 years: 250–500mg/dose given four times daily ☹	
Tiabendazole	By mouth	No dosing information	1 month to 18 years: 25mg/kg/dose (max 1.5g) given twice daily ☹	
Ticarcillin (ticarcillin/clavulanic acid)	Intravenous Infuse over 30–40min Dose expressed as combination of ticarcillin and clavulanic acid combined	Under 2kg: 80mg/kg/dose given 12-hourly 😐 >2kg: 80mg/kg/dose given 8-hourly (increased to 6-hourly in severe infection) 😐	1 month to 18 years (<40kg): 80mg/kg/dose given 8-hourly (increased to 6-hourly in severe infection) 😐 Child <18 years and >40kg: 80mg/kg/dose (max 3.2g) given 6- to 8-hourly (increased to 4-hourly in severe infection) 😐	a. Antacids and products containing aluminium, calcium, iron, magnesium, and zinc salts, and milk may reduce the absorption of tetracycline b. Do not give to children under 12 years, or pregnant or breastfeeding women, as deposits in growing bones and teeth

Tinidazole	By mouth	No dosing information	1 month to 18 years: 50mg/kg/dose (max 2g) given once daily ☺	
Tipranavir	By mouth	No dosing information	2–18 years: 14mg/kg/dose (max 500mg) given twice daily with ritonavir 6mg/kg/dose (max 200mg) twice daily, or 375mg/m^2/dose given twice daily with ritonavir 150mg/m^2/dose twice daily ☺	a. Complex interactions, reduced levels with abacavir and zidovudine
Tobramycin	Intravenous Injection—bolus or infuse over 30min	<32 weeks corrected gestation: 4–5mg/kg/dose given 36-hourly ☹ >32 weeks corrected gestation: 4–5mg/kg/dose given 24-hourly ☹	1 month to 18 years: 7mg/kg/dose given 24-hourly ☺	a. For IV therapy, aim for pre-dose trough level of <1mg/L (<2mg/L for neonate) b. For IV therapy, monitor renal function closely c. Concurrent use with loop diuretics or other aminoglycosides increases the risk of nephrotoxicity and ototoxicity
Triclabendazole	By mouth	No dosing information	6–18 years: 10mg/kg stat dose. Repeat dose 12 hours later in severe infection ☹	

(*Continued*)

Drug	Route	Neonatal dose	Paediatric dose	Comments
Trimethoprim	By mouth	Treatment 0–28 days: 3mg/kg as a single dose, then 1–2mg/kg/dose given twice daily ☹ Prophylaxis of urinary tract infections 0–28 days: 2mg/kg/dose given at night ☹	Treatment 1 month to 18 years: 4mg/kg/dose (max 200mg) given twice daily ☹ Prophylaxis of urinary tract infections 1 month to 18 years: 2mg/kg/dose (max 100mg) given at night ☹	a. On long-term treatment, patients and their carers should be told how to recognize signs of blood disorders and advised to seek immediate medical attention if they occur
Truvada® Tenofovir + emtricitabine	By mouth Tablets—one tablet contains tenofovir 300mg + emtricitabine 200mg	No dosing information	Child: Individual tenofovir and emtricitabine—max dose as for adults Adults: One tablet once daily	a. Can be given with or without food b. Can be cut c. Can be dispersed in water d. Always check potential drug interactions between antiretrovirals and other medicines—see 🖱 <http://www.hiv-druginteractions.org>
Valaciclovir	By mouth	No dosing information	12–18 years: 20mg/kg/dose given three times daily ☺	a. Doses highly dependent upon indication b. Maintain adequate hydration c. Dose adjustments required in renal failure

Valganciclovir	By mouth	0–28 days: 16mg/kg/dose given twice daily 😐	1 month to 18 years: 520mg/m^2/dose (max 900mg) given once daily for long-term suppression and twice daily for treatment 😐	a. Take with or after food b. FBC monitoring required—significant risk of cytopenias
Vancomycin	By mouth	No dosing information	*C. difficile* infection 1 month to 18 years: 5mg/kg four times daily for 10–14 days (increased to 10mg/kg (max 500mg) if infection fails to respond or is life-threatening)	a. Doses to be adjusted, according to plasma concentration b. Injection may be used orally
	Intravenous Infusion over 60min	PMA <29 weeks: 15mg/kg/dose given 24-hourly 😐 PMA 29–35 weeks: 15mg/kg/dose given 12-hourly 😐 PMA > 35 weeks: 15mg/kg/dose given 8-hourly 😐	1 month to 18 years: 15mg/kg/dose given 8-hourly 😐	
Voriconazole	By mouth	No dosing information	Child 2–12 years: 7mg/kg/dose given twice daily (reduced to 4mg/kg/dose given twice daily, if not tolerated) ☺ Child 12–18 years: 10mg/kg/dose (max 400mg) given twice daily for 24 hours, then 7mg/kg/dose (max 200mg) given twice daily 😐	a. In mild to moderate hepatic impairment, use initial dose, and then halve subsequent doses
Zanamivir	Inhaled Dry powder inhaler	No dosing information	5–18 years: 10mg/dose given twice daily for 5 days (for post-exposure prophylaxis, use 10mg/dose given once daily for 10 days) ☹	a. Risk of bronchospasm in asthma b. Use other inhaled drugs prior to zanamivir

