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MANUAL OF CHILDHOOD INFECTIONS

THE BLUE BOOK

FOURTH EDITION

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Manual of Childhood Infections

Fourth edition

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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)
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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) **Polymyxins** (polymyxin B, colistin)	Cell membrane inhibitors	Bactericidal
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).

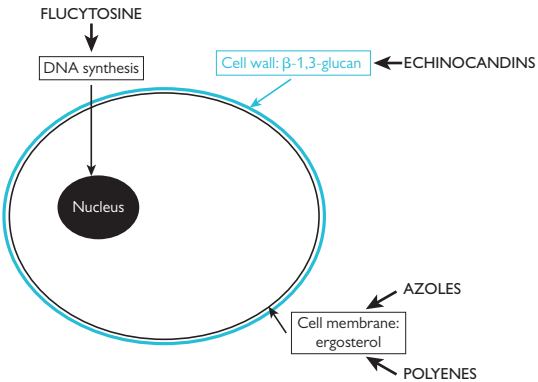

Fig. 2.1 Sites of action of antifungal drugs.

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.

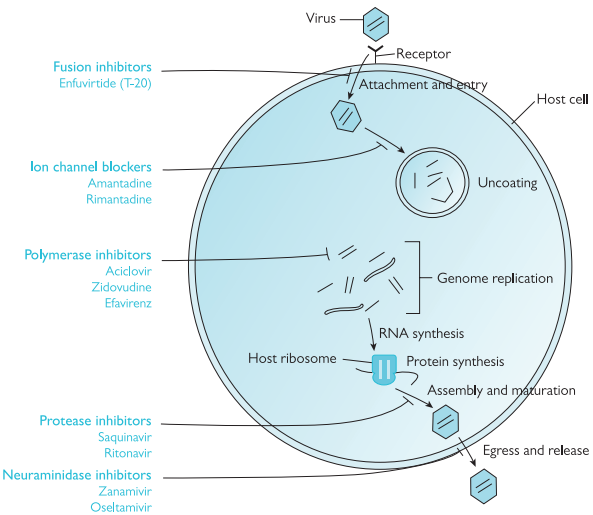

Fig. 4.1 A composite picture of potential sites of antiviral action along the replicative pathway of different viruses in an infected host cell.

(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

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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]

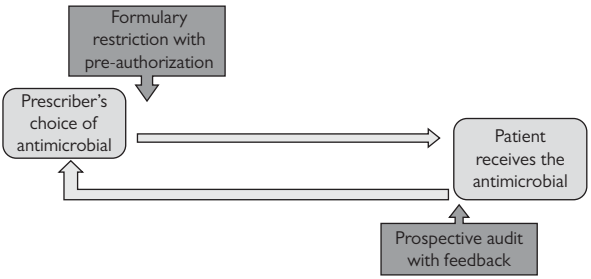

Fig. 5.1 ASP core strategy.

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

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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.

Further reading

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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.