(*Continued*)

Drug	Route	Neonatal dose	Paediatric dose	Comments
Zidovudine		Post-exposure prophylaxis for baby born to HIV-positive mother Refer to <http://www.bhiva.org> PMA <30 weeks: 2mg/kg/dose given twice daily for 4 weeks PMA 30–34 weeks: 2mg/kg/dose given twice daily for 2 weeks, then 2mg/kg/dose given three times daily for 2 weeks PMA >34 weeks: 4mg/kg/dose given twice daily	Child: 180mg/m²/dose twice daily (max dose 300mg per dose twice daily) OR ≥4kg to <9kg: 12mg/kg/dose twice daily (max 300mg per dose twice daily) ≥9kg to <30kg: 9mg/kg/dose twice daily (max 300mg per dose twice daily)	a. Do not co-administer with stavudine
	Intravenous infusion	PMA <34 weeks: 1.5mg/kg/dose given twice daily PMA >34 weeks: 1.5mg/kg/dose given four times daily	No dosing information	

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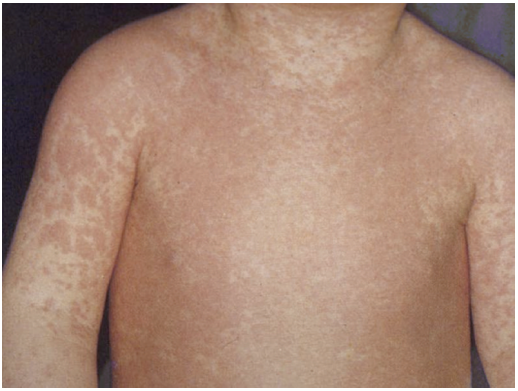


Plate 1 Morbilliform maculopapular erythematous rash in measles.

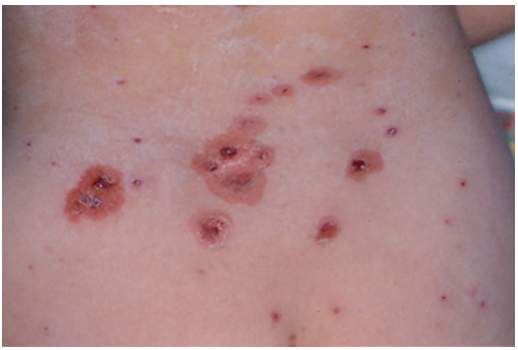
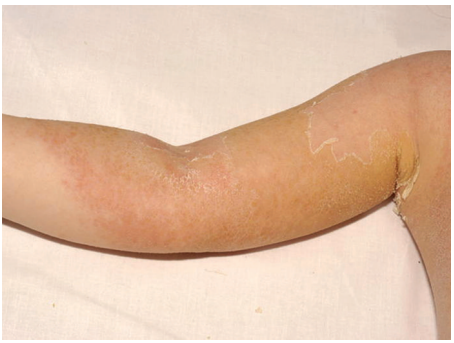


Plate 2 Lesions at various stages, including bullae in haemorrhagic chickenpox.

(A)



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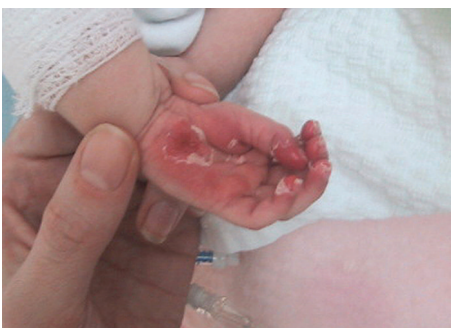

Plate 3 Desquamation in (A) scarlet fever and (B) syphilis.

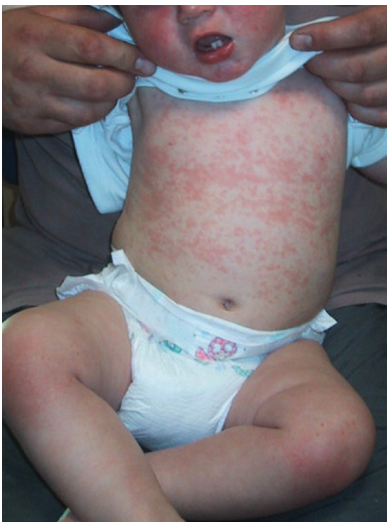

Plate 4 Rash in EBV infection after amoxicillin administration.

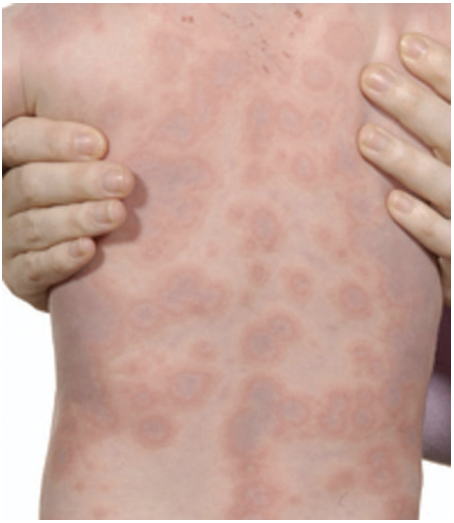

Plate 5 Erythema multiforme.

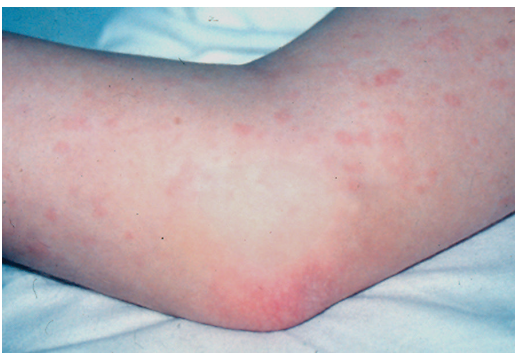

Plate 6 Macular rash in juvenile chronic arthritis.

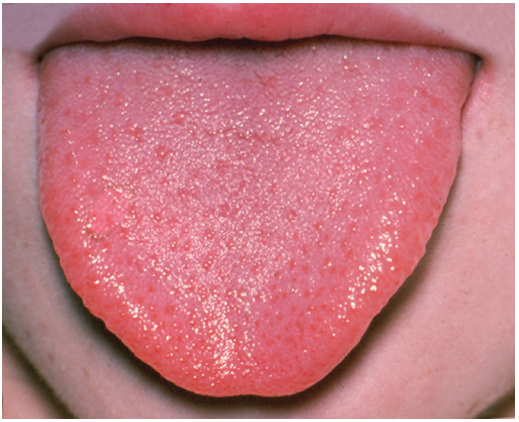

Plate 7 Strawberry tongue in scarlet fever.

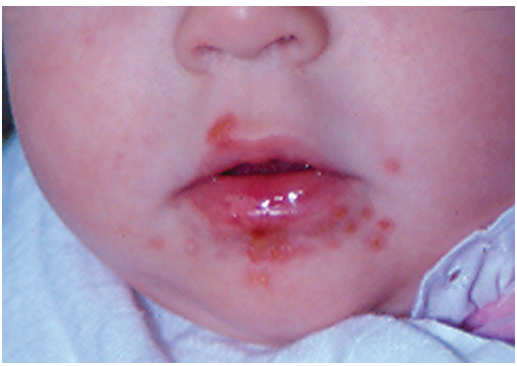

Plate 8 Herpes simplex stomatitis.

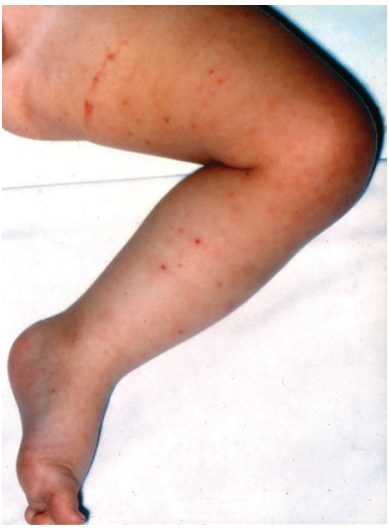

Plate 9 Petechial rash in meningococcal septicaemia.

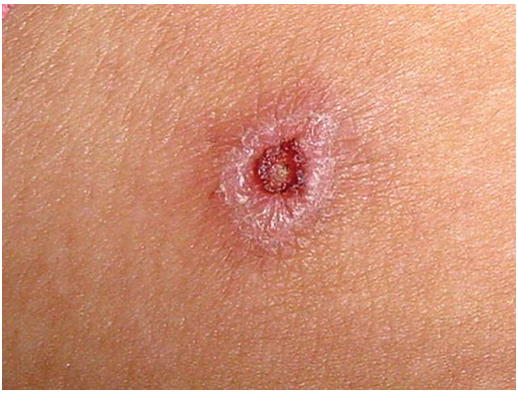

Plate 10 An eschar is a non-painful ulcer covered by a centrally depressed dark scab and surrounded by a red areola.

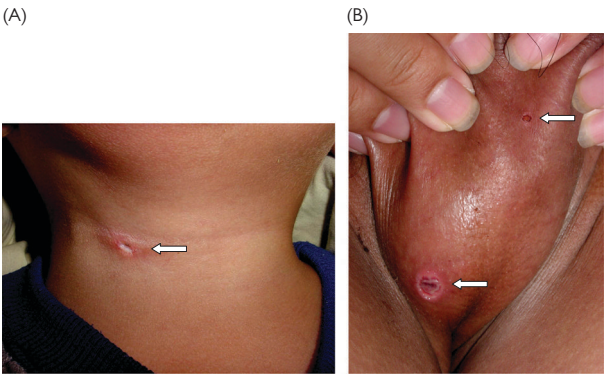

Plate 11 The dark crust scratched off from eschars on neck (A) and scrotum (B).